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Product name: **ViraferonPeg**
Procedure No: **EMEA/H/C/000329/II/0067**

SCIENTIFIC DISCUSSION

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I. SCIENTIFIC DISCUSSION

1.1. Introduction

Viraferonpeg (peginterferon alfa-2b) is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV. Peginterferon alfa-2b is best used in combination with ribavirin. Approximately 33% of Human Immunodeficiency Virus (HIV) infected patients are co-infected with hepatitis C (HCV) in Europe. This represents a serious public health issue that needs special attention, insofar as Hepatitis C infection in HCV-HIV coinfected individuals seems to have a more aggressive course. The Marketing Authorisation Holder (MAH) of peginterferon alfa-2b is now submitting a variation to introduce information in sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SPC of Rebetol (ribavirin) and pegylated interferon alfa 2b based on the clinical experience gained in the HIV-HCV co-infected patients.

Two phase III randomised open label studies, not sponsored by the MAH are submitted in support of this variation:

- P01017 or RIBAVIC study independently conducted in France by the Agence Nationale de Recherches sur le SIDA (ANRS) – study period: February 2000 to October 2003,

- P02080 a smaller investigator initiated study conducted in Spain, study period: April 2001 to February 2004.

Both studies aimed at comparing the efficacy and safety of the standard interferon alfa-2b to the pegylated interferon alfa-2b plus ribavirin combination in HIV-HCV co-infected patients.

1.2. Clinical Efficacy

The main differences in studies P01017 and P02080 are outlined below followed by a description of the studies:

Design

Title

RIBAVIC P01017: A Randomised Controlled Trial of pegylated interferon alfa-2b plus ribavirin versus standard interferon alfa-2b plus ribavirin for initial treatment of Hepatitis C in HIV infected patients.

P02080/ Laguno: Effectiveness of the safety and efficacy of the treatment of chronic hepatitis C in patients infected with the Human immunodeficiency virus comparing two types of interferon and ribavirin.

The dose of ribavirin:

- *P01017 study:* 800 mg regardless of the genotype. The choice of the dose was adapted for safety concerns, particularly the possibility of an interaction with antiretroviral treatment and because HIV positive are usually lighter than HIV negative patients.

- *P02080 study*: weight adjusted dose 800 to 1200 mg as for monoinfected patients.

Table 1 Comparison of Dosing Regimens

Body weight	*P01017 (France)*			*P02080 (Spain)*		
	Interferon alfa-2b	Peginterferon alfa-2b	Ribavirin	Interferon alfa-2b	Peginterferon alfa-2b	Ribavirin
<60 kg	3 MIU. TIW	1.5 µg/kg. QW	800 mg (≥13.3 mg/kg)	3 MIU. TIW	100µg. QW (1.6 µg/kg)	800 mg (>13.3 mg/kg)
60 to 75 kg	3 MIU. TIW	1.5 µg/kg. QW	800 mg (10.6 to 13.3 mg/kg)	3 MIU. TIW	100µg. QW (1.3 to 1.6 µg/kg)	1000 mg (13.3 to 16.6 mg/kg)
>75 kg	3 MIU. TIW	1.5 µg/kg. QW	800 mg (<10.6 mg/kg)	3 MIU. TIW	150 µg[a] QW (≤2 µg/kg)	1200 mg (≤16 mg/kg)

MIU = million international units. TIW = three times a week: QW = once weekly.
a: Row headings specify weights for ribavirin dosing which are the same for peginterferon alfa-2b dosing, except subjects weighing ≥75 kg received 150 µg of peginterferon alfa-2b.

The treatment duration:

- *P01017 study:* 48 weeks regardless of the genotype and HCV viral load with a follow up period of 24 weeks.

- *P02080 study*: 24 weeks for patients with Genotype 2 or 3 and baseline HCV-RNA < 800,000 IU/ml (Stratum 1). Forty eight weeks for patients with Genotype 2 or 3 and baseline HCV-RNA > 800,000 IU/ml and patients with Genotype 1 (Stratum 2). Follow up period of 24 weeks.

The following tables summarise the criteria used for each study.

Inclusion criteria:

Table 2 – inclusion criteria

Protocol Nos. P01017 and P02080

P01017 (France)	P02080 (Spain)
HCV-RNA positive	HCV-RNA positive and ALT >1.5 ULN
Histologic changes with at least mild activity or fibrosis	Necroinflammatory activity and/or fibrosis >1
Stable HIV levels	Control of HIV with HIV <10,000 copies/mL
Stable ART for previous 3 months or untreated	Stable ART or without ART if not required
CD4 ≥200 cells/mm^3	CD4 >250 cells/mm^3

ALT = alanine transaminase; ART = antiretroviral therapy; CD4 = cluster of differentiation antigen 4; HCV = hepatitis C virus; HIV = human immunodeficiency virus; RNA = ribonucleic acid; ULN = upper limit normal.

The Stratification criteria for study P01017 (France) were according to the centre and treatment group. For Study P02080 (Spain) stratification criteria were according to Genotype and HCV viral load.

Efficacy endpoint:

P01017 (France)
Primary: Sustained virologic response (SUR), defined by undetectable serum HCV-RNA at Follow up week 24 (i.e week 72 of the trial).

Secondary: histologic improvement. Histological responses were only analysed in patients who underwent both a pre-treatment and a post-treatment biopsy.

P02080 (Spain)
Primary: Sustained virologic response (SVR) defined as undetectable serum HCV-RNA at Follow-Up Week 24 (FU24).

Statistical method
Both studies expect a 40% therapeutic response in the interferon alfa-2b arm and a 15 (P01017) to 20% (P02080) increase with the peginterferon alfa-2b.

Baseline characteristics

The population enrolled was similar in both studies. Mainly males of approximately 40 years of age with a long past of HIV infection (around 10 years) well controlled under antiretroviral therapy as reflected by the immuno-virologic parameters [$CD4^+$ around 450 (P01017) to 550/mm^3 (P02080) and HIV-RNA level around 2 (P02080) to 3.5 log/copies/ml (P01017)]. Patients were mostly of genotype 1 and 2/3.

The Antiretroviral Therapy at baseline is summarised in the table below (Table 3):

	P01017 (France)		P02080 (Spain)
	Peginterferon alfa-2b /ribavirin (n=205) (n,%)	interferon alfa-2b/ribavirin (n=207) (n, %)	Peginterferon alfa-2b/ribavirin (n=52) (n, %)
Any HAART	171 (83)	169 (82)	48 (92)
NRTI			
DDI	45 (22)	43 (21)	8 (15)
ABC	28 (14)	19 (9)	11 (21)
D4T	93 (45)	92 (44)	26 (50)
AZT	57 (28)	58 (28)	18 (35)
3TC	127 (62)	123 (59)	37 (71)
NNRTI			
NEV	27 (13)	23 (11)	15 (29)
EFV	39 (19)	37 (18)	6 (12)
Protease Inhibitor			
IDV	22 (11)	18 (9)	6 (12)
NEL	25 (12)	41 (20)	7 (13)
RTV	35 (17)	29 (14)	3 (6)
SQL	19 (9)	15 (7)	3 (6)

3TC = lamivudine; ABC = Abacavir; AZT = zidovudine; DDI = didanosine; D4T = stavudine; EFV = efavirenz; HAART = Highly Active Antiretroviral Therapy; IDV = indinavir; NEL = nelfinavir; NEV = nevirapine; NNRTI = Non-Nucleoside analogue Reverse Transcriptase Inhibitors; NRTI = Nucleoside analogue Reverse Transcriptase Inhibitors; RTV = ritonavir; SQL = saquinavir. Source Data: P01017 CSR Section 10.3 and P02080 CSR Section 10.1.

More than 80% of patients were treated with Highly Active Antiretroviral Therapy (HAARTs). This illustrates the representativeness of the population enrolled in 2000-2001 in these studies. Of importance as regards the overlapping toxicity, stavudine (lactic acidosis) and zidovudine (anaemia) accounted for the most frequently combined Nucleoside analogue Reverse Transcriptase Inhibitors (NRTIs) together with lamivudine.

Patient's disposition

Table 4 Patients' disposition Study P01017

Disposition of Subjects	ANRS HC02 RIBAVIC		
	All Subjects (n=383)	PEG + Rebetol (n=194)	IntronA + Rebetol (n=189)
Total Completed Treatment and Follow-Up	229	114	115
Discontinued Treatment	149	76	73
Adverse event(s)	53	25	28
Laboratory abnormalities	9	8	1
Fail to return	6	2	4
Subject did not wish to continue	60	36	24
Insufficient therapeutic response	21	5	16
Completed Treatment and Never Entered Follow-Up	2	1	1
Completed Treatment and Discontinued During Follow- Up	3	3	0
Fail to return	3	3	0
Summary of deaths	5	3	2
During the treatment period	3	2	1
During Follow-up	2	1	1

Table 5 Patients' disposition Study P02080

Subject Disposition	PEG/RBV	IFN/RBV
Treated	52 (100)	43 (100)
Discontinued Treatment Phase	21 (40)	27 (63)
Adverse event	9(17)	5 (12)
Treatment failure[a]	7 (13)	17 (40)
Subject did not wish to continue, reasons unrelated	3(6)	5 (12)
Non-compliance with protocol	2 (4)	0
Completed Treatment Phase	31 (60)	16 (37)

IFN = IntronA; PEG = peginterferon alfa-2b; RBV = ribavirin

a: Subjects with detectable HCV RNA at 24 weeks were discontinued from treatment. In the published manuscript (Laguno manuscript), these subjects were considered as 'completed' and not 'treatment' failures'.

In both studies a higher rate of treatment discontinuation due to insufficient therapeutic response or treatment failure was observed in the interferon alfa-2b arm.

RESULTS

Efficacy results on primary endpoint

Table 6: Summary of Sustained Virologic Response Data by Genotype

	P01017 (France)			P02080 (Spain)		
	Peginterferon alfa-2b (1.5 µg/kg/week) + ribavirin (800 mg)	Interferon alfa-2b (3MIU TIW) + ribavirin (800 mg)	p value [c]	Peginterferon alfa 2b (100 or 150 [a] µg/week) + ribavirin (800 to 1200 mg)[d]	Interferon alfa 2b (3 MIU TIW) + ribavirin (800 to 1200 mg)[b]	p value [d]
All	27% (56/205)	20% (41/205)	0.047	44% (23/52)	21% (9/43)	0.017
Genotype 1,4	17% (21/125)	6% (8/129)	0.006	38% (12/32)	7% (2/27)	0.007
Genotype 2,3	44% (35/80)	43% (33/76)	0.88	53% (10/19)	47% (7/15)	0.730

MIU = million international units; TIW = three times a week.
a: subjects < 75 kg received 100 µg/week peginterferon alfa-2b, and subjects ≥ 75 kg received 150 µg/week peginterferon alfa-2b.
b: ribavirin dosing was 800 mg for subjects <60 kg. 1000 mg for subjects 60 to 75 kg, and 1200 mg for subjects >75 kg
c: p value based on Cochran-Mantel Haenszei Chi square test.
d: p value based on chi-square test

In the RIBAVIC (P01017) study the results observed in the pegylated arm were quite low as compared to the results achieved in the Laguno (P02080) study and in the Pegasys[1] (pegylated interferon alfa-2a) study (see table 7) as well as in the tested hypothesis.

Table 7: Sustained Virologic Response

	Pegylated interferon - ribavirin	IFN+Ribavirin
peginterferon alfa-2b		
Study P01017	27%	20%
Study P02080	44%	21%
peginterferon alfa-2a (Pegasys) Study NR15961	40%	12%

Efficacy results on secondary endpoint for Study P01017 - Histological Response at Week 72: Decrease in the METAVIR Score by at Least One Point (A or F), With Regards Histology at Baseline

Paired pretreatment and post-treatment histological results were available for 210 (51%) patients – [103 (50%) in the peginterferon alfa-2b/Rebetol arm versus 107 (52%) in the IntronA/Rebetol arm]. Sixty-four (64) patients were sustained virologic responders [37 (36%) in the peginterferon alfa-2b /Rebetol arm versus 27 (25%) in the IntronA/Rebetol arm]. The reasons for missing post-treatment results were refusal of biopsy in 148 cases (73%), failure to return in 46 cases (23%), and clotting disorders in 8 cases (4%).

[1] Pegasys (pegylated interferon alfa-2a) and Copegus (ribavirin) are currently authorised in the treatment of HCV in HIV-HCV co-infected patients at the dose of Pegasys 180 mcg once weekly and Copegus 800 mg per day for 48 weeks regardless of the genotype and HCV viral load. The scientific discussion on the extension of indication of Pegasys is available on the EMEA website.

Activity Scores- Metavir A
More patients improved (28%) than worsened (10%) in the peginterferon alfa-2b/Rebetol arm (p=0.0002). In the IntronA/Rebetol arm, no difference was noted (improvement 17%, worsening 17%).

Univariate logistic regression of SVR data - Study P02080

As expected, response rates in Stratum 1 (Genotype 2 or 3 with baseline low viral load) were higher than in Stratum 2 (Genotype 1 or 4 regardless of viral load and genotype 2 or 3 with high viral load) at all measured time points after Week 4.

Relapse rate (only provided for study P02080)

Twenty-two subjects (42.3%) in the peginterferon alfa-2b/ribavirin treatment arm had undetectable HCV RNA at both End of Treatment (EOT) and Follow up week 24 (FU24) compared with 9 subjects (20.9%) in the IntronA/ribavirin treatment arm. Relapse rates, defined as the probability of having detectable HCV-RNA at FU24 given that a subject had undetectable HCV RNA at EOT, were 6/28 (21.4%) in the peginterferon alfa-2b/ribavirin treatment arm and 0/9 (0%) in the interferon alfa-2b/ribavirin treatment arm. Only subjects with available data were included in the calculation of relapse rates.

Predictive Values of an Early Virologic Response

Study P01017
The combination of detectable serum HCV-RNA and a viral load decline of less than 2 log10 IU x 103/l from baseline predicted 91% of failures to achieve a sustained virologic response in the peginterferon group and 96% in the standard interferon group (P=0.15, Fisher's exact test). The corresponding rates at Week 12 were 99% and 100%, respectively (P=0.43). Undetectable HCV-RNA at Week 4 predicted 83% of sustained virologic responses in the peginterferon alfa-2b group and 80% in the standard interferon group (P=1.00). The corresponding rates at Week 12 were 70% and 73% (P=0.84).

Study P02080
An early virological response was defined as undetectable serum HCV RNA at treatment Week 4 (TW4) or treatment Week 12 (TW12). Subjects with missing data were excluded from the analysis.

- TW4 against FU24
As observed in other studies, early virologic response (EVR) to peginterferon alfa-2b/ribavirin at Treatment Week 4 has a strong positive predictive value for SVR. Of the peginterferon alfa-2b /ribavirin-treated subjects that had a virologic response at Week 4, 12/13 (92%) had SVR at FU24. In the interferon alfa-2b /ribavirin arm, 3/6 (50%) subjects with a virologic response at treatment Week 4 had SVR at FU24. The negative predictive value at treatment Week 4 was also calculated. Of the peginterferon alfa-2b /ribavirin-treated subjects that were nonresponders at Week 4, 28/39 (72%) did not reach SVR at FU24. In the interferon alfa-2b/ribavirin arm, 31/37 (84%) subjects that were nonresponders at treatment Week 4 did not reach SVR at FU24.

- TW12 against FU24
Of the peginterferon alfa-2b /ribavirin-treated subjects that had a virologic response at Week 12, 21/28 (75%) had SVR at FU24. In the interferon alfa-2b/ribavirin arm, 8/15 (53%) subjects with a virologic response at treatment Week 12 went on to have SVR at FU24. The negative predictive value at treatment Week 12 was very strong as has been previously reported. Of the peginterferon alfa-2b/ribavirin-treated subjects that were nonresponders at Week 12, 22/24 (92%) did not reach SVR at FU24. In the interferon alfa-2b/ribavirin arm, 27/28 (96%) subjects that were nonresponders at treatment Week 12 did not reach SVR at FU24.

Study P02080 - Analysis by Baseline Factors

HCV Genotype:
Subgroup analysis of the virology data demonstrates a difference between treatment groups in the proportion of subjects with Genotype 1 reaching SVR; 39.3% in the peginterferon alfa-2b/ribavirin treatment arm versus 11% in the interferon alfa-2b/ribavirin arm. For subjects with genotypes 2/3, the rates of SVR between the 2 treatment groups were similar; 53% in the peginterferon alfa-2b/ribavirin arm versus 47% in the interferon alfa-2b/ribavirin arm. Few subjects were infected with Genotype 4 (n=4, peginterferon alfa-2b/ribavirin; n=9, interferon alfa-2b/ribavirin) and of those 13 subjects, only 1 had a SVR

Baseline HCV Viral Load:
A higher percentage of subjects with low Baseline levels of HCV RNA (<800,000 IU/ml) reached SVR in the peginterferon alfa-2b/ribavirin treatment group (59%) compared with the interferon alfa-2b /ribavirin treatment arm (31%). As expected, the number of subjects with high baseline levels of HCV RNA (≥800,000 IU/ml) who obtained SVR was lower overall; however, subjects treated with peginterferon alfa-2b/ribavirin had a higher response rate than those who were treated with Intron A/ribavirin (29%, peginterferon alfa-2b/ribavirin; 15%, interferon alfa-2b/ribavirin).

Liver Fibrosis Score:
The extent of liver fibrosis also affected response rate; more subjects with low fibrosis grades (0 to 2) achieved SVR in the peginterferon alfa-2b/ribavirin treatment arm (49%) compared with the interferon alfa-2b/ribavirin treatment arm (21%). Response rates in subjects with advanced fibrosis (grades 3 to 4) were slightly higher in subjects treated with peginterferon alfa-2b/ribavirin versus interferon alfa-2b /ribavirin (33%, peginterferon alfa-2b /ribavirin; 23%, interferon alfa-2b /ribavirin).

HIV Variables:
Forty-eight percent of subjects with high $CD4^+$ cell count (>560 x 106 cells/mm^3) and in the peginterferon alfa-2b/ribavirin group achieved SVR compared with 20% in the interferon alfa-2b /ribavirin treatment group. The benefit of peginterferon alfa-2b/ribavirin versus interferon alfa-2b /ribavirin can also be observed in subjects with lower $CD4^+$ counts at baseline (40%, peginterferon alfa-2b/ribavirin; 22%, interferon alfa-2b /ribavirin). As expected, response rates based on baseline HIV viral load (≤200 copies/ml versus >200 copies/ml) trended in the same direction as baseline $CD4^+$ counts. Those subjects with low baseline HIV viral load did slightly better than those with higher viral loads and those treated with peginterferon alfa-2b/ribavirin had better response rates than those treated with interferon alfa-2b/ribavirin.

Age and Gender:
All subjects were between 30 and 59 years old (median = 40 years old). Response rates were consistently higher for peginterferon alfa-2b/ribavirin versus IntronA/ribavirin, regardless of age. There were more male subjects in the study and the response rate in that subgroup was lower than in female subjects in the peginterferon alfa-2b/ribavirin treatment arm; however, regardless of gender, peginterferon alfa-2b/ribavirin-treated subjects had higher SVR than did interferon alfa-2b/ribavirin-treated subjects.

Discussion on Clinical Efficacy

Sustained virologic response rates

In the RIBAVIC study the results observed in the pegylated arm were quite low as compared to the results achieved in the Laguno and Pegasys study as well as in the tested hypothesis. These results are mainly driven by the poor response observed in genotype 1 and 4 (17%), that is less than what is observed in the Laguno study (38%). In the APRICOT study with Pegasys, SVR in genotype 1 was 29%.

Overall, given that the population enrolled in the RIBAVIC and Laguno studies were very similar it is difficult to draw a formal explanation as to the differences in SVR that are only observed in the pegylated-interferon alfa-2b arm. It can be questioned however whether the lower than expected

efficacy with peginterferon alfa-2b in the RIBAVIC study might not reflect some over-compensation in dose reduction in order to manage the high rate of haematological adverse events observed.

The CHMP requested a comparison between the RIBAVIC and Laguno studies with regards to dose reduction and discontinuation due to haematological adverse reactions in order to be able to conclude whether a difference in the treatment discontinuation due to anaemia and neutropenia could explain the difference in the response rate in the peginterferon alfa-2b arm between both studies. In this field the CHMP also requested the MAH to provide an analysis of the use of growth factors to manage haematological adverse events (AEs) in each of the studies.

The use of Erythropoietin (EPO) was not allowed in the Spanish study and was minimal in the ANRS study. The use of other growth factors than EPO in the ANRS study pertained to approximately 13% of patients with neutropenia (15% in the peginterferon alfa-2b arm and 10% in the IntronA arm). The CHMP decided that no conclusion could be drawn based on such limited data.

The proportion of patients with dose reduction of ribavirin (in the peginterferon alfa-2b arm) for anaemia and the proportion of patients with dose reduction of peginterferon alfa-2b for neutropenia were both higher in the Laguno study compared to the RIBAVIC study. Moreover, the number of discontinuations due to anaemia or neutropenia in the peginterferon alfa-2b arm was similar in both studies. In view of the large difference in the SVR rate observed in the peginterferon alfa-2b arm in the RIBAVIC study as compared to the Laguno study, which is surprisingly not observed for the IntronA arm, the only reason that could explain this difference would have been a difference in the incidence of neutropenia (which is expected to only impact the peginterferon alfa-2b arm). However, the incidence of neutropenia reported in the Laguno study was higher, which argues against this hypothesis. The MAH suggests that a higher ribavirin dose and closer patient management in the Laguno study explain the difference in the SVR rate observed in the peginterferon alfa-2b arm in the RIBAVIC study, however these factors would have been expected to impact both peginterferon alfa-2b/RBV and standard Interferon/RBV arms and so cannot explain the difference.

Overall, the mechanism behind the lower SVR rate reported in the peginterferon alfa-2b/RBV arm in the RIBAVIC study as compared to the Laguno Study remains unclear.

Weight based ribavirin dose

The CHMP noted that the MAH makes a recommendation using the treatment duration of the pivotal RIBAVIC study and the ribavirin dose close to the Laguno study (in line with the recommended weight based dose in monoinfected patients). Nevertheless, these recommendations are reasonable insofar as a 48 weeks treatment duration may be required to achieve HCV viral clearance. Whilst the CHMP agreed to the 48 week treatment duration, the committee noted that current discussions within the scientific community tend to favour a 24 weeks treatment duration of HIV/HCV co-infected patients with genotype 2/3 as for monoinfected patients, provided that they achieve undetectability at week 4. Therefore the CHMP agreed that this issue will be further discussed by the MAH in the frame of a follow up measure.

In order to ensure a positive benefit/risk ratio of the partially tested recommendation with regards to the ribavirin dose the MAH was requested to propose a modelisation to appreciate whether the gain in efficacy is not outweighed by the deterioration of the safety profile (anaemia).

The modelling approach used by the MAH included a smoothed plot of SVR rates by ribavirin dose expressed as mg/kg, and logistic regression analysis. This approach was considered as acceptable by the CHMP. Based on the modelling provided, a trend towards a well-balanced gain in efficacy versus loss in safety (anaemia) was observed (e.g. as compared to the group receiving <10.6mg/kg RBV, patients receiving >13.3mg/kg RBV showed increase in SVR rate: +16% and increase in anaemia occurrence: +20%). Therefore, a favourable benefit-risk ratio of the weight-base ribavirin dose in co-infected patients is expected. Furthermore, from an efficacy point of view the recommendation of a weight-based ribavirin is considered as a conservative measure in this particularly difficult-to-treat population. This approach is also in line with the current European Consensus conference on HIV/HCV co-infection. Overall, the MAH's proposal to recommend a weight-based dose of ribavirin for co-infected patients, as for monoinfected, is supported by the CHMP.

Histological response

The CHMP noted that only 51% of biopsies were obtained from patients enrolled in the P01017 study. Although it is acknowledged that to some extent obtaining 51% of the biopsies might well have been challenging, it remains that the lack of histological data for approximately half of the population enrolled is unfortunate for a reliable interpretation of the histological data. The MAH was requested to further address this issue in order to specify to what extent the population with biopsies is representative of the overall population. Based on a comparison of demographic and clinical characteristics of subjects who did and did not undergo biopsy (Carrat *et al*[1]), it was found that overall, subjects differed only with respect to the mean fibrosis score. Categorical analysis of the METAVIR fibrosis score, although not significant, showed that the mean difference was mainly due to a difference in the proportions of scores F2 and F3. More subjects who underwent biopsy scored F3 (29%) and fewer scored F2 (36%) compared to subjects who did not undergo biopsy (F3 17%, F2 42%). It is noteworthy that the frequency of cirrhosis (F4) was similar between the groups.

In order to evaluate the bias that may have resulted from this imbalance, ANRS carried out a subgroup analysis of histological follow up data according to the fibrosis score (F2 or F3) (Carrat *et al*[2]). The analysis showed more severe progression of fibrosis in nonresponders with F3 than in those with F2. This result was expected, as progression of liver disease accelerates with time, and longer follow up would no doubt have led to similar conclusion in F2 subjects. However, the patterns of improvement in activity in responders were similar.

The CHMP concluded that extrapolation of the histological response observed in the 51% of patients with available biopsy to the overall population is acceptable.

Predictive Values of an Early Virologic Response

The CHMP consider that information on positive and negative predictive value is important. Therefore, inclusion of data on the predictability of response and non-response in HCV/HIV co-infected patients in the SPC is supported. Although not denying the interest of the predictability based on early response at Week 4, the predictability based on the early virological response at Week 12 should indeed be preferred for inclusion in the SPC at this time since more robust data are available as regards the predictive value of week 12 data (also derived from monoinfected patients).

1.3. Safety Results

Study P01017

Patient exposure

The clinical safety in patients in study P01017 was assessed on a total of 234 patients who remained on study at week 48 ; 118 (60.8%) in the peginterferon alfa-2b and Rebetol arm; 116 (61.4%) in the IntronA and Rebetol arm.

Adverse events

Overall, there were more haematological adverse events in the peginterferon alfa-2b arm compared to the IntronA arm (neutropenia 26% versus 14%, thrombocytopenia 11% versus 5%, anaemia 10% versus 6%) and more injection site reaction in the peginterferon alfa-2b arm (23% versus 2% in the IntronA arm). By contrast a higher proportion of patients experienced psychiatric adverse events in the IntronA arm compared to the peginterferon alfa-2b arm (e.g. depression 28% in the IntronA group versus 23% in the peginterferon alfa-2b group, insomnia 21% versus 14%) and a higher incidence of $CD4^+$ lymphocytes decreased was also observed in the IntronA group.

While it is well-known that peginterferon alfa-2b is associated with more injection site reaction than standard interferon, the differences observed in terms of haematological abnormalities are somewhat surprising, all the more that the distribution of baseline antiretroviral therapy treatment was similar between both treatment groups.

Compared to existing safety data in HCV monoinfected patients, the rate of adverse events reported in co-infected patients in the peginterferon alfa-2b group in this study were overall similar to those reported in HCV monoinfected patients treated with peginterferon/ribavirin therapy. However, as rather expected a higher rate of haematological adverse events (especially thrombocytopenia) was observed in the co-infected population receiving peginterferon alfa-2b/ribavirin treatment as compared to data in HCV monoinfected patients (thrombocytopenia < 5% as noted in the peginterferon alfa-2b SPC).

Severity of adverse events

132 (68%) patients treated in the peginterferon alfa-2b/Rebetol arm had at least one Grade 3 or 4 event versus 113 (60%) in the IntronA/Rebetol arm (P=0.11 Fisher's exact test).

68 (35%) patients had at least one reported SAEs [from Day 0 (D0) to W72)] in the peginterferon alfa-2b/Rebetol arm versus 68 (36%) in the IntronA/Rebetol arm (P=0.92 Fisher's exact test).

No significant differences were observed between both treatment groups in terms of severity of adverse events. However the rate of Grade 2 and Grade 3 adverse events in the System Organ Class (SOC) Blood and lymphatic disorders was twice and three times as elevated in the peginterferon alfa-2b arm as in the IntronA arm respectively, while the proportion of Grade 4 haematological adverse events was similar in both treatment groups.

Death

Overall, there were ten deaths in the RIBAVIC study [7 were presented in the clinical study report (CSR), 2 were not recorded in the CSR since they were registered from cohort follow-up of included patients]: 6 occurred in the peginterferon alfa-2b arm, 3 in the IntronA arm, and one for which it is unknown whether the subject was treated with peginterferon alfa-2b /ribavirin or interferon alfa-2b/ribavirin.

The causes of death were:
In the peginterferon alfa-2b arm:

- 1 anoxia after inhalation of propyle nitrite
- 1 neuroendocrine carcinoma with metastasis
- 1 cirrhosis with hepatorenal syndrome, this case was related to anti-hepatitis C treatment
- 1 vulvar cancer with metastasis (HCV RNA negative, excluded)
- 1 oedemato-ascitic decompensation and hepatic encephalopathy
- 1 hepatic decompensation

In the IntronA arm:

- 1 oedemato-ascitic decompensation of C virus cirrhosis, hepatocellular insufficiency and hepatic encephalopathy
- 1 hepatocellular carcinoma with bone metastasis
- 1 hepatic decompensation

The last fatal case (unknown whether the patient received peginterferon alfa-2b or IntronA) was also due to hepatic decompensation in a patient with history of cirrhosis and oesophageal varicoses veins.

Overall there were seven subjects with cirrhosis at baseline that died during the study. Six of the deaths were due to hepatic decompensation. Of the 7 deaths of subjects with cirrhosis one was a subject who died after randomisation but prior to first dose and another was treated for 4 weeks but was found to be HCV negative (ineligible subject).

HIV-HCV co-infected patients with cirrhosis at baseline were identified as being at higher risk for developing hepatic decompensation. Treatment with didanosine and elevated bilirubin were also identified as a risk factor for severe liver disorders. These data reinforce the need of a strong warning for close monitoring of all co-infected patients receiving both antiretroviral and anti-hepatitis therapy to detect any event suggesting a hepatic decompensation in order to immediately discontinue the treatment in this case.

Adverse events leading to discontinuation

Overall, 33 of 194 patients in the peginterferon alfa-2b arm (17%) and 29 of 189 patients in the IntronA arm (15%) discontinued treatment due to adverse events. The main adverse events leading to treatment discontinuation were depression (5 patients), drug intolerance (4), treatment non compliance (4), anaemia (3) and asthenia (3) in the peginterferon alfa-2b treatment group and depression (7 patients) and drug intolerance (5) in the IntronA treatment group. Of note, two patients stopped peginterferon alfa-2b and Rebetol treatment due to mitochondrial cytopathy and 3 patients due to lactic acidosis or blood lactic increased versus none and 1 patient in the IntronA group respectively.

Adverse events leading to dose reduction

Table 8 below presents the percentage of patients having experienced dose modification in each treatment group:

Table 8 Dose modification

	peginterferon alfa-2b Ribavirin (n=194)	Ribavirin	IntronA Ribavirin (n=189)	Ribavirin	p-value(*)	p-value(*) Ribavirin
Total	45 (23%)	34 (18%)	20 (11%)	17 (9%)	0.001	0.016
Total (one of the two treatment)	54 (28%)		23 (12%)		<0.001	

The proportion of patients with dose modification (interferon and ribavirin or ribavirin alone) was twice as important in the peginterferon alfa-2b arm as in the IntronA arm. The differences were all statistically significant. These differences were mainly supported by higher percentages of haematologic adverse events leading to dose reduction in the peginterferon alfa-2b group (i.e anaemia, neutropenia and thrombocytopenia) as detailed below.

Laboratory findings

Haemoglobin
2% of patients in the peginterferon alfa-2b arm experienced Hb<8g/dl versus 0 in the IntronA arm. The percentage of patients with dose modification and discontinuation for anaemia was higher in the peginterferon alfa-2b group (10% and 1.5% respectively) compared to the IntronA group (4% and 1 % respectively)

Neutrophils
15% and 4% of patients in the peginterferon alfa-2b group had a Grade 3 and Grade 4 neutropenia compared to 9% and 2% respectively in the IntronA group. 7% of peginterferon alfa-2b -treated patients experienced dose modification for neutropenia versus 3% of IntronA-treated patients. Moreover, one additional patient permanently discontinued treatment in the peginterferon alfa-2b arm due to severe neutropenia.

Platelets
4% and 1% of patients in the peginterferon alfa-2b arm developed Grade 3 and Grade 4 decreases in platelets respectively versus 1% and 0% of patients in the IntronA arm. Again, dose modification for thrombocytopenia occurred more often in the peginterferon alfa-2b group (5%) compared to the IntronA-treated patients (1%). Moreover, one additional patient permanently discontinued treatment in the peginterferon alfa-2b arm due to severe thrombocytopenia.

Overall the peginterferon alfa-2b and ribavirin arm was significantly associated with a higher rate of Grade 3/4 haematological abnormalities compared to IntronA arm. When comparing with data in monoinfected patients, it is worth noting that anaemia, neutropenia and thrombocytopenia occurred more frequently in HCV-HIV co-infected patients.

HIV disease-related laboratory findings

$CD4^+$ lymphocytes

13% of patients in the peginterferon alfa-2b arm (n=25) compared to 24% of patients in the IntronA arm (n=45) experienced a $CD4^+$ lymphocyte decrease of $<200/mm^3$ during treatment. It should be noted that safety data in patients with $CD4^+$ cell count$<200/mm^3$ remains very limited since these patients had not the possibility to be included in the study (16 patients had protocol violation with $CD4^+$ cell count $< 200/mm^3$).

$CD4^+$ cell count decreased while on therapy and returned to baseline value after the end of treatment similarly in both treatment groups. In this study, there was no dose modification or permanent study drug discontinuation due to lymphopenia $CD4^+$.

HIV viral load

No significant change in viral load in either treatment group was observed in this study.

Important clinical adverse events

Mitochondrial toxicity (symptomatic hyperlactatemia and pancreatitis)

Symptomatic mitochondrial toxicity was diagnosed during the study period in 11 patients (symptomatic hyperlactatemia and pancreatitis in 6 and 5 patients, respectively). Nine of the eleven patients were in the peginterferon alfa-2b/Rebetol arm. The regimes included didanosine in every case, stavudine in 8 cases and lamivudine in 3 cases, abacavir in 1 case, protease inhibitor in 3 cases and Non-Nucleoside analogue Reverse Transcriptase Inhibitors (NNRTIs) in 5 cases. Antiretroviral treatment was stopped in seven cases. Anti-HCV treatment was discontinued in 8 patients. All but two of the patients had a full recovery (one patient with neuropathy had stable disease and one patient died 15 months later from liver failure despite a sustained HCV virological response).
According to univariate analysis, the intake of didanosine is the only factor significantly associated with an increased risk of symptomatic mitochondrial toxicity. Multivariate analysis showed that didanosine, with or without stavudine, was associated with symptomatic mitochondrial toxicity (OR 46, 95% CI 7.4 to infinity; $p < 0.001$) compared to regimens with neither didanosine nor stavudine.

Spontaneous hepatic decompensation (defined as onset of ascites, jaundice (serum bilirubin >51 µmol/l), hepatic encephalopathy, bleeding from oesophageal varices)

Nine patients presented spontaneous hepatic decompensation. Two of them were related to hepatocellular carcinoma and staphylococcus septicaemia and were therefore excluded. On the remaining seven cases (i.e 3 in the peginterferon alfa-2b arm and 4 in the IntronA arm), 5 also had cirrhosis. All the patients were receiving antiretroviral treatment at the onset of decompensation (didanosine in 5 cases, stavudine in 4 cases, lamivudine in 2 cases, abacavir in one case, nelfinavir in 4 cases, efavirenz in one case and ritonavir/saquinavir in one case). Five patients died as a result of hepatic decompensation (all 3 patients in the peginterferon alfa-2b arm and 2 patients in the IntronA arm). There was also a sixth fatal case as a result of hepatic decompensation but the treatment received by the patient (peginterferon alfa-2b or IntronA) was not specified.
According to univariate analysis, spontaneous hepatic decompensation was significantly associated with higher duration of HIV infection, lower $CD4^+$ cells, higher liver fibrosis score assessed by the METAVIR scoring system, higher total bilirubin, phosphatase Alkalin and gamma glutamyl transferase levels, lower platelets, leucocytes, albumin and prothrombin time, higher duration of antiretroviral treatment, didanosine treatment and higher duration of didanosine treatment. In the multivariate analysis, didanosine (OR, 8.8; 95% CI, 1.2 to 102.3, $p < 0.02$), cirrhosis (METAVIR score of F4) (OR, 8.8; 95% CI, 1.2 to 104.2, $p < 0.02$) and elevated bilirubin (above the normal) (OR, 7.9; 95% CI, 1.08 to 93.3, $p < 0.03$) remained significantly associated with spontaneous hepatic decompensation.

Study P02080

Patient exposure

The extent of exposure was not provided in the study report since subject data regarding start and stop dates of study drugs were not included in the database provided to the MAH. However data on 95 subjects contributed to the assessment of the safety in this study.

Adverse events

There was a higher incidence of adverse events in study P02080 than in the previously discussed RIBAVIC study. One explanation proposed by the MAH is that a bias due to small sample size in study P02080 cannot be ruled out. Moreover, this may be explained by the design of the study i.e. a single-center study with close monitoring and more robust adverse event reporting. However, the safety profile of peginterferon alfa-2b plus ribavirin therapy in HIV-HCV co-infected patients is overall similar between the two studies in terms of adverse events reported.

In line with the results of RIBAVIC study, in the Laguno study there were more flu-like symptoms in the peginterferon alfa-2b arm compared to the IntronA arm (46% versus 32% in the IntronA arm) and more haematological abnormalities (anaemia, thrombocytopenia and leukopenia) in the peginterferon alfa-2b arm compared to the IntronA arm (29% versus 19% in the IntronA arm). However, few patients with blood disorders required dose discontinuation or modification. Psychiatric disorders, in particular depression, were reported more frequently in the IntronA arm (19% versus 22% for the IntronA arm). Irritability was also more frequently reported in the IntronA arm (14% versus 18% for the IntronA arm). Again, the proportion of patients with blood disorders was significantly higher in co-infected patients compared to a population of monoinfected patients.

Severity of adverse events

65% of subjects in both treatment arms experienced a severe or serious adverse event as defined in the Case report Form. The most commonly reported adverse event was depression (20%) and the frequency was comparable between the two groups (19% for peginterferon alfa-2b arm and 21% for IntronA arm).

Concerning blood disorders, there were marked differences in the percentage of patients with mild to moderate blood disorders that were more frequently reported in the peginterferon alfa-2b arm. These data are in line with the results of RIBAVIC study.

Death

No deaths were reported during this study

Adverse event leading to dose discontinuation

There were 14 patients who experienced serious adverse events leading to dose discontinuation (9/52 (17%) in the peginterferon alfa-2b group and 5/43 (12%) in the IntronA group). In both treatment arms, the most common adverse event leading to treatment discontinuation was flu-like symptoms.

Adverse event leading to dose modification

There were 48 patients (51%) who experienced adverse events leading to dose modification (25/52 (48%) in the peginterferon alfa-2b group and 23/43 (53%) in the IntronA group). The most common adverse event resulting in study drug modification was depression in 8 (15%) and 9 patients (21%) in the peginterferon alfa-2b and IntronA group respectively. There were a higher proportion of patients who had leukopenia resulting in dose modification in the peginterferon alfa-2b group (13%) versus 7% in the IntronA group. However, the rate of study drug dose modification for anaemia was greater in the IntronA arm (16% versus 8% in the peginterferon alfa-2b group). The number of patients who had dose modification for thrombocytopenia was similar between both treatment groups (4-5%).

Laboratory findings

Absolute mean $CD4^+$ cell counts decreased in both study arms during treatment and the nadir was reached at week 36. After the completion of HCV therapy, the absolute mean $CD4^+$ cell counts increased to levels above baseline.

Important clinical adverse events

Mitochondrial toxicity

One patient in the peginterferon alfa-2b arm and 3 patients in the IntronA arm experienced hyperlactatemia during the course of the study. The peginterferon alfa-2b -treated patients received also didanosine and stavudine. In the IntronA arm, one patient was treated with didanosine, one was treated with stavudine and the last patient received both didanosine and stavudine.

Hepatic decompensation

No case of hepatic decompensation was discussed in the CSR of study P02080.

Discussion on clinical Safety

Overall, the safety profile of the combination of peginterferon alfa-2b and ribavirin in HIV-HCV co-infected patients is comparable to the one observed in HCV monoinfected patients. However haematological abnormalities (anaemia, neutropenia and especially thrombocytopenia) appear more frequently reported in the co-infected population than in monoinfected patients and at a higher rate in peginterferon alfa-2b –treated patients than in IntronA treated patients. However these adverse events were generally not associated with clinical symptoms, can be adequately managed by dose modification and overall do not require permanent drug discontinuation. A specific paragraph on this issue has been included in section 4.4 and 4.8 of the SPCs of Rebetol and peginterferon alfa-2b.

Concerning HIV-related disease characteristics, no significant change in viral load in either treatment group was observed. $CD4^+$ cell count decreased while on therapy and returned to baseline values after the end of treatment similarly in both treatment groups. There was no dose modification or permanent study drug discontinuation due to lymphopenia $CD4^+$. The limited safety data in patients with $CD4^+$ cell count<200/mm^3 is of concern. This issue is the subject of a warning in section 4.4 of the SPCs of Rebetol and peginterferon alfa-2b.

Mitochondrial toxicities

One of the main safety concerns of the co-administration of antiretroviral treatment and HCV therapies is the risk of overlapping mitochondrial toxicities of both nucleosidic agents. The data derived from these studies confirm that the co-administration of didanosine and ribavirin is associated with a higher risk of mitochondrial toxicity and thus that this combination should not be recommended in clinical practice. The current Rebetol SPC adequately mentions the risk of mitochondrial toxicity in case of co-administration of didanosine or stavudine with ribavirin. The MAH should continue to closely monitor mitochondrial toxicity in co-infected patients receiving both anti-HIV and anti-HCV therapies.

Bani-Sadr *et al.* found that concomitant treatment of zidovudine with anti-HCV therapy was associated with an adjusted 3.3-fold higher risk of anaemia (OR=3.27, p=0.0008). This is in line with the APRICOT trial, where 50% of zidovudine treated patients had moderate to severe anaemia, compared to 30% in other patients (Torriani *et al*). Consequently, Bani-Sadr *et al.* recommend discontinuing zidovudine prior to HCV therapy in order to avoid anaemia and permit the use of higher ribavirin doses. In the SPC of Rebetol there is currently a mention that "patients treated with Rebetol and interferon/peginterferon alfa-2b combination therapy and zidovudine are at increased risk of developing anaemia". However, as the data provided by Bani-Sadr *et al.* lead to the conclusion that zidovudine discontinuation could help to avoid anaemia associated with anti-HCV therapy, it is mandatory to discuss the need for adopting a stronger warning. The MAH will therefore discuss this issue as part of a forthcoming FUM.

In line with clinical guidelines for HIV/HCV co-infection, the MAH suggests zidovudine should be excluded prior to HCV treatment to solve the problem of anaemia. However in one publication (Réndon *et al.*) dealing with this issue (anaemia by weight based ribavirin dosage in HIV co-infected patients) it was found that patients treated with concomitant zidovudine had a significantly higher ribavirin plasma-concentration at week 4. This finding is potentially important from a clinical point of view. The MAH has committed to discuss this finding, as this could imply that concomitant

zidovudine (with a possibly lower dose of ribavirin in case of anaemia) is not a problem from an efficacy point of view.

Finally some published data by Rodriguez-Torres M. *et al.* lead to question the clinical relevance of the *in vitro* inhibition of the zidovudine and stavudine phosphorylation by ribavirin. The MAH has committed to further discuss this issue.

Hepatic decompensation

The risk of hepatic decompensation in co-infected patients with cirrhosis treated with anti-HIV and anti-HCV therapies is already known. Overall, there were six deaths reported due to hepatic decompensation in the RIBAVIC study and during its follow-up period. Of note, a total of six deaths (n=859) was reported in the study supporting the extension of indication of Pegasys in co-infected patients (study NR15961). The SPC's of Rebetol/peginterferon alfa-2b already mention the risk of hepatic decompensation when anti-HCV treatment is added to antiretroviral treatment in co-infected patient as follows: "Co-infected patient with advanced cirrhosis receiving HAART may be at increase risk of hepatic decompensation and death. Adding treatment with alfa interferon alone or in combination with ribavirin may increase the risk in this patient subset". Factors other than cirrhosis that have found to be associated with hepatic decompensation are elevated bilirubin and didanosine treatment. These have also been included in the SPC. Furthermore, recommendations for the management of co-infected patients receiving both antiretroviral and anti-hepatitis treatment have been included in the SPC. Prescribers are advised that the Child-Pugh score should be monitored during treatment and patients progressing to hepatic decompensation should have their anti-hepatitis treatment immediately discontinued and the antiretroviral treatment reassessed.
The MAH has identified cirrhosis and didanosine intake as independent risk factors of spontaneous hepatic decompensation in co-infected patients receiving both antiretroviral drugs and HCV therapy. This reinforces the importance of the existing warning against the co-administration of didanosine and ribavirin that appears all the more warranted in HIV-HCV co-infected patients with history of cirrhosis.

Finally, the CHMP consider that initiation of treatment with interferon alfa-2b in co-infected patients with cirrhosis with Child-Pugh ≥ 6 is contraindicated.

1.4. Risk management

The CHMP agreed that a EU - Risk management plan would not be required for the extension of indication in the HIV/HCV co-infected target population.

1.5. Overall discussion and benefit risk assessment

Overall the MAH used two independently conducted studies to support this type II variation.

- One pivotal multicenter study conducted by the ANRS in a large sample size (RIBAVIC /P01017)
- One smaller investigator initiated performed in a single centre in Spain (Laguno/ P02080).

Whereas both studies are very similar as regards the population enrolled (in terms of immuno-virologic parameters, HIV and HCV history, distribution of HCV genotype) they differ on the ribavirin dose and on the treatment duration; whereas the ribavirin dose in the P02080 was in line with that recommended in monoinfected patients, a 800 mg non weight based dose was selected in the P01017 study. Moreover, whereas a 24 weeks treatment duration is now recommended in monoinfected genotype 2/3 the RIBAVIC study tested a 48 weeks treatment duration regardless of genotype or viral load. As a significant limitation of these studies, their results could not be extrapolated to HIV co-infected patients with low $CD4^+$ ($<200/mm^3$) and high viral load. Such a difficult-to-treat population is nevertheless critical in clinical practice. The MAH has proposed a warning for the SPC on the limited data available in HIV-HCV co-infected patients with $CD4^+$ $<200/mm^3$.

The MAH makes a recommendation using on one hand the treatment duration of the pivotal RIBAVIC study and on the other the ribavirin dose similar to the Laguno study (in line with the recommended weight based dose in monoinfected patients). The CHMP agreed that 48 weeks treatment duration was reasonable and may be required to achieve HCV viral clearance. However the MAH will further discuss the possibility of recommending 24 weeks treatment in HIV/HCV co-infected patients with genotype 2/3 provided that they achieve undetectability at week 4. This reflects current discussions in the scientific community that favour 24 weeks duration in genotype 2/3 patients.

The CHMP had concerns regarding the partially tested recommendation regarding the weight based ribavirin dose. A modelling provided by the MAH showed a trend towards a well balanced gain in efficacy versus loss in safety. Furthermore from an efficacy point of view the recommendation of weight based ribavirin is considered a conservative measure in this difficult to treat population. Therefore a favourable benefit risk balance is expected in this population.

In the RIBAVIC study the results observed in genotype 1 and 4 in the pegylated arm were quite low (17%), as compared to the results achieved in the Laguno study (38%) and the tested hypothesis. This should also be seen in light of the APRICOT study with Pegasys (SVR in genotype 1 in APRICOT was 29%). The difference in SVR rate was surprisingly not observed for the IntronA arm. The only reason that could explain this difference would have been a difference in the incidence of neutropenia (which is expected to only impact the peginterferon alfa-2b arm). However, the incidence of neutropenia as reported in the Laguno study was higher than in the RIBAVIC study, which argues against this hypothesis. Other factors that could explain the difference in the SVR rate observed included a higher ribavirin dose and closer patient management in the Laguno study, however these factors would have been expected to impact both peginterferon alfa-2b/RBV and standard Interferon/RBV and so cannot explain the difference observed. As the use of Erythropoietin was not allowed in the Spanish study and was minimal in the ANRS study, no conclusion on the impact of the use of EPO on the results could be made. Overall this issue remains unclear.

The main safety concerns of the co-administration of antiretroviral and HCV therapies are the risk of overlapping mitochondrial toxicities of both nucleosidic agents. The MAH has been requested to closely monitor mitochondrial toxicity in co-infected patients receiving both antiretroviral and anti-HCV therapy. The SPC of Rebetol adequately mentions the risk of mitochondrial toxicity in case of co-administration of didanosine or stavudine. However, the MAH has been requested to further discuss the need to reinforce the warning pertaining to the higher risk of anaemia in case of co-administration of zidovudine and ribavirin in the frame of a follow up measure in view of the publication by Bani-Sadr *et al.* who found that concomitant treatment of zidovudine with anti-HCV therapy was associated with an adjusted 3.3-fold higher risk of anaemia.

Although the MAH suggests excluding zidovudine prior to HCV treatment in order to solve the problem of anaemia, Réjdon *et al.* found that patients with concomitant zidovudine had a significantly higher ribavirin plasma concentration at week 4. This could imply that concomitant zidovudine (with a possibly lower dose of ribavirin in case of anaemia) is not a problem from an efficacy point of view. The MAH has committed to review this issue.

The second main safety concern of the co-administration of antiretroviral treatment and HCV therapies is the potential risk of hepatic decompensation. Overall, there were six deaths reported due to hepatic decompensation in the RIBAVIC study and during its follow-up period. The SPC of Rebetol/peginterferon alfa-2b already mentions the risk of hepatic decompensation when anti-HCV treatment is added to antiretroviral treatment in co-infected patient. However the data submitted show that factors other than cirrhosis are associated with a hepatic decompensation. These include elevated bilirubin and concomitant didanosine. This has been reflected in section 4.4 of the SPC along with a warning to prescribers to closely monitor patients Child-Pugh score and to discontinue treatment for HCV in patients progressing to hepatic decompensation

Overall the CHMP considered that the benefit risk balance for ViraferonPeg in the treatment of HCV in patients co-infected with HIV is positive. The modelling provided by the MAH to substantiate the benefit risk balance of the partially tested recommendation of higher ribavirin dose for coinfected patients provides reassurance of a favourable benefit/risk balance of the weight-based dose of ribavirin

in the coinfected patient. Furthermore this recommendation is considered a conservative measure on an efficacy point of view, in this particularly difficult-to-treat population. With regards to the agreed 48 weeks treatment duration it is recognised that there are current discussions within the scientific community that tend to favour 24 weeks of treatment for genotype 2/3 patients, provided that they achieve undectability at week 4. This will be further discussed by the MAH in the frame of a follow up measure. The main safety concerns of the co-administration of antiretroviral treatment and HCV therapies is the risk of overlapping mitochondrial toxicities of both nucleosidic agents and the potential risk of hepatic decompensation when antiretroviral treatment and HCV therapies are co-administered. This is reflected in the SPC. This extension of indication will lead to further discussion on the co-administration of NRTIs and ribavirin.

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