SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 1 April 2005. For scientific information on procedures after this date please refer to module 8B.

1.   Introduction

Peginterferon alfa-2a is a polyethylene glycol (PEG)-modified form of human recombinant interferon alfa-2a intended for the treatment of adult patients with chronic hepatitis C (CHC) or chronic hepatitis B (CHB).

Chronic hepatitis C is a major public health problem: hepatitis C virus (HCV) is responsible for a large proportion of chronic liver disease, accounting for 70% of cases of chronic hepatitis in industrialised countries. Globally there are an estimated 150 million chronic carriers of the virus, including 5 million in Western Europe. Without treatment approximately 30% of those infected with HCV will develop cirrhosis over a time frame of 30 years or more. For those with HCV-related cirrhosis, the prognosis is poor – a significant proportion will develop a life-threatening complication (either decompensated liver disease or an hepatocellular carcinoma) within a few years. The only therapy for those with advanced cirrhosis is liver transplantation, which carries a high mortality. In those who survive transplantation, viral recurrence in the new liver is almost inevitable and a significant proportion of infected liver grafts develop a progressive fibrosis that leads to recurrence of cirrhosis within 5 years. Interferon alfa monotherapy has been shown to be effective for the treatment of chronic hepatitis although sustained response rates occurred in approximately 15 to 30 % of patients treated for long duration (12-18 months). The current reference therapy is interferon alpha in combination with ribavirin, which resulted in an increase in biochemical and virological sustained response rates to approximately 40 % in naïve patients. Recently, another pegylated human interferon alpha (subtype 2b) when used in combination with ribavirin has been shown to improve these results.

Hepatitis B virus is currently estimated to contribute to about 1 million deaths annually world-wide. The prevalence varies widely from less than 1% in low prevalence areas such as parts of Western Europe up to 20% in parts of South East Asia. Up to 40% of chronically infected individuals may develop serious sequelae during a lifetime.

The ultimate goal of therapy is to induce remission of the liver disease in order to prevent the development of cirrhosis and hepatocellular carcinoma (HCC). Whether sustained suppression of viral replication is needed (or sufficient in cases of advanced fibrosis) to obtain these objectives is unknown. Covalently closed circular forms of HBV DNA in the liver and viral sanctuaries may make complete viral eradication an unattainable goal.

The most commonly used definition of chronic hepatitis B infection is presence of serum HBsAg for at least 6 months. The outcome of HBV infection is variable, influenced by age at infection, immune response and environmental factors. Chronic hepatitis B in immunocompetent patients typically runs through three potentially successive phases; immune tolerant, immune active and low-/non-replicative. The *immune tolerant phase* is characterised by presence of HBeAg, high levels of serum HBV DNA, normal or minimally elevated serum aminotranferases and minimal or no liver necroinflammation on liver biopsy. In the *immune active phase*, serum HBV DNA levels decrease and serum aminotranferase levels increase, sometimes manifested by symptomatic flares, usually followed by HBeAg seroconversion to anti-HBe and transition to a *non-/low-replicative phase* with remission of disease ("inactive HBsAg carrier state"). Liver biopsy during the immune active phase shows mild to severe necroinflammation. In some patients, HBV variants arise which are unable to produce HBeAg, usually because of mutation in the pre-core or core promoter region. A proportion of these HBeAg-negative patients develops progressive HBeAg negative hepatitis with continued or intermittent necroinflammation and presence of substantial HBV DNA replication. The HBeAg negative chronic hepatitis B is established as a distinct disease entity separated from HBeAg positive hepatitis that requires separate analyses.

The following endpoints may be considered in clinical studies:
- Virological response: HBV-DNA below a predefined level. Whether the use of sensitive assays with a cut off below e.g. 200 copies/ml provides improved prognostic information is unknown;
- Immunological response: HBeAg seroconversion (loss of HBeAg + anti-HBe);
- Biochemical response: Normalisation of ALT;
- Histological response: Decrease in *e.g.*, total HAI score with at least 2 points without worsening of fibrosis.

Two pharmacological classes of agents for the treatment of CHB are currently available in the EU; the interferons (IFN) and nucleos(t)ide analogues. Due to differences in their mode of clinical activity it is not self-evident how to best compare compounds from these classes, either with respect to primary endpoint, or timing. In order to try to capture the most important aspects of the disease it appears advisable to use combined endpoints, such as virological or immunological + biochemical + histological response, but it is acknowledged that the optimal measure of treatment effects in terms of predictability of long-term prognosis remains to be defined.

Pegylation of interferon alfa-2a was developed to improve the pharmacokinetics properties of the active moiety and to reduce number of weekly injections compared to unpegylated interferon. Pegasys is available as a solution for injection in pre-filled syringes and vials containing either 135 or 180 µg of peginterferon alfa-2a.

The approved indication is:

"Chronic hepatitis B:

Pegasys is indicated for the treatment of HBeAg-positive or HBeAg-negative chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis (see 4.4 and 5.1).

Chronic hepatitis C:

Pegasys is indicated for the treatment of chronic hepatitis C in adult patients who are positive for serum HCV-RNA, including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see 4.4).

The optimal way to use Pegasys in patients with chronic hepatitis C is in combination with ribavirin. This combination is indicated in previously untreated patients as well as in patients who have previously responded to interferon alpha therapy and subsequently relapsed after treatment was stopped.

Monotherapy is indicated mainly in case of intolerance or contraindication to ribavirin."

Treatment should be initiated only by a physician experienced in the treatment of patients with hepatitis B or C.
In CHC, the recommended dosage is 180 micrograms once weekly for 48 weeks in patients with genotype 1 and 24 weeks in patients with genotype 2/3.
In CHB, the recommended dosage and duration of Pegasys for both HBeAg-positive and HBeAg-negative chronic hepatitis B is 180 micrograms once weekly for 48 weeks by subcutaneous administration in the abdomen or thigh.

2.   Chemical, pharmaceutical and biological aspects

Composition

Pegasys is supplied in two strengths, 135 µg and 180 µg, in 1 ml solution in vials or in 0.5 ml solution in pre-filled syringes. Sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid and water for injections are used as excipients.

Vials used are 2-ml vials of Type I quality flint glass according to Ph. Eur sealed with a rubber stopper and crimped with an aluminium cap which is fitted with a flip-off disk. The 13-mm stoppers comply with Ph. Eur. and are made of butyl rubber and are laminated on the product-facing side with a fluoro-resin film.

Pre-filled syringes consist of a syringe barrel with a luer tip to permit the insertion of a disposable needle, a tip cap and a plunger stopper which is inserted into the syringe barrel from the back end after filling to ensure that sterility of the syringe content is maintained. A sterile stainless steel needle for s.c. single-dose injection, sealed in a suitable plastic container, is supplied with the pre-filled syringe. All primary packaging materials are of standard quality and are suitable for packaging of parenteral products.

Active substance

Peginterferon alfa-2a (PEG-IFN) active substance is synthesized by the covalent attachment of a branched methoxypolyethylene glycol (PEG) polymer, with a molecular mass of about 44000, to interferon alfa-2a (IFN). Interferon alfa-2a (IFN) is a known active substance commercialised by the same company as Roferon which is authorised under the Mutual Recognition Procedure. The active substance for Roferon is produced in Basel whereas a technology transfer has taken place to Penzberg, Germany to provide interferon alfa-2a for pegylation.

The molecular weight of the PEG-reagent used to pegylate IFNα-2a affects both the specific activity *in vitro* (decreasing with increasing molecular weight) and the clearance (increasing half-life with increasing molecular weight) of the product *in vivo*. A relatively high molecular weight form of PEG has been developed to achieve the desired therapeutic properties of the product.

Interferon alfa-2a

Interferon alfa-2a is produced biosynthetically using recombinant DNA technology and is the product of a cloned human leukocyte interferon gene inserted into and expressed in *E coli*. Purified IFN has 165 amino acids and a molecular mass of 19237.

In the transfer of the Interferon manufacturing process to Penzberg, a fivefold scale up of fermentation and a 10-fold scale-up with respect to purification were made. The fermentation and harvesting process for production of interferon alfa-2a as well as the cultivation media used remain essentially unchanged compared to the Basel process. Process adaptations related to the 10-fold scale-up have been made.

PEG reagent

The reactive PEG reagent contains two monomethoxy PEG (mPEG) chains, each of a molecular mass of 20000, attached to the α- and ε-amino groups of lysine via urethane bonds. The lysine carboxylic acid end group is functionalized to an N-hydroxysuccinimide ester, which reacts with lysine on IFN to form an amide bond with the protein. The control of content of impurities is deemed acceptable by validation and analytical control at release.

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Peginterferon alfa-2a

The covalent attachment of the PEG moiety to IFN is the result of PEG reagent reacting with native IFN in aqueous solution. The N-hydroxysuccinimide group is liberated with the formation of the PEG-IFN conjugate. The resulting PEG-IFN molecule has a molecular mass of approximately 60000. The process conditions chosen, including a relatively high coupling pH, result in pegylation on lysine residues, the conjugates of which are fairly stable towards hydrolysis. Hence, Pegasys could be developed as a stable solution for injection, whereas pegylation at a lower pH results in a product with a major positional isomer on a histidine residue that is inherently less stable and can only be presented as a lyophilisate.

A thorough comparability assessment has been made in support of 1) the similarity of Interferon alfa-2a produced in scaled up facilities for supply of starting material for Pegasys 2) pegylation reagent produced according to various process versions and at optional sites and 3) the scale of PEG-IFN production. During scale-up, one batch, which was used in kinetic comparability studies, appears to be an outlier in respect of positional isomer pattern. The process conditions responsible were identified and corrected. Furthermore, the specification limits have been narrowed. With this correction, the commercial production has been shown in all essentials comparable to the production for clinical trials.

Characterisation

There are potentially twelve sites for pegylation on the polypeptide chain of interferon alfa-2a, comprising the N-terminus and eleven lysine residue side chains. Data of a large number of batches has been provided, and the consistency of product, as regards positional isomer pattern, is deemed well shown. No free interferon or free PEG was detected in any of the clinical batches. N-terminal sequence analysis (PTH-Edman chemistry), amino acid analysis, tryptic mapping and LC ESI MS were used to determine the primary and secondary structure. Circular dichroism spectra were found identical with that of non-pegylated IFN. The intact interferon sequence and di-sulfide-bonded structure are deemed sufficiently verified.

Product development and finished product

A liquid acetate formulation containing polysorbate 80 and benzyl alcohol was chosen and a pH of 6 based on studies on pH dependent aggregate formation. Benzyl alcohol is added to the formulation as a stabiliser to prevent oxidation of PEG-IFN and its choice and concentration are sufficiently justified.

The manufacturing process for Pegasys vials and prefilled syringes is conventional.

3.   Toxico-pharmacological aspects

Pharmacodynamics

The pre-clinical programme is restricted by the fact that no animal model of hepatitis C virus infection exists, that human interferon alfa-2a is inactive in rodents and that its activity is relatively low in primates. Furthermore primates used for toxicology studies developed neutralising anti-interferon antibodies within two weeks. The *in vitro* and *in vivo* pharmacodynamic studies focused therefore on the demonstration that peginterferon retains the functional effects of interferon alpha.

In vitro studies

Several *in vitro* studies showed that the biological activity of both pegylated and unmodified interferon alfa-2a compounds are qualitatively similar. Indeed peginterferon was shown to bind to the interferon alpha receptor, to trigger signal transduction within the cell leading to the induction of interferon alpha inducible genes, resulting in the antiviral and antiproliferative characteristics of interferon alpha but with reduced potency compared to interferon. In the majority of these studies, 50 -

100 times more pegylated test compound (as protein) was required to obtain the same effects as with the unmodified protein. These studies demonstrated biological activity of the 6 dominant positional isomers of peginterferon.

In vivo studies

The *in vivo* studies were limited to the monkey and human xenograft in nude mice because of the species specificity of interferon mentioned above. These studies reported antiproliferative activity against human tumour xenografts in nude mice and antiviral activity in monkeys demonstrated by the induction of 2', 5' OAS (oligo adenylate synthetase), a pharmacodynamic marker for peginterferon, with a trend towards superiority compared to interferon alpha.

Safety pharmacology

The safety pharmacology studies did not reveal any particular effects of peginterferon on body temperature, central nervous system, gastro-intestinal and respiratory functions in rats and mice at doses up to 600 μg/kg (200 times the clinical dose). Decreases in urine volumes were reported in rats after administration of peginterferon but this finding was neither dose-related nor accompanied by changes in electrolytes. No significant effects were reported on the cardiovascular system in monkeys.

Pharmacokinetics

The pharmacokinetic profile of peginterferon was evaluated in the rat and cynomolgus monkey following single intravenous and subcutaneous dose administration. In addition pharmacokinetic parameters were evaluated in cynomolgus monkeys after repeated administration. Peginterferon was determined in serum by using two methods of assays: antiviral bioassay and a competitive immunoassay used in the toxicokinetic studies. The design of the preclinical pharmacokinetic programme for peginterferon was typical for a therapeutic protein in that extensive biotransformation studies were not conducted.

Absorption and distribution

In rats, following iv single bolus administration (0.2-0.4 ml) of peginterferon, a half-life of approximately 15 hours was found compared to 2.1 hours for interferon, although the limited sampling size may have led to an underestimation of the terminal half-life of peginterferon.

The bioavailability of peginterferon has not been determined.

The pharmacokinetic profile of interferon activity in plasma after the subcutaneous administration of peginterferon to rats and monkeys was characterised by sustained absorption and prolonged terminal phase half-life, indicating slower elimination. The terminal phase half-life of interferon activity after administration of peginterferon was approximately 150-200 hours in monkeys, compared to 9 hours after administration of unmodified interferon.

In addition, Tmax of interferon activity after administration of peginterferon is prolonged compared to Tmax for unmodified interferon. This suggests sustained release characteristics.

Dose proportionality was shown for AUC and C_{max} in monkeys after single subcutaneous administration.

Peginterferon was mainly found in blood and there was no localisation of peginterferon to any specific organ or tissue. Following multiple administration of peginterferon in rats, no accumulation was observed in tissues over time, except for the spleen that was the only organ showing a small accumulation of the radioactivity.

Metabolism and elimination

The *in vivo* metabolism of pegylated interferon was studied in rats receiving multiple doses of unlabelled material (4800 µg/kg/daily) for one week. The presence of intact pegylated interferon was demonstrated in serum for up to 7 days following either iv or sc dosing, and no free peg or unmodified interferon were found.The applicant undertook, however, to further investigate the issue of possible depegylation *in vivo* of peginterferon alfa 2a.

Metabolism is the main clearance mechanism for intact peginterferon in the rat and the metabolites are primarily excreted in the urine. The kidney and the liver are therefore the major organs responsible for the elimination of radioactivity.

No gender specific pharmacokinetics was observed.

Toxicology

The toxicology programme for peginterferon was designed to provide a bridge between pegylated interferon alfa 2a and the known toxicity of interferon alfa 2a. In addition a 4 week repeated dose toxicity study of peginterferon combined with ribavirin was conducted. All pivotal toxicological and toxicokinetic studies conformed to GLP standards. Studies were conducted in cynomolgus monkey using subcutaneous and intravenous administration.

Toxicokinetic studies showed that systemic exposure achieved in animals was observed during the chronic toxicity studies.

Single dose toxicity

Transient mild increases in liver transaminases; anaemia, leucopoenia and foci of subacute inflammation in the liver parenchyma were reported in monkeys treated with subcutaneous doses up to 6.75-mg/kg peginterferon, corresponding to approximately 2000 times the intended clinical dose. When administered intravenously, no treatment related toxicity was reported besides bruising at the injection sites and a slightly elevated AST in one female (300 µg/kg).

Repeated dose toxicity

The toxicity profile was evaluated in cynomolgus monkeys receiving peginterferon subcutaneously for 4 weeks administered either twice weekly (dose up to 562.5 µg/kg) or daily (doses up to 600 µg/kg), and for 13 weeks administered twice weekly (doses up to 150 µg/kg).

Generally, peginterferon was well tolerated, with no mortality and only rare serious side effects. The characteristic pattern of interferon alpha toxicity was observed with peginterferon. These referred typically to suppressive effects on the haematopoietic system and increases in liver enzymes. Symptoms usually arose during weeks 1-2 and declined as neutralising anti-interferon antibodies emerged and circulating peginterferon levels declined. After that period a meaningful toxicological assessment was not possible to perform.

The pattern of haematopoietic toxicity induced in monkeys with peginterferon during the first 2 weeks of administration was typical of interferon toxicity in humans. It related to the total dose administered and was characterised by thrombocytopenia and neutropenia in all studies as well as reticulocytosis, decreased prothrombin time and increased APTT in the daily dose study. These effects were reversible.

The severity of liver findings is related to the exposure and dose of peginterferon given to male and female monkeys over 14 days. The most frequent finding was mild, transient increases in liver enzymes (ALT and AST). With twice weekly dosing, slight transient clinical chemistry changes, including decreases in protein, calcium, and in few animals, elevated ALT and/or AST (1.4-2.3 times

baseline) were observed. Similar but more pronounced findings were observed in the daily dosing studies. There were no histopathologic findings in any of the multiple dose toxicity studies.

Serious adverse effects including a poor general condition and elevated liver enzymes were seen in one high-dose female monkey in the 4-week study (600 microgram/kg/day, equivalent to about 1600 times the weekly clinical dose). Two days after treatment withdrawal, the findings reversed began to improve. Considering the long half-life of peginterferon, the quick initiation of reversal of symptoms could not be due to a significant decrease in exposure of peginterferon, rather to neutralising antibodies, or possibly to the rapid elimination of free interferon (1.5 % in this experimental lot) or elimination of unidentified impurities (4.9 %). A similar adverse event has been reported from the clinical studies, and a statement to discontinue therapy if ALT levels are progressively increased, is included in the SPC. Chronic heart inflammation was occasionally seen after long term treatment with interferon in monkeys but this was not considered of clinical relevance.

Specific thyroid-function tests were not performed in the toxicology programme. Although, there were no clinical symptoms of thyroid dysfunction or histopathologic effects on thyroids the occurrence of thyroid abnormalities during interferon alpha therapy is well characterised, and adequate information regarding thyroid function is included in the SPC.

A 4-week repeated dose study was conducted in monkeys to assess the toxicity of peginterferon alfa-2a (using up to 400 times the intended clinical dose) in combination with ribavirin (using doses up to 6 times the intended clinical dose). The combination appeared to result in a slightly increased toxicity compared to the individual treatments but there was no new toxic effect compared to the ones already known with the individual compounds. Toxicity reversed during the recovery period in all groups.

Reproduction studies were not performed as interferon has been shown to be abortifacient in primates. Peginterferon can be assumed also to have this effect, as expressed adequately in the SPC. In the bridging study on menstrual cycle irregularities, both peginterferon and interferon gave similar delays in menstrual cycles associated with a delay in peak 17-β estradiol and progesterone level D in monkeys. Peginterferon is therefore contraindicated during pregnancy as stated in the SPC.

Genotoxicity was studied in the *in vitro* standard battery of tests. Peg-interferon was neither mutagenic nor clastogenic. The lack of *in vivo* genotoxicity studies was acceptable, since human interferon alfa is comparatively inactive in rodents.

Carcinogenicity studies were not performed, which was considered acceptable since human interferon alfa has no apparent effect in rodents, and since antibodies are rapidly formed after administration of the pegylated product.

Local tolerance was not specifically evaluated. Mild subcutaneous inflammation was observed in the preclinical safety studies using the same formulation as intended for clinical use. The severity of the occurrence was considered to be dependent of the injected volume or the injection frequency. A potential for injection site reactions cannot be excluded in humans. However, a trend toward reversibility of the mild subcutaneous inflammation was noted during the recovery period in the toxicity studies.

Impurities

The impurity limits for *mono, di and oligo forms* of peginterferon alfa-2a are considered toxicologically qualified.

The lack of specific studies to assess the toxicity of the polyethylene glycol moiety was acceptable taking into account that the toxicity studies did not reveal any toxic signs that could be due to this moiety and that there is clinical experience with other pegylated products.

Environmental risk assessment

No adverse environmental effects are expected for peginterferon.

4.   Clinical aspects

The clinical database consisted of ten clinical pharmacology studies, one dose ranging study and three confirmatory studies. The programme was designed to compare peginterferon monotherapy versus interferon monotherapy in adults. A total of 429 healthy volunteers and 995 patients with chronic hepatitis C were exposed to peginterferon. Of these, 604 CHC patients received peginterferon at the recommended dose of 180 μg, 495 (82 %) of whom received the planned duration of treatment (48 weeks).

When the confirmatory studies were initiated, combination treatment of interferon alpha and ribavirin was not yet established as the standard of care for the treatment of hepatitis C and there was no general acceptance of sustained viral response as the primary efficacy endpoint. Supplementary data from ongoing studies, evaluating the combination of peginterferon with ribavirin, were provided, including one confirmatory study where approximately 450 (NV15801) patients received the combination therapy.

All the studies were conducted in accordance with the principles of Good Clinical Practices and international ethical considerations.

Clinical Pharmacology

Antiviral activity

Interferons play a major role in the first steps of the response to acute viral infections, being mediators in the non-specific antiviral response that precedes the specific, immune-mediated, response. In addition to their antiviral effect, interferons have a variety of actions, e.g., immunomodulatory, cytostatic, and antitumor. The mechanism by which interferons exert their antiviral effect is complex and not yet fully elucidated.

Interferon acts through the induction of various cellular enzymes. Among them, the 2'-5' oligodenylate synthetase (2'-5'-OAS) is (at least in part) responsible for a direct antiviral effect of interferon-alpha. The function of 2'-5'-OAS is to activate a latent endoribonuclease, responsible for degradation of viral and cellular RNAs. Measurement of 2'-5'-OAS activity in serum, peripheral blood mononuclear cells (PBMC), or various tissues has been widely used as a marker for interferon-alpha activity.

Serum OAS activity was saturable with maximal induction seen at 135/180 μg of peginterferon in different studies and remained maximal throughout a one week dosing interval. No further increases were seen with the 270 μg doseHowever, 135 and 180 μg dose have not been directly compared in the same study. The magnitude and duration of 2'-5'-OAS were reduced in the elderly and patients with severe renal impairment. The clinical relevance of these findings is unknown.

Pharmacokinetics

Peginterferon alfa-2a pharmacokinetics was studied in healthy volunteers and in special population subgroups (renal impaired patients, elderly, sex and race) after single doses. Multiple dose pharmacokinetics was studied in subgroups of patients with chronic hepatitis C in the phase II/III studies (including patients with compensated cirrhosis).

PEG-IFN exists *in vivo* as several isomers and the individual isomers are likely to differ in stability, activity and kinetic behaviour. An immune assay, but no bioassay, has been used in the

pharmacokinetic characterisation. There is, however, a rank order correlation between the recovery of isolated positional isomers in the ELISA and the *in vitro* antiviral activity of each positional isomer.

Absorption, distribution and elimination

Peak serum peginterferon alfa-2a concentrations were reached 80-100 h following a single dose of peginterferon administered subcutaneously, reflecting sustained absorption and low CL/F. Peginterferon alfa-2a is likely to be subjected to flip-flop kinetics with the absorption being the rate-limiting step for elimination.

When peginterferon was administered into the arm, lower exposure was reported compared with studies in which administration was in thigh and abdomen. The relative bioavailability of injection in thigh versus abdomen was 84 %. Peginterferon alfa-2a should therefore be administered in the thigh or abdomen to achieve optimal activity as recommended in the SPC.

After intreavenous administration, systemic clearance was about 60 ml $\pm$ 25 ml/h and the absolute bioavailability of subcutaneous peginterferon was about 80 %.

Peginterferon alfa-2a distributed to a low extent into tissues, reflected by a low V_{ss} (9 ± 5 l), which is close to the volume of plasma and extracellular water. It was shown unlikely that distribution properties of peginterferon alfa-2a are a cause for relapse. It is not known whether peginterferon alfa-2a is excreted in human milk. Therefore in the absence of data, breast-feeding is contraindicated during treatment as stated in the SPC.

Peginterferon serum concentrations declined either mono- or bi-exponentially and the terminal elimination half-life after a single dose was approximately 70h in healthy volunteers,. Peginterferon alfa-2a pharmacokinetics was considered dose-linear within the therapeutic range after single and multiple doses. The peak to trough ratio after multiple dosing was about 1.5 to 2.0 across all doses indicating that serum concentrations were maintained throughout 1 week dosing interval.

In patients, there was a considerable variability, expressed as CV%, ranging from 28 % to 67 % for AUC_{last} after a single dose. In healthy volunteers, the inter-subject variability in CL/F and V/F were 57% and 60%, respectively. The intra-individual variability was approximately 30 %. Body weight explained only a minor part of the between-patient variability and therefore no dose adjustment based on weight was considered relevant.

Special population

The pharmacokinetics was comparable in healthy volunteers and the target population. Following multiple dosing, the exposure was higher and the half-life prolonged compared with what is expected from single-dose data. Roughly, steady state is achieved before week 12, most likely between weeks 6 to 12, indicating that there is a time-dependent effect on peginterferon alfa-2a pharmacokinetics.

A single dose ranging study in patients with end-stage renal disease undergoing haemodialysis, revealed a 25 % to 45 % reduction in the clearance. A starting dose of 135 μg should be used in patients with end stage renal disease and in all patients, monitoring should be done.

Pharmacokinetics parameters were similar between healthy volunteers and patients with hepatitis C. There were no major pharmacokinetic differences in cirrhotic patients and non-cirrhotic patients after single and multiple doses, although the variability was large. Pharmacokinetics was not evaluated in patients with increasing severity of hepatic dysfunction, and peginterferon is contraindicated in patients with severe hepatic dysfunction or decompensated cirrhosis (defined as Child Pugh B/C or bleeding oesophageal varices).

A single dose study in healthy male subjects showed that age has a modest effect on peginterferon alfa-2a pharmacokinetics, characterised by a slower absorption, increased exposure, prolonged half-

life and CL/F reduced by approximately 25 % in older age. Dose adjustment in elderly is not considered necessary.

Pharmacokinetic parameters were comparable for males and females and there was no apparent difference between Japanese and non-Japanese subjects.

The pharmacokinetic profile of peginterferon alfa has not been evaluated in children.

Bioequivalence between clinical trial material and commercial material was studied in two trials. Both used the single remaining lot of clinical trial material out of more than 20 lots used in clinical trials. This lot was later identified to deviate significantly from all other lots regarding positional isomer distribution and activity. The results from these trials are, thus, considered irrelevant. Specification limits currently implemented in the production process preclude further release of such deviant lots and ensure comparability regarding physicochemical characteristics between commercial material and material used in clinical trials. Available data from ongoing trials using commercial material provide adequate reassurance regarding overall clinical comparability.

Interactions

Administration of peginterferon 180 μg once weekly for 4 weeks in healthy male subjects did not show any effect on mephenytoin, dapsone, debrisoquine and tolbutamide pharmacokinetic profiles suggesting that peginterferon has no effect on *in vivo* metabolic activity of cytochrome P450 3A4, 2C9, 2C19 and 2 D6 isoenzymes.

However, co-administration with theophylline resulted in a 25 % increase in theophylline AUC suggesting that peginterferon is an inhibitor for CYP450 1A2. It is therefore recommended in patients who receive concomitantly theophylline and peginterferon to monitor theophylline concentrations and make appropriate dosage adjustment of theophylline as mentioned in the SPC.

Results from multiple dose study in patients with chronic hepatitis C after 12 and 48 weeks of co-administration with peginterferon alfa-2a and ribavirin showed that ribavirin did not affect pharmacokinetic parameters of peginterferon alfa-2a and vice versa.

Clinical Efficacy

The antiviral efficacy of peginterferon monotherapy in adult patients not previously treated was evaluated in the following clinical studies**:**
- Study NV 15489: dose ranging study in patients with chronic hepatitis C without cirrhosis
- Study NV15496: Main study in patients with chronic hepatitis C with or without cirrhosis or bridging fibrosis
- Study N15597: Main study in patients with chronic hepatitis C with or without cirrhosis or bridging fibrosis
- Study NV15495: Main study in patients with chronic hepatitis C with cirrhosis or bridging fibrosis

All these trials were comparative 48-week trials, followed by 24 weeks untreated follow-up, open-label, randomised and multicentre.

When the confirmatory studies were initiated, ribavirin in combination with alpha interferon was not established as the reference therapy for patients with active chronic hepatitis C and there was no general regulatory acceptance of sustained viral response as the primary efficacy endpoint for confirmatory studies. This is reflected in the design. The applicant provided additional results from a main study conducted with peginterferon in combination with ribavirin as well as a supportive study.

- Study 15800: safety and pharmacokinetics in patients with chronic hepatitis C
- Study NV15801: main study in patients with chronic hepatitis C

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Dose response studies and main clinical studies

Dose response study

Study NV15489 was a phase II, open-label, randomised multicentre ascending dose study evaluating the activity of peginterferon 45 µg (n = 20), 90 µg (n = 20), 180 µg (n = 45) and 270 µg (n = 41) once weekly compared with interferon alfa-2a 3 MIU three times a week (n = 33) in non-cirrhotic treatment-naive patients with CHC. At 48 weeks, a virological response was reported in 9 patients (45 %) in the 90-µg arms, versus 23 (51 %) in the 180 µg arm and 21 (51 %) in the 270 µg arm. Safety data favoured dosages lower than 270 µg as there was an increase in adverse events mainly related to neutropenia or thrombocytopenia. This study concluded that doses between 90 and 180 µg could be tested in the main studies.

In patients with cirrhosis (NV15495), it was shown that the dose of 180 µg was significantly superior to 90-µg doses in terms of efficacy.

In one main study (NV15496), two doses of peg-interferon monotherapy were evaluated: 135 and 180 µg per week. From a clinical perspective, the two doses were robustly documented as superior to interferon in licensed dosages, but the anti-viral activity of the tested peginterferon alfa-2a regimens appeared similar., Tolerability data appeared similar for the two doses although 180 µg was associated with more haematotoxicity. There are only limited data available with the 135-µg doses in patients with cirrhosis or in combination with ribavirin.

Based on these data, 180 µg was chosen as the recommended dose. Reduction of the dose (135 µg or in some cases 90 µg) is however recommended when required for moderate to severe adverse events. Given the large inter-individual variability in systemic exposure with peginterferon and in biomarker activity, a concern was raised as to whether 180 µg was the optimal dose for all patients and whether individualised dosing based on early markers of interferon activity would be more appropriate. The applicant therefore undertook to further explore this issue, the results of which will be submitted as part of the follow-up measures to be fulfilled post-authorisation.

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Main studies

An overview of the main studies is given in the table below:

Clinical Studies of PEG-IFN Monotherapy in CHC

Protocol	Population	Study Design	Study Treatment Regimen, Dose, and Route of Administration	Total No. Pts
NV15495	CHC with cirrhosis or bridging fibrosis	Randomised, open-label, parallel-group, multicentre 48-wk trt period followed by 24 wks untreated FU	IFN 3 MIU tiw sc PEG-IFN 90 µg qw sc PEG-IFN 180 µg qw sc	88 96 87
NV15496	CHC with or without cirrhosis or bridging fibrosis	Randomised, open-label, parallel-group, multicentre 48-wk trt period followed by 24 wks untreated FU	IFN 3 MIU tiw sc PEG-IFN 135 µg qw sc PEG-IFN 180 µg qw sc	214 215 210
NV15497	CHC with or without cirrhosis or bridging fibrosis	Randomised, open-label, parallel-group, multicentre 48-wk trt period followed by 24 wks untreated FU	IFN 6 MIU tiw sc for 12 wks followed by IFN 3 MIU tiw sc for 36 wks PEG-IFN 180 µg qw sc	264 267

FU = follow-up; trt = treatment; tiw = three times weekly; qw = once weekly

Clinical Studies of PEG-IFN in combination with ribavirin in CHC

Protocol	Population	Study Design	Study Treatment Regimen, Dose, and Route of Administration	Total No. Pts
NV15801	CHC	Randomised, partially blinded, multicentre 48-wk trt period followed by 24 wks untreated FU	PEG-IFN 180 µg qw sc + placebo PEG-IFN 180 µg qw sc + ribavirin 1000 mg (< 75 kg) or 1200 mg (≥ 75 kg) in split doses IFN alfa 2b 3MIU 3 times weekly + ribavirin 1000 mg (< 75 kg) or 1200 mg (≥ 75 kg) in split doses (ribavirin administered with food)	227 465 457

FU = follow-up; trt = treatment; qw = once weekly

Efficacy in monotherapy

Population

The confirmatory trials were conducted in parallel to the dose-ranging studies. The populations comprised male and female patients aged 18 years and over, with documented CHC who had not previously been treated with interferon. Key eligibility criteria included liver biopsy within 12 months, compensated liver disease, ALT>ULN confirmed 2 weeks apart, anti-HCV positivity and positive HCV RNA Study NV15495 enrolled only patients with either bridging fibrosis or cirrhosis (fibrosis score 3 or 4 in the Knodell scoring system). In this study, patients with lower platelet counts, thyroid disease, chronic pulmonary disease and a history of organ transplantation were not explicitly excluded.

Primary endpoint

The primary endpoint was a combined endpoint of sustained virological response, defined as absence of detectable HCV RNA (i.e. < 100 copies/ml; COBAS Amplicor HCV test, version 2 in 2 consecutives measurements taken ≥ 21 days apart), and sustained biochemical responses (i.e. 2 consecutive normal serum ALT levels taken ≥ 21 days apart), at the end of the untreated follow-up period (72 weeks). According to the original protocol, measurements were to be confirmed ≥ 21 days apart and within a strict time window. The protocols of studies NV 154-95, 96 and 97 were, however, amended ≥ 6 months before database closure as the strict criteria led to too many violations. An independent, treatment-blinded expert group was organised and was instructed to assess biochemical and virological response based on ALT and HCV RNA data at weeks 48, 68 and 72. Altogether 62 patients had differences in assessments of sustained virological response between the original and the amended protocol assessments. Most of these differences resulted from missing week 48, 68 or 72 HCV RNA measurements. Results will be presented only according to the amended protocols.

Histological response was an important secondary endpoint. Paired liver biopsies before and 24 weeks after treatment allowed direct assessment of changes of the liver disease. The Knodell histological index was used to assess overall histological response and improvement was defined as a decrease of at least 2 points. Health related quality of life was also measured. Other secondary efficacy parameters included sustained virological response (week 72) at the end of the untreated follow-up, sustained biochemical response (week 72) at the end of the untreated follow-up, end of treatment (48 weeks) virological response and end of treatment (48 weeks) biochemical response.

This overview mainly focuses on sustained virological response at week 72 and histological data. Some exploratory data as regards the predictive value of genotype and viral load are also presented.

Statistical analysis

The **intent-to-treat population** was prospectively defined as all patients randomised and was used for the analysis of all primary and secondary efficacy parameters except the quality of life data and the change in total HAI score from pre-treatment, which were assessed only in patients with baseline and post-baseline scores, and paired biopsies, respectively.

The **standard population** excluded patients who had less than 12 weeks of treatment or who had major protocol violations. Analyses of primary and secondary parameters using this population were to be performed only if more than a pre-specified number of patients were excluded from the treatment groups.

Study NV15496 was planned as a superiority trial whereas study NV15497 was designed to demonstrate that PEG-IFN was not worse than IFN by more than 5% (one-sided equivalence). This test for equivalence was then to be followed by a test for superiority to demonstrate that the combined sustained response with PEG-IFN was superior to that with IFN.

Subgroup analyses were planned for patients categorised according to the following demographic and disease characteristics: age, sex, body surface area, pre-treatment ALT quotient (calculated as the average of all ALT quotients recorded pre-treatment), baseline HCV RNA titre, pre-treatment stage of liver disease (cirrhosis, transition to cirrhosis, or no cirrhosis), and HCV genotype. Analyses for subgroups of race, body weight, and pre-treatment HAI score were also conducted.

Results

Study NV 15496, recruited altogether 639 patients. Patients were mostly Caucasian (approximately 86 %) male (approximately 60-70 %) As regards baseline characteristics, the study population may be viewed as essentially "typical" with respect to genotype (type 1 65-70%), age (about 40 years), HAI score (9.5), injection drug use (39-47 %) and HCV RNA (approximately 7 million copies).

Patient disposition

	IFN, 3 MIU (N= 214)	PEG-IFN, 135 µg (N= 215)	PEG-IFN, 180 µg (N=210)
No. of patients who completed treatment	144 (67%)	176 (82%)	173 (82%)
No. of patients prematurely withdrawn	70 (33%)	39 (18%)	37 (18%)
Lack of efficacy	24 (11%)	5 (2%)	6 (3%)
Safety	21 (10%)	22 (10%)	21 (10%)
Other	25 (12%)	12 (6%)	10 (5%)

The percentage of patients discontinuing therapy was relatively high, especially in the interferon arm. The difference between study groups mainly related to the categories "lack of efficacy" (11 % versus 2.5 %) and "refused treatment" (7 % versus 3 %).

Number and percentage of patients with virological and/or biochemical response, ITT(according to amended protocol).

	IFN 3 MIU	PEG-IFN 135 µg		PEG-IFN 180 µg	
Week 48	(%)	(%)	Odds ratio, vs. IFN (95% CI)	(%)	Odds ratio, vs. IFN (95%CI)
Virol	47 (22)	114 (53)	4.2 (2.6; 6.8)	115 (55)	4.2 (2.6; 6.6)
Biochem	62 (29)	84 (39)	1.6 (1.0; 2.5)	91 (43)	1.8 (1.2; 2.9)
Week 72					
Virol + biochem	23 (11)	59 (27)	3.1 (1.7; 5.6)	55 (26)	2.9 (1.6; 5.3)
Virol	23 (11)	61 (28)	3.3 (1.9; 5.9)	58 (28)	3.2 (1.7; 5.8)
Biochem	38 (18)	68 (32)	2.5 (1.7; 3.6)	66 (31)	2.1 (1.3; 3.5)

Irrespective of dose, efficacy measure and analysis, PEG-IFN appeared statistically and clinically superior to IFN. An analysis in the standard population confirmed these results.

Study NV 15497 Inclusion and exclusion criteria were similar to those for study NV 15496. The major differences between the trials related to the use of only the 180 µg dose in the peginterferon arm and the use of interferon induction, 6 MIU three times weekly for 12 weeks, followed by 3 MIU three times weekly for 36 weeks as comparator. Baseline characteristics were overall similar to study NV 15496.

A high percentage of patients in the interferon arm did not complete the study, 39 % versus 16.5 % in the peginterferon arm. "Lack of efficacy" was the dominant reason for withdrawal in this group, and accounted for 20 %.

Number and percentage of patients with virological and/or biochemical response, ITT (according to amended protocol)

	IFN 6/3 MIU	PEG-IFN 180 µg	
	(%)	(%)	Odds ratio, vs. IFN (95% CI)
Week 72	N = 264	N = 267	
Virol + biochem	46 (17)	101 (38)	2.8 (1.9; 4.2)
Virol	50 (19)	103 (39)	2.6 (1.8; 3.9)
Biochem	65 (25)	120 (49)	2.5 (1.7; 3.6)

Efficacy results, also in the peginterferon arm, tended overall to be better in this study compared with NV 15496, but there was no obvious explanation to this. The efficacy advantage of peginterferon 180 µg compared with the interferon 6/3 MIU might be slightly less pronounced than compared with 3/3 MIU.

Study NV 15495 was designed to exclusively recruit patients with cirrhosis or bridging fibrosis. In this study, interferon 3 MIU was compared with peginterferon 90 and 180 µg. Altogether 271 patients

were randomised, but two did not receive study treatment. At baseline 76-79 % of the patients fulfilled criteria for cirrhosis.

The overall premature withdrawal pattern was rather similar to that observed in other studies (27 % in interferon arm versus 19 % in peginterferon 90 µg arm and 23 % in peginterferon 180 µg arm). There was a trend towards a higher dropout rate due to safety concerns in the peginterferon 180 µg group (14 %) versus peginterferon 90 µg group (12 %) and interferon group (10 %).

Compared with study NV 15496, there were trends towards a slightly higher mean age (47) and a higher percentage of males (approximately 70 %), while viral load and the percentage of genotype 1 tended to be lower (6 million copies and 55 % respectively). Observed differences are, however, small. More patients in the 180 mcg group showed ALT > 3xULN.

Number and Percentage of Patients with Virological and/or Biochemical Response, ITT according to amended protocol)

	IFN 3 MIU	PEG-IFN 90 µg		PEG-IFN 180 µg	
Week 72	(%)	(%)	Odds ratio, vs. IFN (95 % CI)	(%)	Odds ratio, vs. IFN (95 %CI)
Virol + biochem	7 (8)	14 (15)	1.8 (0.5; 5.9)	26 (30)	4.6 (1.8: 12.2)
Virol	7 (8)	14 (15)	1.8 (0.5; 5.9)	26 (30)	4.6 (1.8: 12.2)
Biochem	13 (15)	19 (20)	1.4 (0.5; 3.6)	30 (34)	3.3 (1.3; 8.1)

These results show that peginterferon 180 µg is superior to interferon 3 MIU.

Efficacy in combination therapy

Study NV15801 aimed to evaluate the efficacy of peginterferon in combination with ribavirin versus peginterferon monotherapy and interferon alfa-2b in combination with ribavirin. The dose of ribavirin was according to body weight (1,000 mg if weight < 75 kg and 1,200 mg if weight ≥75 kg, split in 2 doses and administered with food). This study included HCV positive patients who presented typical characteristics for CHC with respect to sex (majority male), age (around 40 years of age), HCV genotype (around 60 % genotype 1). The primary endpoint was as for the other studies i.e. sustained viral response (< 100) at week 72 (2 measurements > 3 weeks apart) + ALT normalisation.

The number of patients who completed follow-up varied between 63 % (interferon alfa 2b + ribavirin) to 72 % (peginterferon + ribavirin). The reasons for early withdrawal varied between treatment arms but insufficient response dominated followed by adverse events and refusal of further therapy.

Results are presented in accordance with the protocol-defined analysis and according to an "exploratory analysis". In the protocol analysis, all patients randomised were included and sustained viral responses required non-detectable virus in two samples around week 72. The exploratory analysis took into account only patients treated and no confirmatory sample with non-detectable virus at week 60 or later was required.

Number and percentage of patients with virological and/or biochemical response

	PEG-IFN	PEG-IFN + ribavirin		interferon alfa 2b + ribavirin	
Week 48			Odds Ratio vs. PEG (95 % CI)		Odds Ratio PEG + rib vs. IFN + rib (95 % CI)
Protocol Virol Biochem	132 (58%) 91 (40%)	314 (68%) 249 (54%)	1.50 (1.02; 2.20) 1.70 (1.17; 2.49)	231 (51%) 217 (47%)	2.16 (1.58; 2.97) 1.30 (0.96; 1.77)
Week 72					
Protocol Virol + biochem Virol Biochem	55 (24%) 62 (27%9 72 (32%)	210 (45%) 234 (50%) 233 (50%)	2.70 (1.79; 4.10) 2.92 (1.94; 4.14) 2.25 (1.52; 3.32)	180 (39%) 190 (42%) 197 (43%)	1.30 (0.95; 1.78) 1.49 (1.08; 2.05) 1.37 (1.01; 1.87)
Exploratory Virol	65 (29%)	245 (54%)	3.11 (2.06; 4.70)	198 (45%)	1.53 (1.11; 2.21)

These data confirm the added value of ribavirin to interferon therapy. According to the protocol defined primary analysis, peginterferon + ribavirin showed only borderline superiority to interferon + ribavirin (p = 0.057). Using the protocol definition of sustained viral response, statistical superiority was shown versus interferon + ribavirin (p = 0.004).

Histological response

HAI scores were used to evaluate histological response, defined as a ≥ 2 points decrease in total HAI score based on paired biopsies, baseline versus 24 weeks post-treatment. A central pathologist, blinded to therapy, assessed the biopsies.

Histological Responses*, Patients with Paired Biopsies

	NV15497		NV15496		NV15495 "cirrhotics"	
	Interferon alfa-2a	Pegasys	Interferon alfa-2a	Pegasys	Interferon alfa-2a	Pegasys
	6 MIU/ 3 MIU (N=167)	180 μg (N=184)	3 MIU (N=147)	180 μg (N=160)	3 MIU (N=55)	180 μg (N=68)
Histological Response (week 72)	55%	63%	45%	58%**	31%	54%**
Median Baseline HAI	10	9	10	10	13	14
Median change from baseline	-2.0	-2.0	-1.0	-2.0	0.0	-3.0
*Histological response was defined as ≥2 point decrease in total HAI score at end of follow-up as compared to pretreatment. **P<0.025, assessed by Cochran-Mantel-Haenszel test stratified by center.						

The percentage of paired biopsies was low in studies NV15496 and NV15497. Patients treated with peginterferon at a dose of 180 μg per week achieved a significantly higher response rate in all studies compared with interferon and appeared also superior to the 135-μg doses. In patients with sustained viral response approximately 80 % responded histologically, while in non-responders, histological response was seen in about 25 to 40 % of the patients, irrespective of therapy.

In study NV15495, recruiting patients with cirrhosis/bridging fibrosis (HAI F-score mean 3.7, median 4) no significant differences were detected between treatment groups with respect to fibrosis. The overall trend, however, was compatible with reduced fibrosis. Peginterferon significantly improved necro-inflammatory scores compared with IFN (28 % improved with peginterferon 180 μg versus 11 % with interferon).

In study NV15801, histological response was analysed for all patients with paired biopsies (17 % of the ITT population). In patients with sustained virological response, histological response was

observed in about 90 %, e.g. in the peginterferon + ribavirin group 47/53. In patients without viral response improvement was seen in about 60 % (17/27 in peginterferon + ribavirin).

Although the percentage of paired biopsies was low, these data support the fact that virological response is associated with histological improvement and that histological improvement may be seen also in case of non-sustained viral response.

Sustained Virological Response by Viral Genotype and Load, Monotherapy

Population	Subgroup	IFN (3, 6/3MIU		PEG-IFN 180 µg	
		n	% responders	n	% responders
Overall (pooled NV 15496 & 15497)		478	15%	477	34%
Genotype 1	Low viral load[a]	135	13%	148	38%
	High viral load[b]	156	3%	165	14%
Genotype non-1	Low viral load[a]	66	39%	72	63%
	High viral load[b]	107	23%	86	41%
Overall (pooled all cirrhotic patients)		**163**	**6%**	**156**	**29%**
Genotype 1	Low viral load[a]	40	5%	40	25%
	High viral load[b]	53	2%	50	12%
Genotype non-1	Low viral load[a]	28	11%	35	54%
	High viral load[b]	37	11%	28	32%

[a]($\leq 2 \times 10^6$ copies/ml) [b]($> 2 \times 10^6$ copies/ml)
As expected, genotype 1 and high viral load predict worse outcome, but no difference was observed with respect to genotype 1a and 1b.

Sustained Virological Response by Viral Genotype and Load, Combination Therapy

Population	Subgroup	PEG,		PEG + ribavirin,		IFN alfa 2b + ribavirin,	
		n	% responders	n	% responders	n	% responders
Genotype 1	Low viral load[a]	44	36%	115	53%	94	44%
	High viral load[b]	101	13%	182	40%	189	33%
Genotype non-1	Low viral load[a]	25	60%	44	75%	56	68%
	High viral load[b]	54	39%	111	70%	103	55%

[a] ($\leq 2 \times 10^6$ copies/ml) [b] ($> 2 \times 10^6$ copies/ml)

In both relative and absolute terms, the added value of combination therapy seems to be most pronounced in high-risk patients. Numerical superiority for peginterferon + ribavirin versus interferon alfa 2b + ribavirin is seen in all subgroups.

Quality of life

In study NV15801, health-related quality of life was measured using the 36-item Short Form Health Survey derived from the Medical Outcomes Study and the Fatigue Severity Scale. Results present typical pattern for symptoms evolution, i.e worsened symptomatology during therapy and reversal/improvement at the end of follow-up. The addition of ribavirin to peginterferon worsened the QoL compared to peginterferon alone. Due to the open study design no firm conclusion could be drawn as to whether the QoL results were worse with peginterferon + ribavirin or interferon + ribavirin.

Time to virological response

Viral kinetics was evaluated in sub-groups of patients in Phase II/III-studies. As regards to mono-therapy, the viral kinetic sub-study (n = 53) indicated that absence of early viral decline defined as less

than 1 log decline HCV RNA within 48 hours of treatment could be predictive of non-response (sensitivity 82 %, specificity 76 %, negative predictive value 95 %).

In the monotherapy and combination studies, , failure to achieve sustained virological response was predicted by lack of early virological response. As recommended in the SPC, consideration should be given to discontinuation of treatment in patients who do not achieve early virological response especially in the non-cirrhotic stage of the disease.

Duration of treatment

Patients were treated for 48 weeks in the clinical studies. However based on accepted international guidelines for the treatment of hepatitis C, the recommended duration of the combined treatment for patients obtaining virological response is at least 24 weeks. For those with high risk of relapse, such as genotype 1, 48 weeks treatment is recommended. Studies are ongoing to explore shorter duration of treatment, the results of which will be submitted as part of follow-up measures to be fulfilled post-authorisation. When peginterferon is used as monotherapy, the recommended duration is 48 weeks.

Long term follow-up

Preliminary data from an ongoing study evaluating the virological response in long-term follow-up of patients that responded to interferon or peginterferon in studies NV15495, NV15496 and NV15497 showed that for 35 cirrhotic patients, including 30 who were treated with peginterferon, HCV RNA remained undetectable 2 years after end of therapy. Additional data, including clinical events will be provided as part of follow-up measures to be fulfilled post-authorisation.

Supportive study

The efficacy of peginterferon 180 µg + ribavirin 1000 or 1200 mg daily has been assessed in 20 patients treated for 24 weeks (genotype non-1) or 48 weeks (genotype 1). For genotype 1 sustained virological response was 6/9 and 4/4 in genotype non-1.

Clinical safety

The safety database comprised mainly data from the 4 open-label comparative studies with peginterferon monotherapy (NV15495, 96, 97 and 89). In addition safety data from study NV15801 where peginterferon was used in combination with ribavirin were provided.

Patient's exposure

Altogether more than 1000 patients were treated with peginterferon in monotherapy studies, thereof close to 500 for 1 year at the dose proposed for marketing (180 µg). The percentage of patients withdrawn due to adverse events was essentially the same in all treatment groups, 10 %. For depression, however, more patients were withdrawn in the interferon 6/3 MIU group (6 % vs. 1-2 %). Dose modifications due to adverse events were more often undertaken in the PEG-IFN 180 µg group and mainly due to laboratory events dominated by neutropenia.

In the combination study, altogether 451 patients were treated with peginterferon combination therapy and 443 with interferon combination therapy. Approximately 72 % of the patients completed the full scheduled period of treatment. Among adverse events leading to withdrawal, psychiatric disorders, mainly depression, were the most commonly encountered. A slightly higher percentage of patients in the interferon alfa-2b plus ribavirin group (4 %) stopped treatment due to psychiatric disorders compared with the other treatment groups (3 % in combination therapy and 1 % in monotherapy arm). More patients in the PEG-IFN combination group withdrew due to haematological abnormalities (2 %) (mostly to neutropenia and thrombocytopenia) than in the other groups (1 % in each group).

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Discontinuation or Dose Reduction due to Adverse Events or Laboratory Abnormalities

Adverse Events	PEG-IFN (N = 223)	PEG-IFN Ribavirin (N = 451)	Interferon alfa 2b Ribavirin (N = 443)
AEs and laboratory abnormalities leading to withdrawal	15 (7%)	44 (10%)	47 (11%)
AEs and laboratory abnormalities requiring dose modification			
PEG-IFN alfa-2a or IFN alfa-2b	61 (27%)	145 (32%)	81 (18%)
Ribavirin		181 (40%)	164 (37%)

Adverse events and serious adverse events/deaths

Overall, approximately 96 % of patients in each group reported at least one event possibly related to treatment.

The most frequent adverse events were general disorders (e.g incidence of fatigue approximately 50 %), gastro-intestinal disorders (e.g. nausea approximately 24 %), neurological/psychiatric disorders, skin disorders (e.g. alopecia approximately 20 %). The frequency and severity of the most common observed adverse events were similar in patients treated with peginterferon and interferon alfa-2a. Most of them were mild to moderate in severity.

Depression was less frequently observed with peginterferon in either monotherapy (18 %) or in combination (20 %) compared with interferon alfa-2b (28 %) but tended to occur slightly earlier in combination groups (median time to onset approximately 93 versus 103 days in monotherapy). The majority of patients who suffered from depression during treatment did not have a history of depression.

Of a total of 59 patients receiving either peginterferon alfa-2a monotherapy or interferon alfa-2a had a history of a pre-existing cardiac condition; eleven subsequently reported a cardiac adverse event (8 cases of arrhythmia, palpitations, and irregular heart beat and 3 cases of ischemia). Ten serious cardiovascular events in 9 patients were observed in the combination study, 6 in the peginterferon combination group, two in interferon alfa 2b combination group and one in the peginterferon monotherapy group. None of these events was associated with haemoglobin concentration < 10 g/dl. Although the database is still limited, there seems to be a causal relationship between the administration of peginterferon and myocardial disorders. Therefore peginterferon is contraindicated in patients with history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months.

Across all studies, 11 deaths occurred in patients treated with peginterferon, including 3 during the follow-up period after combination treatment with ribavirin, while 1 death occurred in the interferon arms (0.8 % versus 0.2 %). There was no evidence for causal relationship, apart from one case possibly related to peginterferon (pneumonitis).

In the monotherapy studies, the overall incidence of serious adverse events was 9 % in the 180 μg peginterferon arm, 10 % in the 135 μg peginterferon arm and 7 % in the interferon arm. For those probably related to treatment, the overall incidence was respectively for the 3 arms, 5 %, 3 % and 2 %. In the combination study, the incidence of serious adverse events was 12 % in both peginterferon groups versus 9 % in the interferon alfa-2b plus ribavirin group. Serious adverse events judged to be related to treatment by the investigator were equally common in all three groups (4%).

Overall there are no major treatment differences in serious adverse events.

Laboratory adverse events

With respect to peripheral haematology, there is a clear difference between interferon and peginterferon and also a difference related to dose.

Lowest Neutrophil Count (%)

Neutrophils (x10^9/l)	IFN 3 N=323	IFN 6/3 N=261	PEG-IFN 135 N=215	PEG-IFN 180 N=604
1.5-<2.0	29%	30%	17%	14%
1.0-<1.5	29	33	36	35
0.5-<1.0	16	21	34	41
<0.5	1	1	3	4

Time to onset and incidence of grade 3 or 4 neutropenia were clearly dose dependent. Time to onset of grade 4 neutropenia was generally within 8-12 weeks. Dose-modifications were undertaken in 3-4% of the patients treated with peginterferon versus 1-2% of those treated with interferon. Three patients, thereof two treated with PEG-IFN discontinued therapy due to neutropenia.

Compared with peginterferon mono-therapy, the incidence of neutropenia was somewhat more pronounced and, as expected, anaemia was more pronounced with combination therapy. Moderate (ANC: 0.749 – 0.5 x 10^9/l) and severe (ANC < 0.5 x 10^9/l) neutropenia was observed respectively in 22 % patients (99/451) and 4.7 % (21/451) of patients receiving peginterferon + ribavirin.

Most of the cases of neutropenia with peginterferon treatment were observed during the first 2 weeks. The addition of ribavirin to peginterferon increased the incidence of neutropenia after week 8. In the clinical trials, decrease in ANC was reversible upon dose reduction or cessation of therapy. Most of the patients who had dose modifications due to neutropenia (14 %) had their dose reduced to 135 µg. Monitoring is recommended at 2 and 4 weeks, then at regular intervals and as clinically indicated and dosage adjustment is recommended in patients with ANC below 750/mm^3 as mentioned in the SPC. There was no obvious relationship between neutropenia and bacterial infections, or between thrombocytopenia and haemorrhage.

Thrombocytopenia

Among the 32 patients treated with the recommended dose of the peg-interferon alfa-2a (180 µg once weekly) who developed grade 3 or 4 thrombocytopenia, 25 were cirrhotic.

Altogether two of the patients treated with 180 of peg-interferon discontinued prematurely because of thrombocytopenia, and 21 patients had their dose permanently reduced. The addition of ribavirin did not appreciably alter the overall incidence of grade 3 or 4 thrombocytopenia. Most of the patients in the clinical studies had platelet counts ≥ 90,000/mm^3. Considering the sparse safety data available for patients with platelet counts below this limit, it is recommended in the SPC to check the baseline values prior to beginning peginterferon treatment and to perform routine monitoring during therapy.

Anaemia

Haemoglobin levels decreased in all treatment groups within the first 4 weeks of treatment and returned to baseline levels within 8 weeks after the end of treatment. The addition of ribavirin resulted in an increase of patients with low haemoglobin level (10.9 % versus 3.5 % in peginterferon monotherapy and 10.8 interferon alfa-2b + ribavirin).

Liver function

Fluctuation of ALT values is expected in patients with CHC and this variability is also seen during treatment, at least before remission. For 20 of the 25 patients with high ALT (> 10xULN), detectable HCV RNA accompanied the highest ALT value. Dose modifications due to ALT increase were mainly

undertaken in patients with ALT>10xULN and in about 1-2% of the patients. No consistent difference between treatment groups was observed.

Ribavirin added to peginterferon leads to slightly increased median ALT levels during treatment and three patients on peginterferon + ribavirin were withdrawn from therapy due to ALT increase compared with one patient on peginterferon and one patient on interferon alfa-2b + ribavirin.

<u>Thyroid function</u>

The frequency of thyroid abnormalities (4.9 % in patients receiving peginterferon + ribavirin was similar to that observed with interferons.

Patients with cirrhosis

Altogether 461 patients with compensated cirrhosis or bridging fibrosis, thereof 271 in study NV 15495 were included in the clinical study program

With respect to neutropenia and for patients treated with peginterferon 180 µg a modest increase in grade 3/4 events were observed in cirrhotic compared with non-cirrhotic patients (50% vs. 45%). As regards thrombocytopenia, dose reduction was frequently indicated, however, and around 20% of the patients showed thrombocyte levels below $50x10^9/l$. Otherwise, the adverse event profiles were overall similar to those observed in patients without cirrhosis. No patients developed decompensated cirrhosis while on therapy. In an ongoing study evaluating the efficacy of peginterferon alfa 2a monotherapy or in combination with ribavirin compared to interferon + ribavirin in patients with HCV/HIV co-infection, there were 12 cases of hepatic decompensation. All these patients were cirrhotic and received concomitant anti-HIV therapy. HCV/HIV co-infected patients with advanced cirrhosis receiving HAART may therefore be at increased risk of developing hepatic decompensation and death if treated with ribavirin in combination with interferons, including peginterferon. A warning regarding treatment in co-infected patients has therefore been included in the SPC and peginterferon is contraindicated in patients with severe hepatic dysfunction or decompensated cirrhosis (defined as Child Pugh B/C or bleeding oesophagaeal varices). The final results of the study in HCV/HIV co-infected patients will be submitted as part of the follow-up measures to be fulfilled post-authorisation (refer to HIV/HCV co-infection section for final results).

<u>Neutralising antibodies</u> were observed in overall 1 to 5% of the patients treated with interferon alfa-2a, about 3 % of those treated with peginterferon alfa-2a, 5 % on peginterferon alfa-2a + ribavirin and finally 1 % on interferon alfa-2b + ribavirin. No specific adverse events were reported in antibody positive patients, but further analyses indicate that there was a clear loss of activity in interferon alfa-2a treated patients developing neutralising antibodies. This, however, seems not to be the case in patients treated with peginterferon alfa 2a.

Post authorisation activities

Since the approval of the original Marketing Authorisation a number of variations have been authorised which amend the clinical aspects of the Summary of Product Characteristics and relevant parts of the Package Leaflet.

On 23 July 2003, the European Commission approved a type II variation to remove the term "histologically proven" from section 4.1 of the SPC. The main focus of the variation was the results of a clinical study conducted in patients with chronic hepatitis C comparing 24 and 48 weeks of therapy and two dosages of ribavirin (800 versus 1000/1200 milligrams) in combination with Pegasys (Peg-IFN). As a result of the study, the recommended posology of treatment was changed to be genotype specific and the MAH proposed changes to section 4.2, 4.4, 4.8, 5.1 and 5.2 of the SPC.

The MAH justified the removal of the term "histologically proven" from the indication by referring to the French Consensus Conference on Hepatitis C where it is stated that biopsy may not be necessary if a decision to treat already has been made on other grounds and the primary objective is viral

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eradication. This is also largely in line with other National Guidelines. The viral eradication rate is so high for patients with genotype 2/3, for example, that treatment is indicated in many cases even if the histology turns out to be benign. Therefore histology is not always needed.

The CPMP agreed that the term "histologically proven" should be removed from section 4.1 but requested that a warning be added to section 4.4: "*All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (ie patients with genotype 2 or 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment*".

<u>Study NV15942</u>

The main focus of the variation was the results of study NV15942, a randomised, double blind trial comparing 24 and 48 weeks of therapy and two dosages of ribavirin in combination with Pegasys (Peg-IFN) in patients with chronic hepatitis C. Patients who completed the study were followed for an additional 24 week period at the end of which sustained virological and ALT response were assessed.

Sustained response was defined by two consecutive samples with undetectable HCV RNA (Cobas Amplicor, version 2) > 3 weeks apart on or after day 240 (arms A and B) or on or after day 408 (arms C and D). In case of discordant results a third sample was used as arbiter.

The primary hypothesis was that 48 weeks of therapy was superior to 24 weeks, while the secondary objective was that the lower ribavirin dose was "non-inferior" (Odds Ratio ≥0.7) to the licensed dose (1000/1200 mg).

The eligibility criteria were typical for first-line CHC studies and included HCV RNA > 2000 copies/ml, histology within 15 months prior to study entry and compensated liver disease. Patients positive for HIV and HAV were excluded.

Clinical efficacy

Sustained Virological Response Based on Genotype and Viral Load after Pegasys Combination Therapy with Ribavirin in HCV Patients

	Study NV15942				Study NV15801	
	Pegasys 180 mcg & Ribavirin 800 mg 24 weeks	Pegasys 180 mcg & Ribavirin 1000/1200 mg 24 weeks	Pegasys 180 mcg & Ribavirin 800 mg 48 weeks	Pegasys 180 mcg & Ribavirin 1000/1200 mg 48 weeks	Pegasys 180 mcg & Ribavirin 1000/1200 mg 48 weeks	Interferon alfa-2b 3 MIU & Ribavirin 1000/1200 mg 48 weeks
Genotype 1 Low viral load High viral load	29% (29/101) 41% (21/51) 16% (8/50)	42% (49/118)* 52% (37/71) 26% (12/47)	41% (102/250)* 55% (33/60) 36% (69/190)	52% (142/271)* 65% (55/85) 47% (87/186)	45% (134/298) 53% (61/115) 40% (73/182)	36% (103/285) 44% (41/94) 33% (62/189)
Genotype 2/3 Low viral load High viral load	84% (81/96) 85% (29/34) 84% (52/62)	81% (117/144) 83% (39/47) 80% (78/97)	79% (78/99) 88% (29/33) 74% (49/66)	80% (123/153) 77% (37/48) 82% (86/105)	71% (100/140) 76% (28/37) 70% (72/103)	61% (88/145) 65% (34/52) 58% (54/93)
Genotype 4	(0/5)	(8/12)	(5/8)	(9/11)	(10/13)	(5/11)

* Pegasys 180 mcg ribavirin 1000/1200 mg, 48 w *vs.* Pegasys 180 mcg ribavirin 800 mg, 48 w: Odds Ratio (95% CI) = 1.52 (1.07 to 2.17)   P-value (stratified Cochran-Mantel-Haenszel test) = 0.020
* Pegasys 180 mcg ribavirin 1000/1200 mg, 48 w *vs.* Pegasys 180 mcg ribavirin 1000/1200 mg, 24 w: Odds Ratio (95% CI) = 2.12 (1.30 to 3.46)   P-value (stratified Cochran-Mantel-Haenszel test) = 0.002.

For patients with genotype 1 and high viral load the 48-week, high ribavirin dose was superior to alternative posologies. As regards genotype 1 and low viral load the results were less convincing, however, the probability of sustained viral response in patients with HCV genotype 1 increases with increasing ribavirin dose/kg body weight. The CPMP concluded that the recommended posology for patients with genotype 1 should be 48 weeks of therapy with high dose ribavirin.

The MAH provided further analyses on patients with genotype 2 or 3 with and without additional risk factors. There were no trends discernable indicating that prolonged therapy or a higher dose of ribavirin would provide a better treatment outcome. The CPMP concluded that the recommended posology should therefore be 24 weeks of therapy and low-dose ribavirin for genotype 2 and 3

For genotype 4, the MAH supplied evidence from literature and pivotal studies NV15942 and NV15801, which supported the treatment of these patients with the higher ribavirin dose and for 48 weeks in order to achieve optimal response. The CPMP agreed on the following wording: *"In general, patients infected with genotype 4 are considered hard to treat and limited study data (N=49) are compatible with a posology as for genotype 1. When deciding on the duration of therapy, the presence of additional risk factors should also be considered. For patients infected with genotype 5 or 6 this posology should also be considered."*

Clinical safety

Overview of Adverse Events (%)

	ribavirin 800, 24 w	ribavirin 1000/1200 24 w	ribavirin 800, 48 w	ribavirin 1000/1200 48 w
N	207	280	362	436
Any AE	97	98	98	98
Severe	22	23	32	32
Serious AE	3	7	9	10
Related SAE	1	3	4	3
Deaths (n)	0	1	1	2
AE ⇒withdrawal	5	5	16	15
AE⇒dose adj.				
PEG-IFN	30	26	33	36
Ribavirin	19	27	28	38

"Psychiatric disorders" were the most frequent reason for withdrawal from the trial (4.0% vs. 1.6%, at 48 weeks vs. 24 weeks, respectively), however, depression did not seem to be related to duration of therapy or ribavirin dose.
There were four deaths in the study: overdose of opiates, intoxication (alcohol, opiates, amphetamine, etc.), sepsis, suicide.
There were altogether 16 events of serious infections in 15 patients. One patient died of septic shock. There did not appear to be a relationship between neutropenia and infectious events.
Two individuals were withdrawn from therapy due to thrombocytopenia, 3% underwent permanent dose reduction and 1% temporary reduction of the PEG-IFN dose.
As expected the higher dose of ribavirin was associated with a more pronounced reduction in Hb levels. This was also seen in patients treated for 48 weeks. This was reflected in the percentage of patients undergoing permanent dose reduction of ribavirin; 10% in the 48 weeks, high dose group compared with 2% in the 24 weeks, low dose group. No association between anaemia and cardiac events was seen.
One patient developed autoimmune hepatitis and, in addition, 6 patients discontinued therapy due to "ALT flare".

As a result of the trial, the warning relating to anaemia was updated and in the section on psychiatric and central nervous system, suicide was added and suicidal attempts removed.

The SPC already carried a warning about the concurrent use of Highly Active Anti-retroviral Therapy (HAART) in patients co-infected with HIV. Following concerns about the increased risk of adverse reactions in patients co-infected with HIV and treated concurrently with HAART this warning was updated to be more in line with the class labelling.

A warning regarding the teratogenicity and embryocidicity of ribavirin was added to section 4.6 since the recommended use of Pegasys is in combination with ribavirin. The warning on the need to avoid pregnancy was also strengthened.

Statements on the incidences of adverse reactions were modified to incorporate the new data from trial NV15942 and new adverse reactions were added to section 4.8 as a result of the new data: epistaxis, gingivitis, cheilitis, constipation, musculoskeletal pain and chest pain.

Section 4.8 was also changed to a tabular format to bring it in line with SPC guidelines. This resulted in the addition of adverse reaction occurring at the 1% frequency which had previously been excluded: bronchitis, oral candidiasis, thrombocytopenia, migraine, somnolence, hyperaesthesia, nightmares, syncope, vertigo, earache, peripheral oedema, tachycardia, stomatitis, dysphagia, glossitis, arthritis and thirst.

At the request of the Rapporteur, the adverse reactions: thyroiditis, psoriasis, rheumatoid arthritis and SLE were added to the Immune system disorders SOC.

Extension of indication: Treatment in combination with ribavirin of adult patients with chronic hepatitis C and persistently normal alanine aminotransferase levels

On 29 October 2004, the European Commission approved a type II variation concerning the extension of indication for Pegasys (all strengths and formulations), to include treatment in combination with ribavirin of adult patients with chronic hepatitis C (CHC) and persistently normal alanine aminotransferase (ALT) levels with consequential changes to Sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SPC.

It has been estimated that 30% of patients with CHC have persistently normal ALT (defined by detectable hepatitis C virus (HCV) RNA, HCV antibodies and at least three ALT values within the normal reference range over a 6 month period). There appears to be no major difference in terms of viral load or genotype (incl. quasispecies) as compared to patients with CHC and increased ALT. Predictive factors for persistently normal ALT in case of CHC include female sex, age >40 years, no alcohol use and low body mass index. The long-term prognosis is ill defined.

Multiple factors, relating to both the virus and the individual, may influence the benefit/risk ratio of initiating treatment in patients with CHC. These factors should be considered in the evaluation of each individual patient's suitability for treatment and normal ALT status *per se* should no longer be considered a barrier to treatment if other factors support this intervention.

No additional information on clinical pharmacology was obtained during the clinical development programme presented in this application.

The pivotal study designed to evaluate the clinical efficacy and safety of a pegylated IFN alfa plus ribavirin for the treatment of CHC in patients with persistently normal ALT activity was a multicentre (70), randomised, open label study (study NR16071) comparing 3 groups:

- PEG-IFN 180 micrograms once weekly + ribavirin 800 mg daily for 24 weeks;
- PEG-IFN 180 micrograms once weekly + ribavirin 800 mg daily for 48 weeks;
- No treatment/observation for 72 weeks.

The inclusion criteria were as follows:
- HCV RNA >1000 IU/ml (Amplicor ver. 2);
- ALT ≤ Upper Limit of Normal (ULN) at least on three occasions, a minimum of 4 weeks apart, there of one during screening and one 6 to 18 months before screening;
- Biopsy verified chronic liver disease within 36 months prior to first dose.

Clinical efficacy

The Primary Efficacy Parameter was the Sustained Viral Response (SVR) (SVR: HCV RNA <50 IU/ml) 24 weeks after end of therapy or at end of the 72-week observation period.

Patient population: 514 patients were randomised and 491 analysed for safety and efficacy (ITT population).

Patient disposition

Study week	Patient Disposition	24 w PEG-IFN/rib	48 w PEG-IFN/rib	Observation
	Randomised	219	221	74
	Treated	211	210	1*
Week 12	On study	200 (91%)	193 (87%)	70 (95%)
Week 24	-"-	191 (87%)	182 (82%)	69 (93%)
Week 48	-"-	190 (87%)	152 (69%)	69 (93%)
Week 72	-"-	161 (74%)	148 (67%)	61 (82%)

*administered 24 weeks of therapy

Baseline characteristics

	24 w PEG-IFN/rib n=212	48 w PEG-IFN/rib n=210	Observation n=69
Female	58%	61%	62%
Age, median, year	43.5	44.0	41.0
Weight, median, kg	71	73	69
HCV RNA, median, x10^3 IU/ml	525	521	600
ALT, average of 3, median (ULN 30 U/l)	21	21	21
Fibrosis score			
0	27%	24%	28%
1	39%	45%	49%
2	21%	20%	14%
3	9%	7%	7%
4	2%	2%	0%
5	0%	<1%	0%
missing	<1%	<1%	1%
Genotype 1	68%	67%	68%
2	18%	20%	19%
3	9%	9%	9%
4	4%	4%	3%
5	<1%	0%	0%
6	<1%	<1%	1%

Sustained viral response (SVR) based on single HCV RNA determination

	24 w PEG-IFN/rib n=212	48 w PEG-IFN/rib n=210	Observation n=69
All patients	63 (30%)	109 (52%)	0
	48 w vs. 24 w. Odds Ratio 3.13 (95% CI 1.98; 4.95)		
Type 1,	19 (13%)	57 (40%)	
Low viral load*	14 (16%)	42 (47%)	
High viral load	5 (9%)	14 (27%)	

Type 2+3	42 (72%)	46 (78%)
Low viral load	24 (80%)	25 (81%)
High viral load	18 (64%)	21 (75%)
Genotype 4	1/8	5/9

*cut-off 800.000 IU/ml

Sustained Virological Response Based on Genotype and Viral Load after Pegasys Combination Therapy with Ribavirin in HCV Patients

	Study NV15942				Study NV15801	
	Pegasys 180 mcg & Ribavirin 800 mg 24 weeks	Pegasys 180 mcg & Ribavirin 1000/1200 mg 24 weeks	Pegasys 180 mcg & Ribavirin 800 mg 48 weeks	Pegasys 180 mcg & Ribavirin 1000/1200 mg 48 weeks	Pegasys 180 mcg & Ribavirin 1000/1200 mg 48 weeks	Interferon alfa-2b 3 MIU & Ribavirin 1000/1200 mg 48 weeks
Genotype 1 Low viral load High viral load	29% (29/101) 41% (21/51) 16% (8/50)	42% (49/118)* 52% (37/71) 26% (12/47)	41% (102/250)* 55% (33/60) 36% (69/190)	52% (142/271)* 65% (55/85) 47% (87/186)	45% (134/298) 53% (61/115) 40% (73/182)	36% (103/285) 44% (41/94) 33% (62/189)
Genotype 2/3 Low viral load High viral load	84% (81/96) 85% (29/34) 84% (52/62)	81% (117/144) 83% (39/47) 80% (78/97)	79% (78/99) 88% (29/33) 74% (49/66)	80% (123/153) 77% (37/48) 82% (86/105)	71% (100/140) 76% (28/37) 70% (72/103)	61% (88/145) 65% (34/52) 58% (54/93)
Genotype 4	(0/5)	(8/12)	(5/8)	(9/11)	(10/13)	(5/11)

* Pegasys 180 mcg ribavirin 1000/1200 mg, 48 w *vs.* Pegasys 180 mcg ribavirin 800 mg, 48 w: Odds Ratio (95% CI) = 1.52 (1.07 to 2.17)   P-value (stratified Cochran-Mantel-Haenszel test) = 0.020
* Pegasys 180 mcg ribavirin 1000/1200 mg, 48 w *vs.* Pegasys 180 mcg ribavirin 1000/1200 mg, 24 w: Odds Ratio (95% CI) = 2.12 (1.30 to 3.46)   P-value (stratified Cochran-Mantel-Haenszel test) = 0.002.

Viral response by treatment week, all patients treated

	Week 4	Week 12	Week 24	Week 48
Genotype 1				
24 w	17 (12%)	70 (49%)	98 (68%)	
48 w	22 (16%)	72 (51%)	96 (68%)	92 (65%)
Genotype 2/3				
24 w	37 (64%)	51 (88%)	49 (84%)	
48 w	47 (80%)	52 (88%)	51 (86%)	50 (85%)

Prognostic factors

The following potential prognostic factors were evaluated: age, gender, race, body weight, viral load, ALT, histology (fibrosis), treatment duration.
For genotype 1, viral load (>/< 800 000 IU/ml) (Odds ratio 2.2, p=0.01) and treatment duration (odds ratio 4.4, p<0.0001) were found to be significantly associated with treatment outcome, while for non-genotype 1, only age (>/< 40 years) was borderline significant (p=0.045, odds ratio 2.3).
Of a total of 66 patients <u>without</u> viral response at week 12 ($\geq$ 2 $\log_{10}$ drop in viral load or non-quantifiable HCV RNA), one patient achieved SVR (genotype 1, low viral load, 48 weeks of therapy). The negative predictive value of non-response at week 12 is thus rather close to 100%.
The outcome of the exploratory analyses is compatible with similar analyses conducted in prior studies.

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Modelling and Simulation

The dose of ribavirin was lower than the currently approved for the treatment of patients infected with virus genotype 1 and increased ALT. *A priori* there are no good reasons to suspect that patients with normal ALT should be administered a lower ribavirin dose.

This issue was further addressed in a separate report using the same modelling approach as in prior submissions. In short the general method of "generalised additive models" (GAM) was used for analysing the binary outcomes SVR and anaemia. Prognostic factors were those identified for patients with increased ALT. For patients infected with virus genotype 1 the probability of SVR seems to almost linearly increase with increasing ribavirin dose/kg body weight.

Predicted median (95% CI) SVR rate after 48-week PEG-IFN + ribavirin in genotype-1 infections

CHC category	SVR rate	
	800 mg/day	1000/1200 mg/day
Normal ALT	39% (34; 44%)	48% (42; 53%)
Elevated ALT	40% (36; 45%)	49% (46; 53%)

The risk for anaemia increases with dose to levels rather similar to those observed in patients with increased ALT if adjusted for the female preponderance in the normal ALT group.

Clinical safety

Patient exposure

Of the 514 patients enrolled into the study, 491 patients received study medication. Thus the patient population for the analysis of safety data comprised 212 patients in the 24-week treatment group, 210 patients in the 48-week treatment group and 69 patients in the untreated control group. Ninety-one percent of patients in the 24-week treatment group received study drug treatment for at least 21 to 24 weeks and 72% of patients in the 48-week treatment group received study drug treatment for at least 45 to 48 weeks. During the first 24 weeks of therapy, the proportion of patients who remained on therapy was similar in the two treatment groups. The cumulative doses of both PEG-IFN alfa-2a and ribavirin administered to the two treatment groups were comparable for the first 24 weeks of treatment. The cumulative doses of both PEG-IFN alfa-2a and ribavirin administered to the 48-week treatment group after 48 weeks of treatment were lower than would be predicted by doubling the respective cumulative doses of the two study drugs administered during the first 24 weeks of treatment. This is a consequence of additional patients in the 48-week treatment group having their dose of study drugs modified or their treatment prematurely discontinued during the second part of treatment.

Overview of Adverse Events (%)

	24 w PEG-IFN/rib n=212	48 w PEG-IFN/rib n=210	Observation
N	212	210	69
Any AE	99%	99%	77%
Severe	26%	33%	14%
Serious AE	8%	16%	6%
Related SAE	3%	10%	NA
Deaths (n)	0	0	1
AE $\Rightarrow$ withdrawal	7%	18%	NA
AE $\Rightarrow$ dose adj.			
PEG-IFN	25%	38%	NA
Ribavirin	28%	42%	NA

The overall incidence of depression was about 26%, thereof severe in 2% of the cases, *i.e.* rather similar to incidences previously reported.

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Summary of serious infections

	24 w PEG-IFN/rib n=212	48 w PEG-IFN/rib n=210	Observation
Confirmed bacterial	2	1	0
Presumed bacterial	2	7	2
Presumed viral	1	0	0
Presumed fungal	0	1	0
Total "infections" (n)	5 (2%)	9 (4%)	2 (3%)

Summary of lowest neutrophil counts (ANC)

	Normal	Grade 1	Grade 2	Grade 3 (high)	Grade 3 (low)	Grade 4
	($\geq$2.0)	(1.5 - <2.0)	(1.0 - <1.5)	0.75- <1.0	0.5 - <0.75	(<0.5)
24 weeks	8%	13%	37%	25%	12%	5%
48 weeks	4%	19%	33%	24%	16%	5%
Observation	80%	17%	3%	0%	0%	0%

Three patients were withdrawn from treatment due to neutropenia, 10 underwent a permanent dose reduction and 6 underwent temporary dose reductions due to neutropenia.

6% and 12% of the patients at 24- and 48 weeks, respectively, showed a haemoglobin decline to a value below 100g/l and about 6% of patients treated showed a decline in platelet counts to a value below <75 x10^9/l at some point during the treatment.

Median ALT levels decreased from about 23 to about 10 U/l in patients with sustained viral response while in patients with relapse; a return to baseline was seen. In the observation arm, 50% showed an increase above normal at least once and in 5/69 patients untreated there was an increase to above 60 U/l (ULN 30).

Discussion

The high attrition rate in the 48-week treatment arm of study NR16071 is notable, but similar compared with the large Pegasys + ribavirin, dose/duration comparative study in patients with increased ALT. Reasons for withdrawal are also similar.

With respect to baseline characteristics, a higher proportion of women with a lower body weight is notable. Distribution of genotypes is rather similar to studies conducted in patients with ALT increase, but viral load seems lower.

Also fibrosis scores are lower.
Necro-inflammatory scores were not reported. Patients with a fibrosis and a necro-inflammatory score of 0 were not to be included according to the study protocol.
While some histological activity appears to be common in patients with CHC and normal ALT, the high percentage of patients with low or very low fibrosis scores in study NR16071 is notable.
Despite persistently normal ALT, a small proportion of patients may show advanced fibrosis, however in general the prognosis is more favourable in this group.
In study NV16071 and in patients infected with virus genotype 1, none had an Ishak fibrosis score of >4, 8% had a score of 3-4 and 18% a score of 2. In patients with an Ishak score <3, treatment is often deferred.

At the time of the submission of the data from study NV16071, the lack of evidence of long-term benefits of therapy together with the potential safety concerns associated with IFN-based treatment, including ALT flares, led the European consensus conference to recommend that this subgroup of

CHC patients not be treated. It seems therefore reasonable to conclude that a large percentage of patients infected with genotype 1 virus in study NV16071 would not have been treated if treatment guidelines were adhered to. It should be noted, however, that the CHMP does not consider this to be a major problem with respect to the interpretation of study data as regards sustained viral response, rather the opposite. A higher early relapse rate has been suspected in patients with normal ALT. In order to refute this view, it is preferable to study patients far from the typical elevated ALT population.

While it was accepted that normal ALT *per se* should be no barrier to active therapy, watchful waiting was indicated in a large proportion of infected individuals. This view was fully in line with clinical treatment guidelines available at the time of submission. With respect to liver biopsies the AASLD practice guideline (April 2004) may be cited here: "*Regardless of the level of ALT, a liver biopsy should be done when the results will influence whether treatment is recommended, but a biopsy is not mandatory in order to initiate therapy*".

The study data confirm that patients with genotype 1, if treated should be treated for 48 weeks and similarly that most patients infected with genotype 2/3 should be treated for 24 weeks. There are too few patients with genotype 2/3 to make analyses per genotype meaningful.

It is of interest to highlight that the model predicted SVR seems not to be influenced by baseline ALT levels. This is congruent with prior analyses where the degree of elevation of ALT is predictive for response in case of mono-therapy with PEG-IFN but not in case of combination therapy. As indicated above there are no good reasons to believe that patients with normal ALT should be treated with a lower dose of ribavirin than those with elevated ALT. The submitted analyses support this notion.

Based on the submitted NV16071 data, the concept "CHC with persistently normal ALT" is at least partly challenged in the sense that the majority of patients in the observation group, despite fulfilling stringent criteria for the disorder, showed elevated ALT levels at least once during the observational period. Covariates associated with CHC with normal ALT are also those associated with "low-normal" ALT in a healthy population. As a corollary, ALT levels decreased from "high-normal" to "low-normal" in sustained responders. From this perspective strict distinction between patients with "elevated" and "normal" ALT may be regarded as less crucial.

Most patients with CHC and normal ALT show some degree of histological activity (inflammation, fibrosis), but, in general terms, the activity is lower than in patients with increased ALT and the progression rate is slower. Nevertheless, it is accepted that, for example, liver fibrosis warranting therapy may be observed also in patients with normal ALT.

It has been rather widely accepted that patients infected with genotype 2/3 and elevated ALT may be treated with IFN/ribavirin without prior liver biopsy, while it is advisable to biopsy patients infected with genotype 1, due to poorer sustained response rates and the toxicity of long-term therapy. In the currently approved SPC, the following is stated in section 4:

"*All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (ie, patients with genotype 2 or 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.*"

There are additional factors besides ALT and histology, which should be considered in a decision whether treatment or watchful waiting is indicated. These factors include age, gender, co-morbidity, extrahepatic manifestations, etc. It would be unreasonable to require liver biopsies in all patients with infections caused by virus genotype 2/3 and normal ALT and the following wording is therefore proposed in section 4.4 of the SPC:

"*In patients with normal ALT, progression of fibrosis occurs on average at a slower rate than in patients with elevated ALT. This should be considered in conjunction with other factors, such as HCV*

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genotype, age, extrahepatic manifestations, risk of transmission, etc. which influence the decision to treat or not.”

Clearly, there are patients with CHC and normal ALT warranting therapy. There are also individuals where a decision to treat (or not) can be made without knowledge of the histological status. Also for patients with normal ALT, the current absence of “histologically proven” in section 4.1 therefore seems justified.

In summary, PEG-IFN in combination with ribavirin has been shown to be active also in patients with CHC and persistently normal ALT. If dosed in accordance with the currently approved posology, efficacy in terms of SVR is likely to be very similar to that observed in patients with elevated ALT. The MAH has also committed to submit long term follow up data from patients with sustained viral response in order to provide reassurance as regards the expected very low long-term relapse rate.

The safety profile in patients with normal ALT is similar to that in patients with increased ALT. The frequency of reported adverse reactions were slightly higher in study NR16071 as compared with the dose/duration comparative study. This was also the case for the percentage of patients undergoing dose reductions, especially related to ribavirin. However, this might be a consequence of the inclusion of a higher percentage of women and/or patients with lower body weight.

Effects on peripheral blood cell counts were rather similar to what has been reported previously with the exception of anaemia, which was slightly more commonly observed in the current study. This mainly reflects the larger proportion of women in the current study.
In the absence of a reasonable mechanistic explanation, the CHMP is inclined to view this as a spurious finding and does not recommend that the SPC should be amended with respect to this observation. Nevertheless, the MAH has committed to provide further data as a post-approval commitment on the incidence of anaemia (<10 g/dL) in CHC patients infected with HCV genotype 1 and having normal level of transaminases when treated with pegylated interferon alfa-2a plus1000/1200 milligrams of ribavirin.

Extension of indication: Treatment in combination with ribavirin of patients co-infected with HIV-HCV

On 26 January 2005, the European Commission approved a type II variation concerning the extension of indication for Pegasys (all strengths and formulations), to include treatment in combination with ribavirin of patients co-infected with HIV-HCV with consequential changes to SPC sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1.

Clinical pharmacology

A pharmacokinetic interaction study was conducted as a substudy of the pivotal study (see below). *In vitro* data have indicated that ribavirin may reduce the phosphorylation of pyrimidine analogues such as d4T, 3TC and ZDV. Altogether, 56 patients entered the substudy. Patients were to be maintained on exactly the same HAART regimen *(stable antiretroviral therapy)* throughout the study period. The HAART regimen should contain either ZDV + 3TC or d4T + 3TC. The comparison was made after 12 weeks* of therapy with ribavirin or placebo (+PEG-IFN) as add-on, i.e. as an interpatient comparison.
*The estimated time to ribavirin steady state is about 8 weeks.

The results were expressed as ratios of intracellular AUC $_{0-12h}$ of triphosporylated nucleoside reverse transcriptase inhibitors (NRTI) / corresponding endogenous triphosphate in PBMC. Possible effects on endogenous triphosphates were also estimated.

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Intracellular AUC ratios	Treatment	N	Week 12 least square mean	95% CI for difference
3TC-TP/deoxycytidine-TP	Ribavirin	18	1.783	-0.37; 0.91
	Placebo	17	1.509	
d4T-TP/deoxythymidine-TP	Ribavirin	10	0.173	-0.06; 0.08
	Placebo	5	0.164	
ZDV-TP/deoxythymidine-TP	Ribavirin	6	0.235	-0.40; 0.24
	Placebo	10	0.316	
deoxycytidine-TP	Ribavirin	18	3.753	-0.38; 1.90
	Placebo	19	2.991	
deoxythymidine-TP	Ribavirin	18	5.882	-1.77; 1.53
	Placebo	18	6.001	

No statistically significant interactions were detected. The low number of patients and the interpatient comparison are caveats, however, and the wide CI especially for ZDV should be noted. Therefore, it cannot be concluded that clinically meaningful interactions have been excluded. No effects on plasma ribavirin levels were observed based on historical data.

At the time of designing the study, the *in vitro* interaction between ribavirin and ddI resulting in increased ddI-TP levels was unknown and ddI was not included in the interaction study.

The apparently increased risk for mitochondrial toxicity when combining ddI with ribavirin + IFN has often been interpreted in the light of in vitro interaction data and the potential for a dynamic interaction with IFN, e.g. through induction of fatty liver by IFN, has less frequently been considered.

In the current trial, lactic acidosis and pancreatitis were seen in a similar number of "ddI patients" across the three treatment arms (PEG-IFN + HAART arm [1+1], PEG-IFN + ribavirin + HAART group [1+3], and IFN + ribavirin + HAART arm [1+1]). These findings rather indicate that a PK interaction between ddI and ribavirin does not explain the increased risk.
Available data, however, indicate that d4T should be avoided. It is notable that out of 17 patients with pancreatitis and/or lactic acidosis, 13/17 patients were concomitantly receiving d4T with or without ddI. Whether the increased risk associated with concomitant use of ddI is due to an interaction with ribavirin or PEG-IFN is of less clinical importance as co-administration is the rule.
The seemingly higher exposure to d4T in women is in line with what has been reported in the literature for 3TC and ZDV, but these observations (3TC, ZDV) were not corroborated in this study. There were no obvious differences related to ribavirin exposure.

Clinical efficacy

Pivotal Study NR15961 was a randomised, partially blinded, multicentre (95 centres, North and South America, Europe, Australia), three-armed trial conducted between June 2000 and September 2003:
Group 1: PEG-IFN 180 mcg once weekly + placebo for 48 weeks;
Group 2: PEG-IFN 180 mcg once weekly + ribavirin 800 mg daily for 48 weeks;
Group 3: IFN alfa-2a 3MIU tiw + ribavirin 800 mg daily for 48 weeks.
Primary efficacy criterion: HCV RNA < 50 IU/ml, ≥ week 68.

Inclusion/Exclusion criteria:

With respect to CHC status, the inclusion/exclusion criteria may be regarded as conventional.
With respect to HIV status the following was required:
1/ Serological evidence of HIV-1 infection by HIV-1 antibody or detection of HIV-1RNA;
2/ CD4+ cell count ≥200/μL, regardless of HIV-1 RNA load (Roche Amplicor HIV-1 Monitor Test, v1.5);
OR
CD4+ cell count ≥ 100/μL but <199/μL and plasma HIV-1 RNA <5000 copies/mL.

Stable status of HIV-1 infection in the opinion of the investigator, *i.e.* patients whose HIV infection was not expected to progress during the study.
Patients on stable antiretroviral therapy (HAART) for at least 6 weeks before the start of study drugs whose HAART regimen (drugs and dosage) was expected to remain unaltered for the first 8 weeks of this study;
OR
Patients who had not been on HAART for at least 8 weeks before the start of study drugs and were willing to delay initiation of HAART for at least 6 weeks.

As a protocol amendment, the following exclusion criteria were added: History or evidence of decompensated liver disease and/or a Child-Pugh score >5. Ascites, coagulopathy, hyperbilirubinemia, hepatic encephalopathy, or hypoalbuminemia and a Child-Pugh score >6 were conditions considered to be consistent with decompensated liver disease.
Patients with unstable or advanced HIV disease were excluded.

Baseline Characteristics:

HCV

	PEG-IFN + placebo N=286	PEG-IFN + ribavirin N=289	IFN + ribavirin N=285
ALT (xULN) 0-1 %	<1%	<1%	0%
>1-1.5 %	19%	19%	16%
>1.5-3 %	47%	44%	48%
>3 %	34%	37%	36%
HCV RNA Million copies (SD)	14 (14)	12 (14)	12 (13)
Cirrhosis (%)	16%	15%	16%
Total HAI score, mean (SD)	7.9 (3.7)	8.0 (3.8)	8.0 (3.8)
Genotype 1	61%	61%	60%
2	6%	4%	5%
3	26%	28%	26%
4	7%	6%	8%
other	<1%	<1%	<1%

HIV

	PEG-IFN + placebo N=286	PEG-IFN + ribavirin N=289	IFN + ribavirin N=285
HAART - yes	85%	84%	84%
NRTI	84%	84%	84%
PI	47%	43%	45%
NNRTI	36%	35%	35%
HIV RNA Copies (SD)	8278 (39576)	10097 (48322)	8426 (46515)
% <50	60%	60%	60%
CD4 count (cells/mcl) Mean (SD)	530 (265)	520 (278)	542 (270)
<200	5%	6%	7%

In comparison with PEG-IFN studies conducted in patients with CHC and not co-infected with HIV, baseline characteristics are rather similar. Viral load, however, was considerably higher (2-3x). With respect to HIV, heterogeneity as regards viral control at baseline is notable as well as the low percentage of patients with CD4 count below 200.

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Efficacy Results

Viral response over time and sustained response (primary endpoint) (All patients treated)

	PEG-IFN + placebo N=286	PEG-IFN + ribavirin N=289	IFN + ribavirin N=285
Week 4	14%	21%	4%
12	33%	45%	19%
24	37%	53%	18%
36	37%	52%	15%
48	31%	47%	14%
Sustained response	20%	40%	12%
Odds ratio (95% CI) P+R vs. I+R P+R vs. P I+R vs. P	5.40 (3.2; 9.1) 2.89 (1.83; 4.58) 0.53 (0.30; 0.91)		

The seemingly inferior results in co-infected patients compared to mono-infected CHC patients may partly relate to impaired immunological control of HCV virus in HIV infected patients resulting in increased viral load at baseline and consequently a harder to treat population. In a naïve comparison subgrouped by baseline viral load, however, the difference is still evident.

Sustained viral response by genotype and viral load

	Study NR 15961 *(co-infected pts)*			Study NV15801 *(monoinf.)*	Study NV15942 *(monoinf.)*	Study NV15801 *(monoinf.)*	Study NV15942 *(monoinf.)*
	PEG-IFN + placebo	PEG-IFN+ ribavirin 800	IFN + ribavirin 800	PEG-IFN+ placebo	PEG-IFN+ ribavirin 800	PEG-IFN+ ribavirin 1000/1200	PEG-IFN+ ribavirin 1000/1200
Genotype 1	14% (24/175)	29% (51/176)	7% (12/171)	21%	41%	45%	52%
Low viral load*	38% 5%	61% 18% (23/130)	19% 3%	39%	55%	53%	65%
High viral load*				13%	36%	40%	47%
Genotype 2/3 Low viral load	36% (32/90) 38%	62% (59/95) 61%	20% (18/89) 27%	45%	79%	71%	80%
High viral load	35%	63%	17%	58% 40%	88% 74%	76% 70%	77% 72%

* Cut-off 800.000 IU/ml

This observation rather supports the hypothesis that impaired host antiviral mechanisms influence the results reflected by both a higher baseline viral load and a poorer response to therapy. It should be noted, however, that baseline CD4 count seemingly did not influence the outcome. Another important observation was the poor outcome in patients infected with genotype 1 virus and with a high viral load. As in other studies in patients with CHC, absence of viral response at week 12 (irrespective of genotype and defined as non-quantifiable HCV RNA, or at least a 2 log drop from baseline) correlated strongly with absence of sustained response; negative predictive value 98-100%.
The importance of ribavirin for maintenance of of viral response was also shown. In the PEG-IFN + placebo arm, maintained response at follow up was demonstrated in 54% of the patients versus 75% in both arms containing ribavarin.

The *response rate at week 4* was about 37% in genotype 2/3 co-infected patients versus about 72% in mono-infected subjects. A pretreatment HCV RNA (800,000 IU/mL), a histological diagnosis of noncirrhotic and the absence of HAART were weakly associated with a higher likelihood of achieving a week-4 response. An undetectable HCV RNA titre at week 4 was predictive of a sustained virological response in 80% (4 of 5) of patients with genotype 2 and in 97% (29 of 30) of patients with genotype 3 infection who were treated with PEG-IFN plus ribavirin.

Histological Response - All patients with paired biopsies

	PEG-IFN + placebo N=286	PEG-IFN + ribavirin N=289	IFN + ribavirin N=285
No with paired biopsies	134	135	132
% with histological response	39%	57%	41%
% with no change	34%	30%	39%
% with worsening	27%	13%	20%

Numerically improved histology with PEG-IFN + ribavirin, compared with IFN + ribavirin, although less pronounced than differences observed with respect to viral response, is an important finding in this group of patients where the progression rate is considered to be higher than in mono-infected patients.

Efficacy in women:
Efficacy results in women receiving PEG-IFN alfa-2a in combination with 800 mg of ribavirin in the pivotal study NR15961 were similar to those in men. Although women with genotype 1 infection treated with PEG-IFN alfa-2a plus ribavirin achieved a numerically higher sustained virological response than men, a multiple logistic regression analysis of baseline prognostic factors showed no effect of sex on sustained virological response in this treatment group.
In contrast, in co-infected patients receiving PEG-IFN alfa-2a monotherapy, sustained virological response in women was lower than in men, a result consistent with the finding that sex is a significant baseline prognostic factor for sustained virological response in patients treated with PEG-IFN alfa-2a monotherapy but not with PEG-IFN alfa-2a plus ribavirin.
However, because of the smaller proportion of women (approximately 20%, 163 women) in the study compared with men (approximately 80%, 697 men), comparison of the efficacy results in women and men should be interpreted with caution.

Discussion on Clinical Efficacy

Overall clinically relevant activity has been demonstrated for PEG-IFN 180 mcg weekly + ribavirin 800 mg daily in co-infected patients with non-advanced HIV disease. Somewhat surprisingly, baseline CD4 count and baseline HIV viral load do not appear to influence outcome.

The poor activity [sustained response 18% (23/130) PEG-IFN + ribavirin] in patients infected with virus genotype 1 and high viral load constitutes a concern. The selected dose of ribavirin, 800 mg daily, is, from an efficacy point of view, today known to be suboptimal in monoinfected patients. The sponsor has shown that higher baseline body mass index is related to poorer response rates. Whether this relates to lower ribavirin exposure or, e.g. a higher incidence of fatty liver, is unknown. There is currently an ongoing investigator-initiated trial (PRESCO) in co-infected patients using the standard regimen of PEG-IFN + ribavirin in the treatment of CHC, genotype 1. Safety and efficacy results from this trial will be submitted in 2006.
Of interest in this context is an academic substudy indicating that the early (2 days) viral response seems to be blunted in co-infected patients, thus indicating that the IFN component might be less active in this group of patients. Further exploratory viral kinetics and mechanistic studies appear indicated.

In patients infected with virus genotypes 2/3, 48 weeks of therapy has been studied. The overall results are compatible with a favourable benefit/risk balance and the sustained response rate was 62% (59/95), PEG-IFN + ribavirin.

The sponsor has shown that co-infected patients appear to respond more slowly than mono-infected patients, since about 50% of co-infected patients achieving a response at week 12 had achieved a virological response by week 4 as compared with about 75% of mono-infected patients. In patients achieving viral response at end of treatment, the relapse rate tended to be higher in co-infected patients (16%) than in mono-infected patients after 24 (12%) and 48 weeks (5%) of therapy.

The response rate at week 4 was about 35% in co-infected patients versus about 70% in mono-infected. As discussed earlier, co-infected patients, reasonably, represent a non-homogeneous group of patients from nearly "normal" to advanced disease. It is therefore not implausible that early (week 4) responders may be treated as mono-infected patients, i.e. for 24 weeks without loss in efficacy and with the benefit of meaningfully reduced toxicity. The actual study cannot provide solid evidence in that direction, but it is noted that an undetectable HCV RNA titre at week 4 was predictive of a sustained virological response in 4 of 5 patients with genotype 2 and in 29 of 30 patients with genotype 3 infection who were treated with PEG-IFN plus ribavirin. In the PRESCO trial, 24 weeks of HCV treatment (180 µg weekly of PEG-IFN alfa-2a in combination with 1000 or 1200 mg daily of ribavirin) will be evaluated in patients co-infected with virus genotype 2/3.

Clinical safety

A total of 868 randomised patients were included in the pivotal trial. Ongoing or completed supportive studies encompassed more than 2,000 patients, not all of them co-infected, however.

Overview of Safety in Coinfected and Monoinfected Patients

	HIV/HCV Coinfected Patients		HCV Monoinfected Patients		
	NR15961		NV15496 NV15497 NV15801	NV15942	NV15801 NV15942
	PEG-IFN alfa-2a 180 µg Placebo (N = 286)	PEG-IFN alfa-2a 180 µg Ribavirin 800 mg (N = 288)	PEG-IFN alfa-2a 180 µg Placebo (N = 696))	PEG-IFN alfa-2a 180 µg Ribavirin 800 mg (N = 361)	PEG-IFN alfa-2a 180 µg Ribavirin 1000/1200 mg (N = 887)
Serious Aes	21%	17%	7% - 12%	9%	10% - 12%
Related serious AEs[a]	10%	9%	4% - 5%	4%	3% - 4%
Deaths	5	4	0 -2	1	0 - 2
Premature withdrawal for AEs and lab abnormalities	16%	15%	7% -10%	16%	10% - 15%
Dose modification for AEs and lab abnormalities					
PEG-IFN alfa-2a	38%	39%	19% - 27%	33%	32% - 36%
Ribavirin	NA	37%	NA	28%	38% - 40%
Neutrophil count					
<0.75 x 10^9/L	36%	40%	19% - 21%	28%	27% - 31%
<0.50 x 10^9/L	13%	11%	4% - 5%	5%	5%
Platelet count					
<50 x 10^9/L	10%	8%	2% - 6%	4%	5%
<20 x 10^9/L	<1%	<1%	0%	0%	0%
Hemoglobin					
<10.0 g/dL	8%	14%	1% - 4%	6%	11% - 15%
<8.5 g/dL	3%	4%	<1% - 1%	<1%	1% - 2%

Note: The treatment regimen was 48 weeks of treatment and 24 weeks of treatment-free follow-up. NA = not applicable. Values in this table represent the percentage of patients who experienced the event.
[a]Events judged by the investigator to be remotely, possibly, or probably related to study treatment.

Overview of Adverse Events during Therapy and 24 Weeks Posttreatment, Study NR15961

	PEG-IFN alfa-2a 180 µg Placebo (N = 286)	PEG-IFN alfa-2a 180 µg Ribavirin 800 mg (N = 288)	IFN alfa-2a 3 MIU Ribavirin 800 mg (N = 285)
No. of Pts with Any AE	271 (95%)	276 (96%)	273 (96%)
Severe Aes	103 (36%)	82 (28%)	74 (26%)
Life-threatening AEs	8 (3%)	9 (3%)	3 (1%)
Related AEs[a]	263 (92%)	271 (94%)	265 (93%)
AIDS-defining events	3 (1%)	4 (1%)	3 (1%)
Serious Aes	59 (21%)	50 (17%)	44 (15%)
Related serious AEs[a]	30 (10%)	27 (9%)	16 (6%)
Deaths	5 (2%)	4 (1%)	3 (1%)
During treatment	0	2	2
During follow-up	5[b]	2[b]	1
Premature withdrawals for AEs, laboratory adverse events, or AIDS-defining events	47 (16%)	43 (15%)	44 (15%)
Dose modification for AEs and laboratory adverse events			
PEG-IFN alfa-2a or IFN alfa-2a	109 (38%)	111 (39%)	47 (16%)
Ribavirin or Placebo	90 (31%)	107 (37%)	81 (28%)

Note: Values in this table represent number and percentage of patients who experienced the event.
[a]Events judged by the investigator to be remotely, possibly, or probably related to treatment.
[b]One death in the PEG-IFN alfa-2a plus placebo group and two deaths in the PEG-IFN alfa-2a plus ribavirin group occurred beyond the 24-week posttreatment follow-up period.

It is noted that while serious AEs and serious related AEs were observed in higher frequencies in co-infected patients, premature withdrawal due to safety concerns was observed in similar frequencies in the combination arms. As expected, bone marrow toxicity was more frequently observed in co-infected patients. Deaths during therapy and follow-up constitute a concern.

Twelve patients died during treatment or follow-up in study NR15961, thereof 6 due to hepatic decompensation. In addition there was one case each of: pericariditis and heart arrest (PEG-IFN + placebo, "unrelated"); suicide (PEG-IFN + ribavirin, "possibly related"); myocardial infarction/respiratory failure (IFN + ribavirin, possibly related); metastatic carcinoma; pneumonia (IFN + ribavirin, "remotely related"); oeosophageal erosions and bleeding, non-cirrhotic (PEG-IFN, "unrelated").

Hepatic decompensation was reported in a total of 14 patients. All 14 patients were cirrhotic, and many had evidence of hepatic dysfunction at baseline as reflected by high Child-Pugh scores. The patients were distributed almost equally across the three treatment groups. All patients but one were receiving concomitant HAART at the time of onset of signs or symptoms associated with hepatic decompensation. All 13 patients were receiving nucleoside reverse transcriptase inhibitors, including five patients who were receiving didanosine, nine who were receiving stavudine, and seven who were receiving lamivudine. Six of the 14 patients died as a result of hepatic decompensation. None of the deaths occurred while the patients were still receiving study drug treatment.

Summary of Pancreatitis

	PEG-IFN alfa-2a 180 µg Placebo (N = 286)	PEG-IFN alfa-2a 180 µg Ribavirin 800 mg (N = 288)	IFN alfa-2a 3 MIU Ribavirin 800 mg (N = 285)
No. of pts with pancreatitis	4 (1%)	2 (<1%)	1 (<1%)
Serious pancreatitis	2 (<1%)	1 (<1%)	0
Premature withdrawal for pancreatitis	1 (<1%)	1 (<1%)	0
Dose modification for pancreatitis			
PEG-IFN alfa-2a or IFN alfa-2a	1 (<1%)	0	0
Ribavirin or placebo	1 (1%)	0	0
HAART at time of pancreatitis	4	1	1
Stavudine	3	1	1
Lamivudine	3	0	0
Didanosine	1	1	1
Efavirenz	2	0	1
Abacavir	1	0	1
Ritonavir	1	1	0
Nelfinavir	1	0	0
Saquinavir	1	0	0
Amprenavir	0	1	0

Summary of Lactic Acidosis

	PEG-IFN alfa-2a 180 µg Placebo (N = 286)	PEG-IFN alfa-2a 180 µg Ribavirin 800 mg (N = 288)	IFN alfa-2a 3 MIU Ribavirin 800 mg (N = 285)
No. of pts with lactic acidosis or symptomatic hyperlactatemia	4 (1%)	4 (1%)	3 (1%)
Serious lactic acidosis	4 (1%)	3 (1%)	1 (<1%)
Premature withdrawal for lactic acidosis	2 (<1%)	1 (<1%)	0
Dose modification for lactic acidosis or symptomatic hyperlactatemia			
PEG-IFN alfa-2a or IFN alfa-2a	0	1 (<1%)	1 (<1%)
Ribavirin or placebo	2 (<1%)	2 (<1%)	1 (<1%)
HAART at time of lactic acidosis or symptomatic hyperlactatemia	4	4	3
Stavudine	3	3	3
Lamivudine	3	1	2
Didanosine	1	3	1
Zidovudine	1	1	1
Efavirenz	1	1	1
Ritonavir	1	2	0
Nelfinavir	1	1	1
Nevirapine	1	0	1
Indinavir	0	1	0
Amprenavir	0	1	0
Saquinavir	1	0	0

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It is notable that out of 17 patients with pancreatitis and/or lactic acidosis, 13/17 patients were concomitantly receiving d4T with or without ddI. Whether PEG-IFN + ribavirin increases the risk of these complication when added to HAART in a co-infected population cannot be assessed as there was no CHC placebo group.

Haematological toxicity

Summary of Patients' Worst Neutrophil or Platelet Count in Study NR15961

	PEG-IFN alfa-2a 180 µg Placebo (N = 286)	PEG-IFN alfa-2a 180 µg Ribavirin 800 mg (N = 288)	IFN alfa-2a 3 MIU Ribavirin 800 mg (N = 285)
Lowest neutrophil count			
0.50 - <0.75 x 10^9/L	66 (23%)	84 (29%)	18 (6%)
<0.50 x 10^9/L	37 (13%)	31 (11%)	1 (<1%)
Three-grade decrease from BL[a]	92 (32%)	102 (35%)	16 (6%)
Four-grade decrease from BL[a]	26 (9%)	23 (8%)	1 (<1%)
Lowest platelet count			
20 - <50 x 10^9/L	27 (9%)	21 (7%)	8 (3%)
<20 x 10^9/L	1 (<1%)	1 (<1%)	0
Three-grade decrease from BL[b]	18 (6%)	14 (5%)	4 (1%)
Four-grade decrease from BL[b]	1 (<1%)	1 (<1%)	0

[a]ACTG grading system for neutrophil counts in 10^9/L is grade 0 = >99, grade 1 = 75 – 99, grade 2 = 50 - <75, grade 3 = 20 - <50, grade 4 = <20.
[b]ACTG grading system for platelet counts in 10^9/L is grade 0 = >1.5, grade 1 = 1 – 1.5, grade 2 = 0.75 - <1, grade 3 = 0.5 - <0.73, grade 4 = <0.5.

A serious infection was temporally associated with ANC <0.5 in one single patient. Serious bleeding associated with a platelet count between 20 and 50 was reported in three patients, thereof 2 haemophiliacs. No serious bleeding was temporarily associated with a platelet count <20.

Neutropenia, Dose Modifications, and Use of Growth Factors in Study NR15961

	PEG-IFN alfa-2a 180 µg Placebo (N = 286)	PEG-IFN alfa-2a 180 µg Ribavirin 800 mg (N = 288)	IFN alfa-2a 3 MIU Ribavirin 800 mg (N = 285)
Neutrophil counts			
<0.75 x 10^9/L	103 (36%)	115 (40%)	19 (7%)
<0.50 x 10^9/L	37 (13%)	31 (11%)	1 (<1%)
Dose modification of study treatment for neutropenia[a]			
PEG-IFN alfa-2a or IFN alfa-2a	77 (27%)	79 (27%)	8 (3%)
Ribavirin or placebo	8 (3%)	3 (1%)	0
Permanent dose reduction of study treatment for neutropenia[b]			
PEG-IFN alfa-2a or IFN alfa-2a	27 (9%)	32 (11%)	2 (<1%)
Ribavirin or placebo	0	0	0
Prematurely withdrawn from treatment for neutropenia	2 (<1%)	3 (1%)	0
Neutropenia as a			
Clinical adverse event[c,d]	35 (12%)	37 (13%)	4 (1%)
Serious adverse event[c,d]	1 (<1%)	1 (<1%)	0
Received growth factors for	34 (12%)	33 (11%)	4 (1%)

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neutropenia

Thrombocytopenia, Dose Modifications and Use of Growth Factors in Study NR15961

	PEG-IFN alfa-2a 180 μg Placebo (N = 286)	PEG-IFN alfa-2a 180 μg Ribavirin 800 mg (N = 288)	IFN alfa-2a 3 MIU Ribavirin 800 mg (N = 285)
Platelet counts			
$<50 \times 10^9$/L	28 (10%)	22 (8%)	8 (3%)
$<20 \times 10^9$/L	1 (<1%)	1 (<1%)	0
Dose modification of study treatment for thrombocytopenia[a]			
PEG-INF-IFN alfa-2a or IFN alfa-2a	21 (7%)	18 (6%)	4 (1%)
Ribavirin or placebo	7 (2%)	4 (1%)	0
Permanent dose reduction of study treatment for thrombocytopenia[b]			
PEG-IFN alfa-2a or IFN alfa-2a	13 (5%)	6 (2%)	2 (<1%)
Ribavirin or placebo	0	0	0
Pematurely withdrawn from treatment for thrombocytopenia	7 (2%)	4 (1%)	1 (<1%)
Thrombocytopenia as a			
Clinical adverse event[c,d]	11 (4%)	5 (2%)	1 (<1%)
Serious adverse event[c,d]	5 (2%)	1 (<1%)	0
No. of patients receiving platelet transfusions for thrombocytopenia	2 (<1%)	0	0

Overview of Anaemia

	PEG-IFN alfa-2a 180 μg Placebo (N = 286)	PEG-IFN alfa-2a 180 μg Ribavirin 800 mg (N = 288)	IFN alfa-2a 3 MIU Ribavirin 800 mg (N = 285)
Hemoglobin			
<10 g/dL	22 (8%)	41 (14%)	29 (10%)
<8.50 g/L	10 (3%)	11 (4%)	4 (1%)
<6.5 g/dL	5 (2%)	2 (<1%)	0
Dose modification of study treatment for anemia[a]			
PEG-INF-IFN alfa-2a or IFN alfa-2a	5 (2%)	4 (1%)	3 (1%)
Ribavirin or placebo	18 (6%)	46 (16%)	32 (11%)
Permanent dose reduction of study treatment for anemia[b]			
PEG-IFN alfa-2a or IFN alfa-2a	1 (<1%)	0	1 (<1%)
Ribavirin or placebo	7 (2%)	20 (7%)	13 (5%)
Prematurely withdrawn from treatment for anemia	3 (1%)	2 (<1%)	2 (<1%)
Anemia as a			
Clinical adverse event[c]	25 (9%)	43 (15%)	17 (6%)
Serious adverse event[c]	7 (2%)	7 (2%)	3 (1%)
Receiving treatment for anemia			
Growth factors	14 (5%)	30 (10%)	12 (4%)
Transfusions	13 (5%)	12 (4%)	6 (2%)

*Note: Values in this table represent the number and percentage of patients who experienced the event. Anemia included hemolytic anemia, autoimmune hemolytic anemia, aplastic anemia, Coombs positive hemolytic anemia and pancytopenia.

[a] Excludes patients who did not have the dose of study drug modified for anemia before being prematurely withdrawn for anemia.

[b] Excludes patients prematurely withdrawn for anemia.

[c] Anemia was classified as an adverse event if it met at least one of the following criteria: (1) was serious, (2) led to withdrawal from treatment, or (3) resulted in treatment with a concomitant medication or modification of an ongoing concomitant medication.

While haematological toxicity is common and more frequently encountered than in mono-infected patients, clinical sequelae and permanent withdrawal are rather uncommon. As expected, thrombocytopenia (<50x 10^9/l) was more commonly encountered in patients with cirrhosis, for PEG-IFN +ribavirin 18% *vs.* 8% in the overall population.

Hypertriglyceridaemia
Hypertriglyceridaemia occurred more frequently in patients receiving PEG-IFN and in 6% (monotherapy) and 3% (combination) of the patients compared with <1% in the IFN arm, treatment for the lipid disorder was initiated. No case of pancreatitis related to triglyceridaemia was reported.

ALT disorders
The majority of patients (70% to 73%) in all three treatment groups had baseline ALT levels that were grade 1 (1.25 to 2.5 times ULN) or grade 2 (2.5 to 5 times ULN). Few patients (0 to 4 patients per group) experienced a shift from a grade 0, 1, or 2 at baseline to grade 4 (>10 times ULN) during the study. Of those patients whose ALT activity was 2.5 times ULN (grade 0 or grade 1) or less at

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baseline, between 3% and 5% (9 to 14 patients) experienced a shift to grade 3 (5 to 10 times ULN) during the study.
A total of seven patients (<1%) experienced elevated ALT levels during treatment and follow-up that resulted in dose modification of their study drug or premature withdrawal from treatment (two patients).

HIV-related events
No negative effects on HIV viral load were observed. Actually a slight decrease with return to baseline after end of therapy was noted for PEG-IFN containing regimens. As expected CD4+ T-cell count was reduced while on therapy with return to base line some weeks after end of therapy. The decrease was most marked in the PEG-IFN + ribavirin arm, median about 140 cells/mcl. The percentage of CD4+ T-cells was, however, not affected. Ten AIDS defining events were reported, mainly oesophageal candidiasis.

Adverse Events by Sex

Body System Adverse Event	PEG-IFN alfa-2a 180 µg Placebo (N = 286)		PEG-IFN alfa-2a 180 µg Ribavirin 800 mg (N = 288)		IFN alfa-2a 3 MIU Ribavirin 800 mg (N = 285)	
	Males N= 234 No. (%)	**Females N= 52 No. (%)**	**Males N= 231 No. (%)**	**Females N= 57 No. (%)**	**Males N= 231 No. (%)**	**Females N= 54 No. (%)**
SKIN & SUBCUTANEOUS TISSUE DISORDERS						
Alopecia	17 (7)	4 (8)	22 (10)	14 (25)	7 (3)	10 (19)
GASTROINTESTINAL DISORDERS						
Abdominal Pain	16 (7)	11 (21)	21 (9)	4 (7)	18 (8)	5 (9)
INFECTIONS AND INFESTATIONS						
Oral Candidiasis	10 (4)	6 (12)	14 (6)	7 (12)	7 (3)	3 (6)
Sinusitis	13 (6)	6 (12)	8 (3)	7 (12)	10 (4)	2 (4)
BLOOD AND LYMPHATIC SYSTEM DISORDERS						
Anemia	18 (8)	4 (8)	26 (11)	13 (23)	6 (3)	6 (11)

Note: No. (%) = number and percentage of patients.

The sex-related difference as regards anaemia is expected. With respect to alopecia there seems to be a consistent pattern, while this is less obvious for abdominal pain.

Discussion on Clinical Safety

The safety profile of PEG-IFN alfa-2a plus ribavirin was generally similar to that of IFN alfa-2a plus ribavirin. The safety profile is not well-defined in patients with advanced HIV, *e.g.* in terms of CD4+ T-cell count below 200.
Hepatic decompensation occurred in similar proportions of patients in the three treatment groups. All patients who experienced hepatic decompensation had bridging fibrosis or cirrhosis and had more advanced liver disease at baseline.
Neutropenia, thrombocytopenia, anaemia, and hypertriglyceridaemia occurred more frequently in patients treated with PEG-IFN alfa-2a plus ribavirin. These laboratory abnormalities were generally not associated with clinical symptoms, and were in most cases managed without premature discontinuation of study treatment.
Elevated serum ALT activity with clinical consequences that required clinical intervention (leading to dose modification or premature withdrawal from study treatment) was infrequent in the three treatment groups and was not associated with signs or symptoms of hepatic decompensation.
With the exception of hepatic decompensation and thrombocytopenia, which occurred more frequently in the cirrhotic population than in the overall population, the adverse event profile in the cirrhotic population was similar to that of the overall population.

Total lymphocytes, CD4+ cell counts, and CD8+ cell counts decreased from baseline during the 48-week treatment period in all three treatment groups and returned to baseline levels following completion of the 48 weeks of HCV treatment.
In the three treatment groups evaluated in this study, treatment for HCV did not adversely impact the effect of HIV antiretroviral therapy on HIV viral titres.

Section 4.4 of the SPC has been strengthened in order to draw the attention of prescribers to the increased risk of hepatic decompensation, lactic acidosis and pancreatitis for coinfected patients receiving HAART, if treated with ribavirin in combination with interferons. In addition, the following statements were included in the SPC:

"Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with Pegasys with or without ribavirin. In study NR15961, patients concurrently treated with stavudine and interferon therapy with or without ribavirin, the incidence of pancreatitis and/or lactic acidosis was 3% (12/398)."

"Baseline variables in co-infected cirrhotic patients that may be associated with hepatic decompensation include: increased serum bilirubin, decreased haemoglobin, increased alkaline phosphatase or decreased platelet count, and treatment with didanosine (ddI)."

"Co-infected patients should be closely monitored, assessing their Child-Pugh score during treatment, and should be immediately discontinued if they progress to a Child-Pugh score of 7 or greater."

Extension of indication: Treatment of patients with HBeAg-positive or HBeAg-negative chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis.

On 23 February 2005, the European Commission approved a type II variation concerning the extension of indication (all strengths and formulations) of Pegasys monotherapy to include treatment of patients with HBeAg-positive or HBeAg-negative chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis. As a consequence, changes to SPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 were agreed.

Clinical Pharmacology

Pharmacokinetics and pharmacodynamics

PK sampling was undertaken in the exploratory study NV16037 and in substudies of the two pivotal studies. There are no reasons to suspect that the pharmacokinetics of PEG-IFN differ between patients with Chronic hepatitis C (CHC) and Chronic hepatitis B (CHB) and sparse data do not violate this assumption.
The correlation between PEG-IFN exposure and neopterin and 2', 5'-OAS was also investigated. Some correlation was found for neopterin at both weeks 1 and 12 (R^2 about 0.5) but not for 2', 5'-OAS (R^2 <0.03).
In the pivotal studies WV16240 and WV16241, signs of PK interaction between PEG-IFN and lamivudine were also looked at without positive findings. Due to high inter-patient variability the sponsor considered especially the results in WV16240 inconclusive. This constitutes no concern, as there are no good mechanistic reasons to suspect a kinetic interaction. Furthermore, safety and efficacy data are available for the combination and combined therapy is not recommended.

Study NV16037

This is an exploratory, dose and standard IFN comparative study. A total of 18 centres in the Asia-Pacific region participated. After screening**,** 194 HBeAg-positive CHB patients with HBVDNA levels

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> 500,000 copies/mL and ALT levels between 2x and 10 x ULN were randomised to the 90 mcg (N = 49), 180 mcg (N = 46) and 270 mcg (N = 48) PEG-IFN groups and also to the 4.5 MIU IFN group (N = 51). Study drugs were administered over a 24-week period and patients were followed for an additional 24-week period.

Study NV16037: Summary of Main Efficacy Results at End of Follow-Up (Week 48) - ITT Population

Endpoint+	Responses	IFN 4.5 MIU N= 51	PEG 90 µg N= 49	PEG 180 µg N= 46	PEG 270 µcg N= 48	p-values* any trt diff	p-values++ Dose-response
		n(%)Patients with Response at Week 48					
Primary Efficacy Endpoint							
HBeAg loss	n (%)	13 (25.5%)	18 (36.7%)	16 (34.8%)	14 (29.2%)	0.2955	0.4324
Secondary Efficacy Endpoints							
DNA**	n (%)	13 (25.5%)	21 (42.9%)	18 (39.1%)	13 (27.1%)	0.0963	0.1082
ALT	n (%)	13 (25.5%)	21 (42.9%)	16 (34.8%)	15 (31.3%)	0.2901	0.2358
HBeAg seroconversion	n (%)	13 (25.5%)	18 (36.7%)	15 (32.6%)	13 (27.1%)	0.4277	0.3109
HBsAg loss	n (%)	0 (0.0%)	2 (4.1%)	0 (0.0%)	0 (0.0%)	0.1102	0.087
Triple endpoint#	n (%)	6 (11.8%)	13 (26.5%)	13 (28.3%)	9 (18.8%)	0.0881	0.3768

+ For the primary and secondary efficacy endpoints, p < 0.05 was considered statistically significant
++ Conditional Logistic regression analysis testing for any difference between treatment arms and for a significant linear dose-response relationship across the PEG-IFN treatment arms
Factors in the model include anti-HBe & HBeAg status at baseline, center and cirrhotic status
** < 500,000 copies/mL
#Loss of HBeAg, ALT normalization and suppression of HBV-DNA <500,000 copies/mL

Discussion on Clinical pharmacology

At "end of follow up", there was no evidence of a positive dose-response relationship for PEG-IFN. It is of interest to note, however, that there was an apparent dose-activity relationship on therapy in the sense that the 180 and 270 mcg dosages seemed more active than the 90-mcg dose. Post-therapy rebound, however, appeared less evident in the 90-mcg arm. Whether this should be regarded as just an accidental finding, or actually relates to the complex pharmacology of interferons, including direct anti-viral activity and immune modulating properties, remains speculative.

With respect to dose selection, the sponsor concludes that it is reasonable to bring forward for phase III the 180-mcg dose since there was no evidence from study NV16037 that the 90 µg, or 270 µg doses were more efficacious than the 180 µg dose and data from NV16037 suggested that the 180-µg dose produced the fastest decline in HBV-DNA levels during the treatment phase. Traditionally, higher doses of conventional IFN are used to treat CHB compared to CHC and since 180 µg is the approved dose of PEG-IFN in CHC, there was no obvious reason for using a lower dose in CHB. Furthermore, there is an extensive safety database available for the 180-µg dose of PEG-IFN in CHC patients.

Given the large inter-individual variability in PEG-IFN exposure, it is also acknowledged that it is likely to be impossible to define an "optimal dose" that fits everyone.

Clinical Efficacy

Two pivotal studies have been undertaken: *Study WV16240* in HBeAg-positive patients and *Study WV16241* in HBeAg negative patients.

Pivotal study WV16240 (HBeAg positive)

This trial was a randomised multicentre trial conducted in 67 centres in 16 countries/districts (n=820). The primary objective was to compare the efficacy and safety of PEG-IFN with and without lamivudine to lamivudine monotherapy in the treatment of HBeAg positive patients with chronic HBV infection. The study was blinded with respect to lamivudine or placebo in combination with PEG-IFN. Patients were randomised at 1:1:1 to the PEG-IFN/placebo (n=272), PEG-IFN/ lamivudine (n=272), or lamivudine monotherapy (n=276). The dose of PEG-IFN was 180 mcg once weekly and the

lamivudine dose 100 mg once daily and the duration of therapy was 48 weeks with a 24-week treatment-free follow up.

There were two primary efficacy endpoints:

- HBeAg seroconversion (absence of HBeAg and presence of anti-HBe) at the end of follow-up
- HBV-DNA below 10^5 copies/ml at the end of follow-up (COBAS AMPLICOR HBV MONITOR).

The sponsor is planning for prolonged follow-up (5 years) in responding patients, which is of importance in order to define durable response.

Inclusion criteria included:

- Positive HBsAg for more than 6 months, positive HBeAg, detectable HBV-DNA (> 500,000 copies/mL as measured by PCR), and negative anti-HBs;
- Elevated serum ALT above the upper limit of normal (ULN) but $< 10 \times$ ULN as determined by two abnormal values taken > 14 days apart during the six months before the first dose of study drug administration with at least one of the determinations obtained < 35 days prior to the first dose;
- A liver biopsy obtained within the past 12 months (and more than 6 months after the end of any previous therapy for CHB) demonstrating liver disease consistent with CHB. Patients with cirrhosis or marked fibrosis on liver biopsy had to have a liver imaging study to rule out hepatic carcinoma;
- A maximum of about 30% of participating patients could have cirrhosis or marked fibrosis.

Exclusion criteria were typical for IFN studies. Antiviral therapy for CHB within the previous six months was not accepted.

About 85 to 90% of the patients completed follow-up and the percentage prematurely withdrawn from therapy was up to 7% in the PEG-IFN arms. This should be regarded as acceptable for a 48-week IFN study.

Summary of Major Efficacy Results at the End of Follow-Up (Week 72), Intent-To-Treat Population

Efficacy Endpoint[a]	PEG-IFN/Plac n = 271	PEG-IFN/Lam n = 271	Lam Mono n = 272	Overall p value[b]
Primary Efficacy Endpoints				
HBeAg seroconversion	87 (32.1%)*	74 (27.3%)	52 (19.1%)	0.003
HBV-DNA < 10^5 copies/mL	86 (31.7%)*	91 (33.6%)*	60 (22.1%)	0.007
Secondary Efficacy Endpoints				
Response variables				
Loss of HBeAg	91 (33.6%)*	77 (28.4%)*	57 (21.0%)	0.004
Loss of HBsAg	9 (3.3%)*	11 (4.1%)*	2 (0.7%)	0.043
HBsAg seroconversion	8 (3.0%)*	8 (3.0%)*	0 (0.0%)	0.016
Normalization of ALT activity	111 (41.0%)*	106 (39.1%)*	76 (27.9%)	0.003
Paired liver biopsy response[c]	102 (49.3%)	112 (52.1%)	93 (50.5%)	0.786
Triple endpoint response	62 (22.9%)*	56 (20.7%)*	28 (10.3%)	< 0.001
Quantitative variables[c,d]				
Adjusted mean $\log_{10}$ ALT	1.59	1.61	1.67	0.107
Adjusted mean $\log_{10}$ HBV-DNA	7.98*	7.84*	8.58	0.030
Adjusted mean $\log_{10}$ (HBeAg+1)	1.49	1.51	1.64	0.284
Adjusted mean total HAI score	7.41	6.86	7.00	0.195

Note: plac = placebo; lam = lamivudine; mono = monotherapy.
* Significantly different from the lamivudine monotherapy group.
[a] For primary efficacy endpoints, $p < 0.0125$ was considered statistically significant; for secondary efficacy endpoints, $p < 0.05$ was considered statistically significant.
[b] Differences among three treatment groups were based on Cochran-Mantel-Haenszel test or ANCOVA as appropriate.
[c] Sample size may differ from the number of patients in the intent-to-treat population for a given group.
[d] Units of the quantitative variables: $\log_{10}$ ALT = U/L, $\log_{10}$ HBV-DNA = copies/mL; $\log_{10}$ (HBeAg+1) = IU/mL.

Histological response was defined as proportion of patients with improvement in total HAI score ≥ 2 points (Ishak). Triple endpoint response in the table above refers to ALT normalisation, HBV-DNA $<10^5$ copies/ml and HBeAg seroconversion. As discussed above, the "optimal" outcome measure may be disputed, but a combined endpoint such as the "triple endpoint response", may be preferable to single measures. In any case, all the secondary efficacy endpoints, including the combined endpoint,

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are in the same direction as the primary efficacy endpoints. Irrespective of response measure, the treatment results are essentially consistent and compatible with superior activity for PEG-IFN. Combination therapy provides no add-on activity.

Pivotal Study WV16241 (HbeAg negative)

This trial was a randomised, multicentre trial conducted in 53 centres (n=552). The primary objective was to compare the efficacy and safety of PEG-IFN with and without lamivudine to lamivudine monotherapy in the treatment of HBeAg negative patients with chronic HBV infection. The study was blinded with respect to lamivudine or placebo in combination with PEG-IFN. Patients were randomised at 1:1:1 to the PEG-IFN/placebo (n=182), PEG-IFN/ lamivudine (n=186), or lamivudine monotherapy (n=184). The dose of PEG-IFN was 180 mcg once weekly and the lamivudine dose 100 mg once daily and the duration of therapy was 48 weeks with a 24-week treatment-free follow up.

The primary efficacy endpoints were:
- Normal ALT at end of follow up.
- HBV-DNA < 20 000 copies/mL by AMPLICOR HBV MONITOR at end of follow up.

1–2 years of treatment with non-pegylated IFN was recommended by the EASL consensus conference on hepatitis B held in 2002. At the same meeting it was concluded ("evidence grade C") that most patients would need more than 1 year of treatment with lamivudine.

Inclusion criteria included:
- Positive HBsAg (with negative anti-HBs), positive anti-HBe for at least the prior 6 months, and HBV DNA >100 000 copies/mL by COBAS AMPLICOR MONITOR within the screening period. (At sites which did not have historic anti-HBe status, patients had to be documented as HBeAg negative for at least the prior 6 months);
- Elevated serum ALT >ULN but <10× ULN as determined by two abnormal values taken >14 days apart during the six months before the first dose of study drug with at least one of the determinations obtained <35 days prior to the first dose;
- A liver biopsy obtained at least 6 months after completing any previous anti-HBV therapy and within the past 24 months (when anti-HBe positive) demonstrating liver disease consistent with chronic hepatitis B. In addition, there had to be a prominent necroinflammatory component to the biopsy. Patients with cirrhosis or marked fibrosis (e.g. Metavir F3, Knodell fibrosis score = 3) on liver biopsy also had to have a liver imaging study to rule out hepatic carcinoma;
- A maximum of about 30% of participating patients could have cirrhosis or marked fibrosis.

Exclusion criteria were typical for IFN studies. Antiviral therapy for CHB within the previous six months was not accepted.

About 85 to 95% completed follow-up and up to 8% discontinued PEG-IFN. This is satisfactory for a 48-week IFN study.

Overview of Efficacy outcomes

Response at end of follow-up	PEG-IFN/ placebo N=177	PEG-IFN/ lamivudine N=179	Lamivudine N=181	p-value overall 1*
Co-primary endpoints				
Serum ALT [a]	105 (59%)	107 (60%)	80 (44%)	0.003
HBV-DNA[b]	76 (43%)	79 (44%)	53 (29%)	0.005
Secondary endpoints				
HBsAg loss	7 (4%)	5 (3%)	0	0.029
HBsAg seroconversion	5 (3%)	3 (2%)	0	0.086
Histological[c]	85/143 (59%)	68/143 (48%)	72/125 (58%)	0.101
Triple Response	4 (2%)	3 (2%)	0	0.0143
Quantitative Endpoints				

Adjusted mean $\log_{10}$ ALT	1.48	1.47	1.58	0.017
Adjusted mean $\log_{10}$ HBV-DNA	4.83	4.96	5.59	0.007

[a] <ULN; [b] < 20000 copies/mL [c] ≥ 2 point decrease in HAI score (patients with paired biopsies only)
* p-value overall - from the Cochran-Mantel-Haenszel test for differences in responses between the treatment groups, controlling for Region and ALT Strata

For the two primaries, p< 0.025 was defined as statistically significant, for secondary endpoints p<0.05. The results seem overall consistent. The availability of paired biopsies was higher than in the HBeAg positive study, but slightly fewer patients in the lamivudine group than in the PEG-IFN groups underwent biopsies.
A combined response analysis (normal ALT <u>and</u> HBV-NDA <20.000 copies) showed similar results, odds ratio 1.84, p=0.01.

Supplementary efficacy analyses – Study WV16240 and Study WV16241

Histology
Regardless of treatment, approximately half the patients with paired biopsies (44%-48%) in WV16240 and 46%-55% in WV16241) achieved a ≥2 point decrease in total HAI score (with no change in fibrosis score) whilst one quarter to one third achieved a ≥ 4 point decrease in total HAI score without worsening of fibrosis. These data also suggest that amongst histologic responders, very few experienced a worsening in fibrosis.
More patients in the lamivudine monotherapy group withdrew during follow-up to reinitiate new anti-HBV therapy; these patients generally did not have post-treatment biopsies performed leading to a smaller overall number of patients with paired-biopsies. Hence the estimate of histologic response in the paired biopsy analyses are likely to be an overestimate in the lamivudine monotherapy arm since patients withdrawing during follow-up were probably virologic/serologic non-responders and as such were more likely to be histologic non-responders.
Previous studies with nucleos(t)ide analogues have shown histologic responses (defined as a ≥2 point decrease in total HAI score) ranging from between 25% to 33% amongst placebo-treated patients after 1 year of observation, suggesting that such improvement may be linked with the natural history of the disease, sampling error or inconsistent interpretation by the histopathologist. The histologic responses in these studies were largely accounted for by improvements in necro-inflammation with little or no impact on fibrosis.
All in all, the submitted data according to alternative definitions of histological response show a consistent pattern indicating that none of the definitions bias the results in favour of PEG-IFN. It is agreed that in the "paired analyses", there is a likely bias in favour of lamivudine.
Due to the importance of fibrosis, response definitions excluding worsening of fibrosis seem preferable, but it is acknowledged that sample variability, etc. may account for apparent worsening. This, however, should not bias the results in any direction.

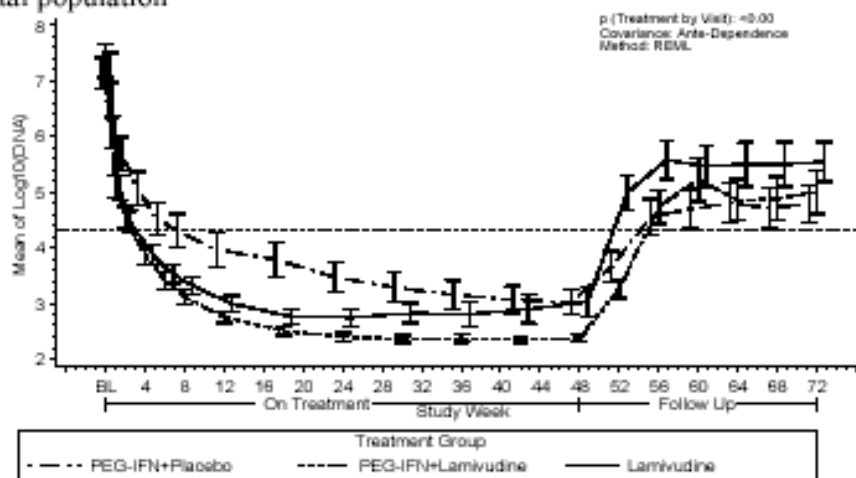*HBV-DNA (mean log, 95% CI) Study WV16240, ITT*

Total population
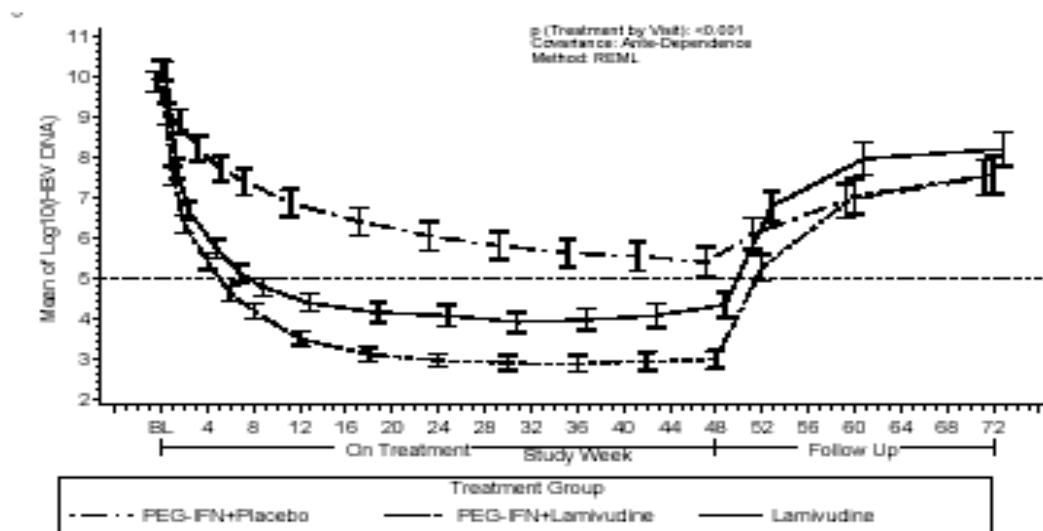
Dashed horizontal lines indicate cut-off for response of 100,000 copies/mL.

HBV-DNA (mean log, 95% CI) Study WV16241, ITT

Total population

Dashed horizontal lines indicate cut-off for response of 20 000 copies/mL.

Undetectable HBV-DNA (<200 copies/ml)

	PEG-IFN/placebo	PEG-IFN/lamivudine	Lamivudine
WV16240 (HBeAg-positive)			
Week 48, end of treatment	63/271 (23%)	178/271 (66%)	92/272 (34%)
Week 72, end of follow-up	30/271 (11%)	31/271 (11%)	14/272 (5%)
WV16241 (HBeAg-negative)			
Week 48, end of treatment	100/177 (56%)	151/179 (84%)	124/181 (69%)
Week 72, end of follow-up	29/177 (16%)	27/179 (15%)	9/181 (5%)

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On-therapy data show add-on activity in the combination arm, but increased rebound eliminates the difference. The difference between HBeAg positive and negative patients on-therapy seems mainly to relate to difference in viral load at baseline. The difference in viral dynamics (onset and rebound) between IFN and lamivudine underscores the complexity of IFN activity. In both studies and at week 48, no plateau in HBV-DNA seems to have been reached in the PEG-IFN arms.

HBeAg seroconversion at end of therapy and during follow up WV16240

Visit	Responses	PEG-IFN+ Placebo N=271	PEG-IFN+ Lamivudine N=271	Lamivudine N=272
Week 48	n (%) 95% CI	72 (26.6%) (21.4 - 32.2)	64 (23.6%) (18.7 - 29.1)	55 (20.2%) (15.6 - 25.5)
Week 52	n (%) 95% CI	74 (27.3%) (22.1 - 33.0)	58 (21.4%) (16.7 - 26.8)	55 (20.2%) (15.6 - 25.5)
Week 60	n (%) 95% CI	86 (31.7%) (26.2 - 37.6)	71 (26.2%) (21.1 - 31.9)	43 (15.8%) (11.7 - 20.7)
Week 72	n (%) 95% CI	87 (32.1%) (26.6 - 38.0)	74 (27.3%) (22.1 - 33.0)	52 (19.1%) (14.6 - 24.3)

HBeAg mean values over time (mean, log, 95% CI)
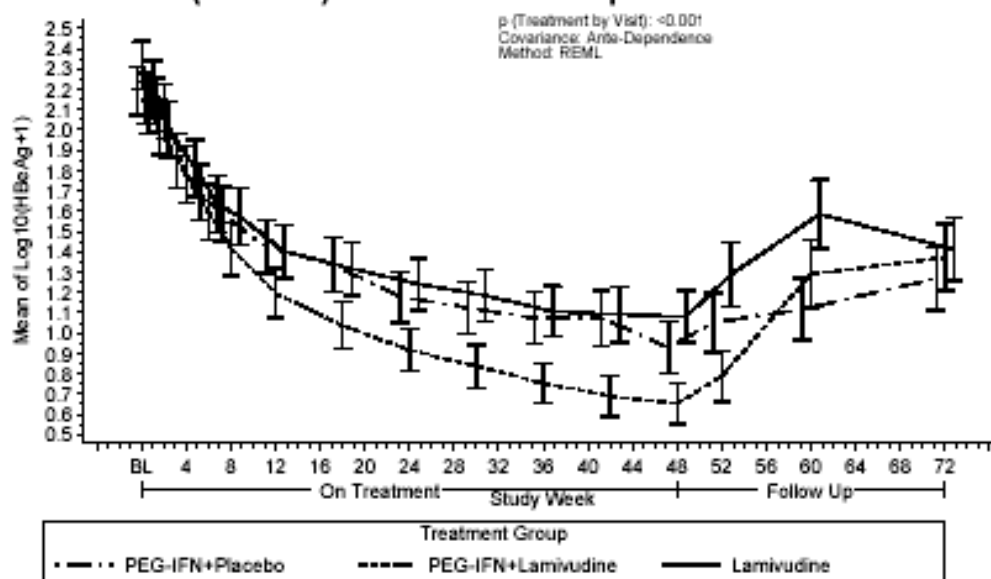
The experience until now with respect to quantitative HBeAg as activity measure is limited. On-therapy, HBeAg levels decrease over time without reaching an obvious plateau, at least for lamivudine containing arms.

With respect to seroconversion, a plateau seems to be reached before week 48, but the difference between week 24 and week 48 is non-trivial, 16% vs. 27% (PEG-IFN). This provides at least some support for a duration of therapy longer than 24 weeks. It is also of some interest to note that at week 24, the seroconversion rates were identical in the PEG-IFN arm and the lamivudine arm.

After end of therapy there is an increase in mean HBeAg levels, more pronounced in the lamivudine containing regimens, but numbers of patients with seroconversion are relatively stable in the lamivudine arm and tend to increase over time in the IFN arms.

In patients with seroconversion, HBV-DNA levels remained essentially stable after end of therapy irrespective of treatment group. The post-therapy increase is thus confined to patients without seroconversion (not shown here).

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Efficacy results in patients with cirrhosis (grade 4)

Study WV16240: Summary of Efficacy Results in Cirrhotic (F4) vs Non-Cirrhotic (F0-3) Patients (ITT Population)

Response Parameter	PEG-IFN/ placebo N=256	PEG-IFN/ lamivudine N=262	Lamivudine N=254	PEG-IFN/ placebo N=15	PEG-IFN/ lamivudine N=9	Lamivudine N=18
Fibrosis Category	F0-3			F4		
HBeAg seroconversion	**84 (33%)**	**69 (26%)**	**48 (19%)**	**3 (20%)**	**5 (56%)**	**4 (22%)**
HBV-DNA	**82 (32%)**	**87 (33%)**	**55 (22%)**	**4 (27%)**	**4 (44%)**	**5 (28%)**
ALT	107 (42%)	104 (40%)	72 (28%)	4 (27%)	2 (22%)	4 (22%)
HBeAg Loss	88 (34%)	72 (28%)	52 (21%)	3 (20%)	5 (56%)	5 (28%)
HBsAg loss	7 (3%)	11 (4%)	2 (1%)	2 (13%)	0 (0%)	0 (0%)
HBsAg seroconversion	6 (2%)	8 (3%)	0 (0%)	2 (13%)	0 (0%)	0 (0%)
Histology (unpaired)	98 (38%)	107 (41%)	83 (33%)	4 (27%)	5 (56%)	10 (56%)
Histology (paired)	98/195 (50%)	107/208 (51%)	83/171 (49%)	4/12 (33%)	5/7 (71%)	10/13 (77%)
Triple*	59 (23%)	54 (21%)	26 (10%)	3 (20%)	2 (22%)	2 (11%)

*Triple response: HBeAg seroconversion, HBV-DNA <100,000 copies/mL, normal ALT

Study WV16241: Summary of Efficacy Results in Cirrhotic (F4) vs Non-Cirrhotic (F0-3) Patients (ITT Population)

Response Parameter	PEG-IFN/ placebo N=159	PEG-IFN/ lamivudine N=164	Lamivudine N=171	PEG-IFN/ placebo N=18	PEG-IFN/ lamivudine N=15	Lamivudine N=10
Fibrosis Category	F0-3			F4		
ALT	**99 (62%)**	**96 (59%)**	**77 (45%)**	**6 (33%)**	**11 (73%)**	**3 (30%)**
HBV-DNA	**71 (45%)**	**73 (45%)**	**49 (29%)**	**5 (28%)**	**6 (40%)**	**4 (40%)**
HBsAg loss	6 (4%)	5 (3%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)
HBsAg seroconversion	5 (3%)	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Histology (unpaired)	79 (50%)	59 (36%)	67 (39%)	6 (33%)	9 (60%)	5 (50%)
Histology (paired)	79/131 (60%)	59/131 (45%)	67/119 (56%)	6/12 (50%)	9/12 (75%)	5/6 (83%)
Triple*	4 (3%)	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Triple response: HBsAg seroconversion, HBV-DNA <20,000 copies/mL, normal ALT

Predictive value of on-therapy changes for clinical response

The <u>negative predictive value</u> reached 95% in patients not achieving a level of HBeAg ≤ 100IU/ ml at week 24. This group accounts for about 25% of the patients in the study.
For HBV DNA it was not possible to achieve a higher negative predictive value than about 85% referring to HBV DNA≥ 10^9 copies/m at week 12l. This refers to about 25% of the patients.
The best <u>positive predictive value</u> about 70% was achieved in patients with HBV DNA < 1000 copies/ml at week 24. This refers to about 20% of the patients. Based on HBeAg no better predictions were obtained.
No validated test is yet available as regards HBeAg. Furthermore, the good negative predictive value of HBeAg with a cut-off at ≤ 100IU/ ml has to be confirmed in future studies. Irrespective of this, the results are undoubtedly interesting as there seems to be an overall correlation between levels of HBV-DNA and HBeAg. Therefore it is of interest to find out under what conditions HBeAg levels add independent prognostic information.

Proportion of responders/non-responders to previous therapies across treatment groups and the possible impact on study results

In both pivotal studies, no information was collected about whether patients were relapsers or non-responders to previous anti-HBV therapies. However, the study protocols stipulated that prior anti-HBV therapy must have been stopped more than 6 months before study entry.

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In the PEG-IFN treatment groups in both studies, response to therapy did not appear to be influenced by prior exposure to either IFN or lamivudine. However, in the lamivudine monotherapy group, patients that previously received lamivudine demonstrated a lower efficacy response compared with lamivudine-naïve patients.

The percentage of patients previously treated with anti-HBV therapies was limited to 23% in the HBeAg positive Study and 14% the in HBeAg negative Study. The distribution of patients with prior exposure to lamivudine or IFN was, overall, well balanced across treatment groups.

HBeAg positive patients with previous exposure to IFN show slightly higher HBV-DNA and HBeAg seroconversion response rates whilst HBeAg negative patients show slightly lower HBV-DNA and ALT response rates than those without previous exposure. However, the number of patients in these subgroups, mainly in the HBeAg negative Study, is too limited to drawn firm conclusions.

Patients with previous exposure to lamivudine showed a reduction in the virological, biochemical and serologic response rates, consistently across studies, when they were allocated to receive lamivudine therapy. However, again, data are too limited to support any conclusions.

These data suggest that prior exposure to lamivudine might negatively affect response rates to lamivudine and this could have lead to an overestimation of the efficacy differences of PEG-IFN over lamivudine. However, since the percentage of patients previously treated with lamivudine was rather small (9.5%), the possible impact on the efficacy results is negligible.

Baseline characteristics and outcome

Three factors, HBV-DNA (higher levels – lower response rates), ALT (higher levels – higher response rates) and treatment were found to independently predict response in both studies. In WV1640 HBeAg was also found to independently predict response (higher levels – lower response rates).

Baseline ALT (including distribution) and viral load were compared for patients seroconverting prior to and after 24 weeks of therapy and no differences were detected. Thus at baseline no easy-to-treat patient group is possible to identify. Even if this would be the case, it is unknown to what extent post conversion PEG-IFN therapy is needed to consolidate the response. It should also be noted that post-therapy patients continue to seroconvert after end of therapy.

The sponsor has committed to perform further analyses on study WV16240 data in order to identify an early stopping hypothesis for potential testing.

Sustained response and ALT levels, HBV-DNA and HBeAg levels

HBeAg positive disease: With respect to baseline ALT the pattern is rather consistent as regards the relationship between treatment regimens in different risk strata. For HBV DNA and HBeAg apparent superiority for PEG-IFN in monotherapy vs. combination therapy seems to be confined to low risk patients. This probably tells us something of biological relevance about the interaction between disease, host and compounds, but it is not self-evident how to interpret the information. Modelling attempts exploring the relationship between ALT increase, HBV DNA and treatment outcome for combination vs. PEG-IFN mono-therapy would be of interest, but, given the weak basis, cannot be requested as a commitment.

HBeAg negative disease: Compared with HBeAg positive disease, baseline ALT and HBV DNA levels seem less important for outcome of PEG-IFN therapy (but the overall lower HBV DNA levels should be noted).

Inflammatory score and sustained response

For both the HBeAg seroconversion and HBV-DNA response, the pre-treatment necro-inflammatory score although significant in the univariate analysis was not significant in the multivariate model (p = 0.172 for HBeAg seroconversion and p=0.395 for HBV-DNA response in the multivariate analysis). Thus, necro-inflammatory score provides no independent prognostic information. ALT increase (if not confounded by other conditions) is likely to provide the information needed about inflammatory activity.

Subgroup analyses

In general and in both pivotal studies, the response rates were higher in female patients

There seems to be no obvious relationship between genotype and response in WV16240, but numbers are small for other genotypes than B and C. In HBeAg negative patients the response rate appears

lower in genotype D. As this genotype is common in the Mediterranean area, this might at least partly explain the apparently lower response rate in Europeans/Caucasians.

The low incidence of genotype A in this study compared with WV16240 relates to the intrinsically reduced tendency for genotype A to form pre-core mutants.

Prior exposure to lamivudine seems to reduce response rates in lamivudine arms. The numbers of individuals were too low to meaningfully influence the overall results in the ITT population. At baseline altogether 21 out of 97 patients with prior lamivudine exposure showed virus with lamivudine resistance mutations.

Discussion on Clinical Efficacy

It has been convincingly demonstrated that 1 year of treatment with PEG-IFN in the dose proposed for marketing is superior in terms of sustained response to appropriately dosed lamivudine for 1 year, both in HBeAg positive and negative patients. A treatment strategy comparative study allowing for prolonged suppressive therapy with lamivudine would have been of major clinical importance, but it is accepted that such a study should not be a requirement for licensing.

Available data also indicate that PEG-IFN is at least as active as conventional IFN therapy, but 1 year of therapy with IFN in HBeAg positive patients cannot be regarded as well established. On treatment study data in the pivotal trial, however, indicate that seroconversion occurs in a higher than expected rate also after 24 weeks of therapy, supporting the notion that at least some patients benefit from prolonged therapy (>24 weeks).

Without questioning the favourable benefit – risk of 1 year of therapy with PEG-IFN therapy in patients with HBeAg positive disease, the possibility exists that the optimal duration of therapy for a given patient could be tailored according to time of seroconversion. The sponsor has committed to provide a detailed analysis with respect to this issue post approval of this variation.

In HBeAg negative patients, an independent Italian study exploring 2 versus 1-year of PEG-IFN therapy is in the planning stage. This is welcomed and the sponsor should commit to inform the CHMP, first whether the study actually will be initiated (together with a synopsis of the protocol) and secondly to submit the results of this study.

Clinical Safety

Safety has been assessed primarily based on the pooled data of 898 patients treated with PEG-IFN (448 PEG-IFN alone, 450 PEG-IFN with lamivudine) at the recommended dose of 180 μg from the two phase III studies (WV16240 and WV16241). Of the 898 CHB patients, the proportion that received between 45 and 48 weeks of PEG-IFN therapy was comparable between the PEG-IFN/placebo (92%) and PEG-IFN/lamivudine (94%) groups.

Overview of Safety (WV16240 + WV16241, Safety Population)

	PEG-IFN/ placebo N=448 n (%)	PEG-IFN/ lamivudine N=450 n (%)	Lamivudine N=453 n (%)
Any AEs (up to 8 weeks post-treatment)			
Any event	395 (88)	395 (88)	238 (53)
Severe events	39 (9)	51 (11)	20 (4)
Serious AEs (up to 24 weeks post-treatment)	27 (6)	35 (8)	17 (4)
Deaths (up to 24 weeks post-treatment)	1 (<1)	3 (1)	1 (<1)
Premature withdrawals for safety reasons			
Total (any treatment)	21 (5)	19 (4)	2 (<1)
Stopped PEG-IFN and lam/placebo	13 (3)	15 (3)	-
Stopped PEG-IFN only (continued lam/plac)	8 (2)	4 (<1)	-
Stopped lamivudine monotherapy	-	-	2 (<1)
Dose modifications/interruptions for AEs	33 (7)	46 (10)	2 (<1)

If anything the event rate, e.g. leading to withdrawal was lower than in studies conducted in patients with CHC, overall 4% for PEG-IFN in CHB vs. 9% in CHC.

Deaths
The investigators reported all deaths as being unrelated to PEG-IFN. In the lamivudine arm hepatic flare after end of therapy led to death in one patient.
There was one case of TTP in the PEG-IFN arm where a causal relationship appears reasonable. Hepatic flare in patients withdrawn from lamivudine is well known.

Serious adverse events
More SAE:s were reported in the PEG-IFN arms (6% and 8%) than in the lamivudine alone arm (4%). The most common type was infections.
Fifteen cases of serious hepatic flare were reported (4 + 6 + 5). Ten occurred post-therapy thereof one in the PEG-IFN + placebo arm. In the lamivudine alone arm one patient died and one underwent a liver transplant.
Two cases of serious thyroid disorder were reported (see below) and 3 cases of hearing loss, two in PEG-IFN arms. In the cases of hearing loss, there were significant confounding factors, but hearing loss has been reported previously for interferons and there are some experimental data showing an effect on hearing threshold.

Withdrawals for safety reasons
Seven patients (<1%) withdrew from PEG-IFN due to laboratory adverse events and about 3% (27 individuals) from a wide variety of AEs, thereof altogether 6 individuals due to psychiatric events and 6 due to skin events.

Dose modifications due to safety concerns
There were more cases of dose reductions in HBeAg negative patients, reasonably reflecting more patients with advanced fibrosis. Conversely, ALT disorder more commonly led to dose reductions in HBeAg positive patients.
Compared with patients with CHC, more patients underwent dose reductions due to laboratory events, mainly ALT flare which is characteristic for CHB and responding patients.

Adverse events over time
As expected flu-like symptoms decreased over time, while alopecia increased. The incidence of fatigue, asthenia and anorexia, however, seemingly did not increase.

Serious infections
The incidence of serious infections was overall about 1% (1%, 3% and 1%, respectively) and was in no case associated with neutropenia <0.5.

Depression
The incidence of depression was clearly lower in CHB patients than in patients with CHC, about 4% vs. 20-25%. The incidence in the CHB studies was also lower in Asians (about 2%) than in Caucasians (10 – 15%). Similar findings have been reported for conventional IFN.

ALT flare
In HBeAg positive patients 3 patients stopped therapy due to ALT flare and about 10% underwent dose reduction while no individual was withdrawn and slightly fewer underwent dose reduction in the HBeAg negative group.
Overall, ALT flare was less common in HBeAg negative patients on and off therapy. On therapy there were more reports for PEG-IFN treated than lamivudine treated, while the opposite was true off therapy, at least in study WV16241.
In HBeAg positive disease, on-treatment ALT flares (>5x ULN) were more common in the PEG-IFN treatment arms and were associated with response to therapy. This is not the case for lamivudine.
In HBeAg negative disease, on therapy ALT flares (>5x ULN), were less commonly encountered in general and were not associated with response in the PEG-IFN arms.
ALT peaks above 5x ULN were more likely to occur in the first 12 weeks of therapy.

Thyroid disorders
Thyroid disorders requiring intervention was reported for altogether 29 PEG-IFN treated patients (3%) vs. 2 lamivudine treated. Two events were reported as SAEs – autoimmune thyroiditis leading to withdrawal and hyperthyroidism leading to hospitalisation for treatment. The reported incidence is consistent with the experience from CHC and with conventional IFN.

Thrombocytopenia
The incidence of thrombocytopenia was clearly lower in WV16240. As regards percentage of patients with platelets below 50 and for the PEG-IFN + placebo arms 9% vs. 31%. Bleeding events were reported in 11/114 PEG-IFN treated patients with nadir <50, all non-serious.

Neutralising antibodies
Anti-IFN antibodies were measured only in the Phase II study NV16037. The results showed that PEG-IFN was less immunogenic than IFN. The overall incidence of binding anti-IFN antibodies was 29% with PEG-IFN (9/49 with 90 μg, 16/46 with 180 μg and 17/48 with 270 μg) and 43% (22/48) with IFN-á2a. The proportion of patients with neutralising anti-IFN antibodies was lower with PEG-IFN (19/143 or 13%) compared with IFN-alpha 2a (19/51 or 37%). No effects on efficacy and safety were observed.
A higher incidence of neutralising anti-interferon antibodies (NA) has been reported in patients with HBV compared with HCV.
The incidence of NA with PEG-IFN is 2-3 fold lower than with conventional interferon, with no dose relationship seen between the three PEG-IFN dose groups.
The development of NA had no impact on either efficacy or safety. Of note, there was no effect of NAs production on the absolute neutrophil or lymphocyte counts with either conventional IFN-⟨2a or PEG-IFN at three dose levels in phase II study (NV16037).
It is agreed that the most likely explanation to the higher incidence of NA in patients with CHB compared with CHC is disease-related and not explained by differences in ethnicity, etc. It is not implausible that the desired immune activation in CHB patients also may account for a higher incidence of NA.
Further data are needed, however, on the actual incidence in the pivotal trials. More data are also needed to assess whether NA are associated with change in neutrophil count, i.e. whether the level is high enough to neutralise IFN effects in vivo. A possible difference between HBeAg negative and positive patients should also be explored. The applicant intends to conduct further analyses on NA using samples collected from the phase III studies.

Cirrhosis
Adverse events reported at a higher incidence in the cirrhotics compared with noncirrhotics (incidence in PEG-IFN/placebo and PEG-IFN/lamivudine arms, respectively) included:
- Abdominal pain: 24% and 33% in cirrhotics vs 10% and 8% in non-cirrhotics.
- Diarrhoea 21% and 17% in cirrhotics vs 9% and 8% in non-cirrhotics.
- Gingival bleeding: 8% and 9% in cirrhotics vs 5% and 4% in non-cirrhotics.
As expected a numerically higher incidence of thrombocytopenia was seen in cirrhotic patients treated with PEG-IFN alone or in combination: 16/57 (28%) vs. 13% in non-cirrhotics.
On-treatment ALT flares (>5x ULN and > 10x ULN) were numerically more common in cirrhotic patients receiving PEG-IFN/placebo compared with non-cirrhotic patients; these were managed by dose modifications where appropriate and were not associated with hepatic decompensation.
The number of patients with cirrhosis is small. It is, nevertheless, somewhat interesting to note the apparently higher response rates in patients on combination therapy in both studies. No safety concerns are raised questioning the benefit – risk relationship in this group of patients.

Hearing loss/impairment
As of August 31, 2004 a total of 30 cases of hearing loss/impairment were recoded on the MAH's Global Drug Safety Database, while during the same time period the total number of patients exposed to PEG-IFN is estimated to be approximately 209 000. The 30 reported events of hearing loss/impairment result in a calculated incidence of 0.14 per 1000. Since these data also include spontaneous reporting we have to assume that many patients did not take a full course of treatment and

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if we therefore assume conservatively that patients took the drug for approximately 3-6 months, the corrected annual incidence is 0.28 – 0.56 per 1000.

In the CHB trials there were 5 cases of hearing loss/impairment (0.5%) vs. 2 cases in the lamivudine arm (0.4%). Unfortunately, the PEG-IFN development programme until now encompasses a very limited number of patients not treated with IFN.

In the assessment of spontaneous reports, both general under-reporting and selective reporting of cases not considered to be caused by other conditions have to be considered. Whether the margin reported here 0.5 per 1000 vs. expected 5 per 1000 is reassuring or not is in the eye of the beholder.

In two published papers (Kanda et al. 1995, Gorur et al. 2003) the results of dedicated, prospective studies are reported. Very high incidences of mild, reversible, sensorineural hearing loss were reported.

Altogether, whether IFN increases the risk for irreversible hearing loss cannot be assessed, but it appears very likely that the risk for reversible hearing loss is increased. Reversible hearing loss is reported as a common adverse reaction in the SPC.

Discussion on Clinical Safety

The toxicity profile of PEG-IFN is considered well known from studies in patients with CHC. In comparison with CHC, there was an apparently reduced incidence of AEs (89 vs. 98%) and SAEs (7 vs. 11%) in CHB. Pyrexia, however, was more commonly reported in patients with CHB. Similarly and at least partly due to more advanced liver fibrosis in HBeAg negative patients, thrombocytopenia was more commonly encountered. The incidence of depression was clearly lower in the CHB studies and only partly explained by a lower percentage of Caucasians.

A surprisingly high incidence of neutralising antibodies was reported in the dose exploratory study, 13% (19/143) compared with studies conducted in CHC about 1-3%.

5.   Overall conclusions, benefit/risk assessment and recommendation

Quality

Pegylation reduces the *in vitro* antiviral activity of the molecule to about 1-3% of that of its un-pegylated counterpart, as estimated by the cell-based bioassay. Reduction of specific biological activity is a well-known phenomenon, especially with pegylation reagents of high molecular weight. Since efficacy of the product has been demonstrated in clinical trials, the biological activity, as assayed, is not considered a sensitive measure of the *in vivo* function. In response to the questions raised in the primary round, extended characterisation studies on the isomer profile have been conducted, and the specification limits for the positional isomers have been narrowed. Furthermore, the biological activity of the separate isomers has been assessed and found to vary between 40% and 140% of the specific activity of the mixture. As shown in the original dossier, no free interferon, that would contribute to activity, was detected in any of the clinical batches, and the confidence in this information has now been improved by further analytical validation. Altogether, the indirect control of the consistency of function of the molecule has been improved. Clarifications have been made on the validation of the bioassay and justifications have been given as concerns the reference materials. The significant reduction of the *in vitro* biological activity would call for studies on receptor interactions. Although information in this regard would contribute to the state of knowledge on mechanisms of action, the lack of such data so far is deemed not to preclude a marketing authorisation. In conclusion, the analytical methods chosen are deemed adequate and there is enough evidence provided to show that the consistency of quality of Pegylated interferon alfa-2a at release is well controlled.

Stability data for the finished product indicates that the product is stable at 2-8°C, and the claimed shelf-life, i.e. three years, is acceptable. Although aggregates have not been detected at conditions intended for storage, assessment of SE HPLC results of current and future stability studies by individually addressing main peak area % and aggregates area % will be carried out also in on-going studies.

Preclinical pharmacology and toxicology

Pegylated interferon alfa-2a retained similar *in vitro* biological activity as unmodified interferon alfa-2a but with a lower potency. The *in vivo* studies reported antiviral and antiproliferative activity for pegylated interferon with a trend towards superiority compared to unmodified interferon.

The design of the preclinical pharmacokinetic/ADME programme for PEG-IFN was typical for a protein therapeutic, in that extensive biotransformation studies were not conducted. The applicant, however, undertook to continue investigating the possible metabolism of PEG-IFN alfa-2a *in vivo*. The pharmacokinetic profile of peginterferon was characterised by a more sustained absorption compared to unmodified interferon, low distribution, renal excretion.

The toxicology programme for Pegasys was designed to provide a bridge between peginterferon and the known toxicity of interferon. Only expected findings, known from interferon toxicity studies were seen and referred typically to suppressive effects on the haematopoietic system and increases in liver enzymes. Symptoms usually arose during weeks 1-2 and declined as neutralising anti-interferon antibodies (Nab) emerged. After that time period a meaningful toxicological assessment was not possible to perform.

Subcutaneous inflammation was observed, but the severity was dependent on the injected volume or the injection frequency, which was exaggerated, compared to the clinical situation. A trend towards reversibility of the mild subcutaneous inflammation was noted during recovery and it is anticipated that any subcutaneous inflammation in patients will be reversed upon treatment cessation. *In vitro* peginterferon was not mutagenic. The lack of *in vivo* mutagenicity, carcinogenicity and reproduction toxicity studies was adequately justified considering the characteristics of interferons.

When peginterferon was combined with ribavirin, pharmacokinetic parameters of peginterferon levels showed a large variability, the toxicity was slightly increased compared to the individual treatments but reversed during the recovery period.

Clinical efficacy and safety

The pharmacokinetics of PEG-IFN has been well defined and is characterised by a sustained absorption, low CL/F, low distribution and a large variability.

From a clinical perspective, peginterferon 135 and 180 μg per week have been essentially robustly documented as superior to interferon in licensed dosages. As regards the recommended dose, 180 μg, sustained virological response rates were numerically identical in a direct comparison of 135 and 180 μg. The clinical benefit of 180 μg peginterferon has been demonstrated in monotherapy and in combination with ribavirin, including in cirrhosis patientsgiven the large inter-individual variability in exposure and in dynamic markers, the applicant undertook to further explore whether individualising the dose in relation to early markers of interferon activity would be more appropriate.

The clinical benefit of peginterferon has been evaluated in 3 monotherapy, open-label 48 weeks studies including patients of 18 years of age and older with histologically proven hepatitis C with elevated transaminases and with positive serum HCV-RNA, thereof one study in patients with documented cirrhosis or bridging fibrosis. Approximately 700 interferon-naïve patients received the recommended dose of peginterferon. The virological response with peginterferon was statistically and clinically superior to interferon alfa-2a therapy. In non-cirrhotic and cirrhotic patients, the response at the end of treatment ranged from 55 to 69 % in peginterferon group compared to 22 to 28 % in interferon alfa-2a group and the overall sustained response accounted for 28 %- 39 % and 11 %-19 % in the two groups respectively. The relative superiority appeared more pronounced in hard-to-treat patients, such as those with genotype 1 and high viral load, or patients with cirrhosis. For genotype 1 and high viral load, however, the response rate is still low. The clinical benefit of peginterferon over interferon was also demonstrated in terms of histological response.

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Since the current standard treatment of hepatitis C is the combination of interferon with ribavirin, the clinical benefit of the combination peginterferon alfa-2a + ribavirin was also evaluated compared to peginterferon monotherapy and interferon alfa-2b + ribavirin in over 1000 patients (study NV15801). Results confirmed the added value of combining peginterferon alfa-2a + ribavirin in terms of virological and/or biochemical responses. According to the protocol defined primary analysis, the combination was superior to peginterferon in monotherapy (odds ratio about 3 for sustained viral response). Peginterferon + ribavirin showed only borderline superiority to interferon alfa-2b + ribavirin (odds ratio about 1.5 for the sustained virological response). The limited histological data showed that the virological response was associated with histological improvement. Histological improvement could also be seen with non-sustained virological responses.

Apart from haematotoxicity, there were no major qualitative or quantitative differences in terms of safety between interferon 3MIU thrice weekly and peginterferon 135 or 180 µg once weekly. Neutropenia and thrombocytopenia normally developed early during therapy, were peginterferon dose-related, but were not associated with serious clinical events and responded to dose adjustment. Laboratory surveillance is, however, recommended in the SPC.

The add-on of ribavirin to peginterferon 180 µg once weekly further increased the incidence of neutropenia and added anaemia as a clinically significant adverse event. Otherwise ribavirin caused no major alterations in tolerability.

Since approval of the original Marketing Authorisation a number of variations have been authorised which amend the clinical parts of the SPC and PL.

As part of these post-authorisation activities, the CHMP considered that the benefit/risk balance of treatment with PEG-IFN and ribavirin is considered favourable in selected patients with CHC and persistently normal ALT. The original reference to increased transaminases was deleted in the therapeutic indications described in section 4.1. Further, the safety information was updated in section 4.4 and 4.8 in order to better reflect the current safety knowledge. The following information was added in section 4.4:

"In patients with normal ALT, progression of fibrosis occurs on average at a slower rate than in patients with elevated ALT. This should be considered in conjunction with other factors, such as HCV genotype, age, extrahepatic manifestations, risk of transmission, etc. which influence the decision to treat or not." and *"The risk of developing anaemia is higher in the female population."*

The following adverse reactions were added in section 4.8:

"Pneumonia, sarcoidosis, anaphylaxis diabetes suicidal ideation, wheezing, retinopathy, retinal vascular disorder, retinal hemorrhage, papilledema, optic neuropathy, vision loss supraventricular tachycardia, CHF, angina, MI hepatic failure, bilirubin increase.
The decrease in haematological values was further described (leukopenia, neutropenia, lymphopenia, thrombocytopenia and hemoglobin)."

In addition, the study NR 16071 was described in section 5.1 as follows:

"HCV patients with normal ALT
In study NR16071, HCV patients with normal ALT values were randomized to receive Pegasys 180 micrograms/week and ribavirin 800 milligrams/day for either 24 or 48 weeks followed by a 24 week treatment free follow-up period or no treatment for 72 weeks. The SVRs reported in the treatment arms of this study were similar to the corresponding treatment arms from study NV15942."

The MAH has undertaken additional studies to define the efficacy of peginterferon in HCV/HIV co-infected patients as well as in non-responders or in relapsers, the results of which have been provided, as part of follow-up measures post-authorisation.

Patients chronically mono-infected with HCV and with signs of inflammatory liver disease without decompensation are usually treated with a combination of pegylated alfa interferon and ribavirin.

Chronic hepatitis C infection is a more serious disease in patients co-infected with HIV. In the pivotal study for this submission (discussed above) it was demonstrated that patients with essentially well controlled underlying HIV disease can be treated with PEG-IFN + ribavirin as add-on to HAART with a favourable outcome in terms of sustained viral response.

Remaining concerns relate to the poorer outcome in patients with genotype 1 and high viral load, as discussed above, and the likelihood that a non-trivial proportion of patients infected with genotype 2/3 may be treated too long. The sponsor has identified an ongoing study that will be able to provide additional prospective information regarding 24-week treatment duration for coinfected patients with genotype 2 or 3 infection. This investigator-initiated, multicentre study (PRESCO) is currently being conducted. The study is evaluating the safety and efficacy of 24 weeks of HCV treatment (180 µg weekly of PEG-IFN alfa-2a in combination with 1000 or 1200 mg daily of ribavirin) for patients infected with genotype 2 and 3. Final data will be available in the middle of 2006.

On 23 February 2005, the European Commission approved a type II variation concerning the extension of indication (all strengths and formulations) of Pegasys monotherapy to include treatment of patients with HBeAg-positive or HBeAg-negative chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis *(discussed above)*.

Compared with treatment with lamivudine for 48 weeks, PEG-IFN 180 mcg for 48 weeks seemingly relevantly increases the percentage of patients with sustained response, i.e. patients without need for further therapy. This, however, has to be corroborated in supplementary analyses.

The tolerability to PEG-IFN is clearly worse than for lamivudine. Even if it appears hard to capture the increased burden of IFN toxicity over time in study reports, it is clearly evident in clinical practice. It is therefore of importance to try to identify patients with early vs. late HBeAg seroconversion in order to define hypotheses to be tested prospectively in a duration-of-therapy comparative study.

Provided that auxiliary efficacy analyses corroborate the data presented, the benefit risk relationship is found favourable. Further studies are needed, however, in order to improve the benefit risk relationship in subgroups of patients, e.g. with respect to duration of therapy (24 weeks in low risk patients) and perhaps also higher dose in HBeAg positive patients with high viral load at baseline or longer duration in patients with HBeAg negative disease.

The CHMP finds it acceptable that HBeAg positive and HBeAg negative disease is mentioned in the indication as this refers to separate entities of the disease and there is a need for conclusive clinical data to support both "sub-indications".

As requested by the CHMP, the MAH agreed to submit additional information as follow-up measures within agreed timeframes including results of the long-term (5 years) follow-up study WV16866, data on neutralising antibodies from phase III studies WV16240 and WV16241, further data comparing 2 years treatment versus 1 year in patients with HBeAg negative disease.

Benefit/Risk Assessment and recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers that the benefit/risk profile of peginterferon is favourable for the following indication:

"Chronic hepatitis B:

Pegasys is indicated for the treatment of HBeAg-positive or HBeAg-negative chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis (see 4.4 and 5.1).

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Chronic hepatitis C:

Pegasys is indicated for the treatment of chronic hepatitis C in adult patients who are positive for serum HCV-RNA, including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see 4.4).

The optimal way to use Pegasys in patients with chronic hepatitis C is in combination with ribavirin. This combination is indicated in previously untreated patients as well as in patients who have previously responded to interferon alpha therapy and subsequently relapsed after treatment was stopped.

Monotherapy is indicated mainly in case of intolerance or contraindication to ribavirin."