European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

London, 23 October 2008
EMEA/CHMP/650637/2008

ASSESSMENT REPORT FOR PEGASYS

International non-proprietary name/Common name: peginterferon alfa-2a

Procedure No: EMEA/H/C/000395/II/0036

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

LIST OF ABBREVIATIONS

AE	adverse event
CHC	chronic hepatitis C
CHMP	Committee for Human Medicinal Products
DITTO-HCV study	Dynamically Individualized Treatment of Hepatitis C Infection and Correlates of Viral/Host Dynamics study
FDA	Food and Drug Administration
HALT-C study	Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis study
HbeAg	hepatitis B e antigen
HCV	hepatitis C virus
IFN	interferon
NIH	National Institutes of Health
NNT	number needed to treat
NPV	negative predictive value
PPV	positive predictive value
PEG-IFN alfa	peginterferon alfa
PEG-IFN alfa-2a	peginterferon alfa-2a (Pegasys)
PEG-IFN alfa-2b	peginterferon alfa-2b (PegIntron)
RBV	ribavirin
RNA	ribonucleic acid
sc	subcutaneous
SVR	Sustained Virological response

III. SCIENTIFIC DISCUSSION

3.1. Introduction

Pegasys (peginterferon alfa-2a, PEG-IFN alfa-2a) is a chemically modified interferon alfa formed by the covalent attachment of a 40-kilodalton single branched methoxy polyethylene glycol moiety to recombinant interferon alfa-2a.

PEG-IFN alfa-2a, alone or in combination with ribavirin, is currently approved for the treatment of chronic hepatitis C (CHC) in treatment-naïve adult patients who are positive for hepatitis C virus (HCV) infection, including patients with compensated cirrhosis and/or clinically stable human immunodeficiency virus. PEG-IFN alfa-2a is also indicated for the treatment of chronic hepatitis B in patients with either hepatitis B e-antigen (HBeAg)-positive or HbeAg-negative disease. The optimal way to use PEG-IFN alfa-2a in patients with CHC is in combination with ribavirin. PEG-IFN alfa-2a monotherapy is mainly reserved for patients who are intolerant of ribavirin or in whom ribavirin is contraindicated.

Chronic Hepatitis C is a worldwide health problem with 170 million HCV carriers globally including 4 million in the United States and 9 million in Europe**.** Of those who become infected with HCV, approximately 80% will progress to chronic liver disease that may ultimately lead to cirrhosis, hepatocellular carcinoma, liver transplantation and death. The prevalence of end-stage liver disease secondary to HCV accounts for approximately 50% of the liver transplants in the United States and Europe. Despite the decreased number of new HCV infections in the last decade, the prevalence of advanced CHC-related liver disease is on the rise as a result of the significant lag period between the onset of infection and the development of decompensated cirrhosis and hepatocellular carcinoma.

The goal of HCV treatment is achievement of a SVR, which is defined as the absence of HCV RNA in serum by a sensitive test at the end of treatment and 6 months later. Over the past several years, considerable advances have been made in the treatment of treatment-naïve patients with CHC. The first effective treatment identified used IFN alfa monotherapy and resulted in SVRs of between 15% and 20%, which later increased to between 35% and 40% with the use of IFN alfa in combination with ribavirin and more recently to greater than 50% with the combination of PEG-IFN alfa and ribavirin. This combination is considered to be the current standard of care for treatment-naïve patients.

As improvements in treatment outcome and the widespread use of PEG-IFN alfa plus ribavirin combination therapy have led to an increase in the number of treatment-naïve patients receiving treatment for CHC, a growing patient population of treatment failures from this regimen has emerged. Patients with certain demographic and disease characteristics have been found to be less likely to achieve an SVR. Thus, nearly half of the patients with HCV genotype 1 and 20% to 30% of patients with genotype 2 or 3 infection do not respond to the current standard of care, and patients with advanced cirrhosis, high baseline HCV RNA viral load, higher body weight, and black race have a lower probability of achieving an SVR.

Several small clinical studies in non-responders to previous treatment have identified the importance of patient and disease characteristics, type of previous treatment regimen and the potency of the re-treatment regimen on re-treatment outcome. Several pilot studies have been conducted in non-responders and relapsers to previous IFN alfa monotherapy or IFN alfa plus ribavirin combination therapy and have demonstrated that these patients can achieve an SVR when re-treated with PEG-IFN alfa-2a plus ribavirin combination therapy but also to a lower extent than that attained in treatment-naïve patients. Studies demonstrated that the overall SVR achieved after re-treatment is widely variable and depends on the pattern of previous treatment failure (relapse or non-response), the type of previous treatment (IFN alfa or PEG-IFN alfa), and baseline prognostic factors known to impact treatment outcome in treatment-naïve patients (genotype, fibrosis stage, baseline viral load).

Unfortunately no clear treatment strategy has emerged from the multiplicity of small pilot studies conducted in non-responders and relapsers to a first course of treatment.

In this clinically challenging environment associated with re-treatment, the 2002 National Institutes of Health consensus statement remains pertinent even today, advising that retreatment decisions should be based upon multiple considerations (previous type of response, previous type of treatment, the relative potency of the re-treatment regimen, severity of the underlying liver disease, and viral genotype). New drug development directed at a number of different viral targets is anticipated to provide new treatment strategies and improve outcomes for all patients with CHC. However, until these potential new treatments become available for CHC non-responder and relapser patients who remain at risk for further liver disease progression, this unmet medical need requires identification of the best available treatment strategy utilizing currently available agents.

The basis of this variation is to support an extension of the indication for PEG-IFN alfa-2a and ribavirin combination therapy to include re-treatment of patients who failed previous IFN alfa- or pegylated IFN alfa-based therapy. The submission is based on one pivotal study, study MV17150, conducted in patients not responding, i.e. not achieving non-detectable hepatitis C virus at week 12 or later on treatment with PEG-IFN alfa 2b and weight adjusted ribavirin. Supportive data derive from an NIH sponsored study, HALT-C where the primary objective was to study the hypothesised anti-fibrotic effects of low dose IFN and two small single (relapsers) arm studies. Supportive safety data was also available from 3 further studies.

Clinical efficacy

The clinical development program to support the extension of the indication include an international, pivotal study, MV17150. This was a phase III, randomised, open-label, multicenter (n=106), efficacy and safety study examining the effects of duration of treatment and of a high induction dose of Pegasys in combination with daily ribavirin in patients with chronic hepatitis C who did not respond to previous peginterferon alfa-2b/ribavirin combination therapy.

In addition to the pivotal study, the lead-in phase of the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial provided both efficacy and safety data in non-responders who were treated with PEG-IFN alfa-2a and ribavirin for 48 weeks. The HALT-C trial was a prospective, randomised, controlled study of long-term PEG-IFN alfa-2a monotherapy versus no therapy in patients with chronic hepatitis C and advance fibrosis or cirrhosis who failed to achieve an SVR following treatment with IFN with or without ribavirin and remained virus-positive after 20 weeks of re-treatment with PEGIFN alfa-2a plus ribavirin in the lead-in phase. Patients who achieved undetectable levels of virus at week 20 remained on combination therapy for a total of 48 weeks and were then followed for 24 weeks.

Efficacy data from two supportive studies in relapsers after previous treatment with PEG-IFN alfa-2a plus ribavirin who were re-treated for 72 weeks or for 48 weeks are also provided:

- Study WV16143 was an open-label, multicenter, re-treatment trial in 64 CHC Patients.
- Kaiser *et al* (2007)[1] study was an academic study and evaluated 120 mostly genotype 1 CHC patients.

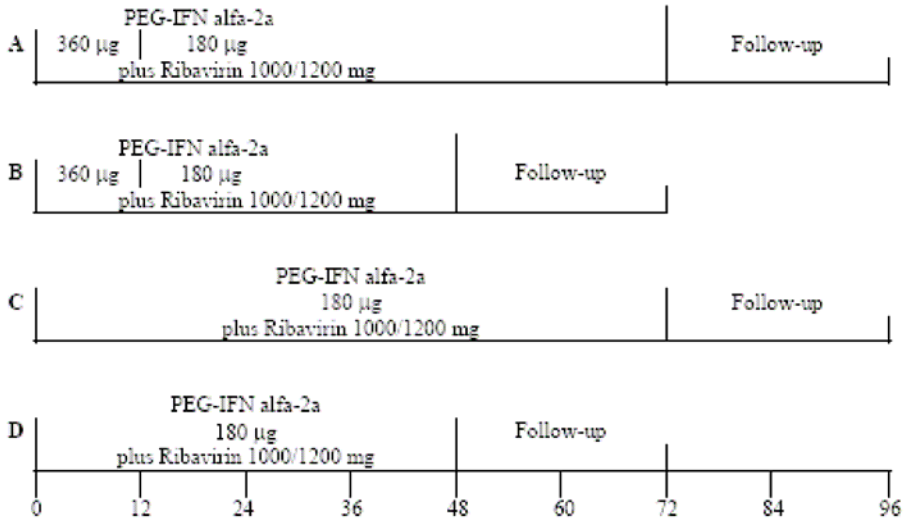
[1] Kaiser S, Lutze, B, Sauter B, et al.Retreatment of HCV genotype 1 relapse patients to peginterferon/ribavirin therapy with an extended treatment regimen of 72 weeks with consensus interferon/ribavirin versus peginterferon alfa/ribavirin. Presented at the 58th Annual Meeting of the American Association for the Study of Liver Disease, November 2-6, 2007.Boston MA.

Study MV17150

Study Design and treatment

Study MV17150, which is also referred to by the acronym REPEAT, was a phase III, multicenter, international, randomised, open-label, parallel-group trial designed to evaluate the efficacy and safety of the combination of an induction dose of PEG-IFN alfa-2a, 360 µg given for 12 weeks followed by 180 µg for 60 weeks, and ribavirin, 1000 or 1200 mg given for 72 weeks, compared with 48 weeks of treatment with 180 µg of PEG-IFN alfa-2a and 1000 or 1200 mg of ribavirin in CHC patients who had not responded to previous PEG-IFN alfa-2b and ribavirin combination therapy given for at least 12 weeks. See Figure 1.

Figure 1 Study Design



Patient Selection

- Serological evidence of HCV infection confirmed by an anti-HCV antibody test.
- Serum HCV RNA quantifiable at >600 IU/ml by the Roche Amplicor HCV Monitor Test v2.0 or another quantitative HCV RNA polymerase chain reaction (PCR)-based test, which reported the HCV RNA assessment at screening in international units.
- Non-responders to previous therapy with PEG-IFN alfa-2b and ribavirin combination therapy given for at least 12 weeks (defined as detectable HCV RNA at every assessment after initiation of PEG-IFN alfa-2b and ribavirin combination therapy, with at least one HCV RNA test performed on treatment after a minimum of 12 weeks of therapy). Patients had to have received at least 1.0 µg/kg of PEG-IFN alfa- 2b weekly and 800 mg of ribavirin daily as the starting dose.
- Compensated liver disease.
- Patients who had prematurely discontinued previous PEG-IFN alfa-2b and ribavirin treatment for haematological adverse events were excluded from this study.

Randomisation

Enrolled patients were randomised in a 2:1:1:2 ratio to one of the four treatment groups (A, B, C, D). See Figure 1. The permuted blocks randomization was stratified by geographical region, HCV genotype (type 1 vs non-1), and cirrhosis stage (cirrhosis or transition to cirrhosis vs no cirrhosis).

Statistical Hypothesis

The primary objective of the study was to demonstrate that the sustained virological response in group A (high induction dose and 72 weeks of treatment) was superior to that in group D (180-µg dose and 48 weeks of treatment). The test was stratified by HCV genotype, geographical region, and cirrhosis status.

The secondary objectives of this study were to investigate:
a) Whether the induction PEG-IFN alfa-2a dose of 360 µg was superior to the standard PEG-IFN alfa-2a dose of 180 µg.
b) Whether the treatment duration of 72 weeks was superior to the treatment duration of 48 weeks.
c) Whether group A was superior to group B.
d) Whether group C was superior to group D.
e) Whether group A was superior to group C.
f) Whether group B was superior to group D.
g) Whether group B was superior to group C.

For the secondary objective (a), the sustained virological response in groups A + B was compared with that in groups C + D. The Cochran-Mantel-Haenszel test was stratified by the study treatment duration (48 vs 72 weeks), genotype, geographical region, and cirrhosis status. For the secondary objective (b), the sustained virological response in groups A + C was compared with that in groups B + D. The Cochran-Mantel-Haenszel test was stratified by the PEG-IFN alfa-2a induction dose (360 vs 180 µg), genotype, geographical region, and cirrhosis status.

All tests were two-sided at a significance level of 0.05. No alfa adjustment was considered necessary because only the statistical test for the primary objective was considered confirmative, whereas the statistical tests of the secondary objectives were considered supportive only.

Other secondary efficacy parameters included virologic response at the end of treatment and after 12, 24, and 48 weeks of treatment (groups A + B vs groups C+ D) and evaluation of the safety of the high induction dose of 360 µg PEG-IFN alfa-2a for the first 12 weeks and of the PEG-IFN alfa-2a and ribavirin combination therapy given for 72 weeks .

Results

Baseline Characteristics

Approximately two thirds of the patients were males and the majority was Caucasians (88% to 90%). The median age was 48 to 50 years in the four groups. The median body weight was between 79 and 80 kg, and the median body mass index in the four groups was very similar (26.6 to 27.4 kg/m^2).

The HCV genotype distribution was balanced across the four treatment groups. In each group, 91% of the patients were infected with HCV genotype 1. Of the patients infected with HCV genotype non-1, the most common genotype was HCV genotype 4.

Overall, as can be seen in table 1 patient's characteristics are those expected for a CHC study conducted in patients not responding to PegIntron plus ribavirin, as there is an enrichment of poor prognosis factors.

Table 1 *Summary of Baseline Demographic and Baseline Disease Characteristics in Study MV17150, All Patients Treated*

	PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 72 weeks N = 317	PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 48 weeks N = 156	PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 72 weeks N = 156	PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 48 weeks N = 313
Genotype				
1	288 (91%)	142 (91%)	142 (91%)	284 (91%)
2	2 (<1%)	3 (2%)	1 (<1%)	1 (<1%)
3	7 (2%)	4 (3%)	5 (3%)	8 (3%)
4	19 (6%)	5 (3%)	8 (5%)	19 (6%)
5	1 (<1%)	1 (<1%)	-	1 (<1%)
6	-	1 (<1%)	-	-
n	317	156	156	313
Pretreatment/baseline HCV RNA (IU/mL)				
Mean	5393273	5345800	4903294	4921283
SD	6411966	7146967	5124631	5983619
SEM	367148.1	579695.6	414301.9	348379.8
Median	3015000	2972500	3230000	2680000
Min-Max	3560 - 34200000	15700 - 57900000	2190 - 27700000	2470 - 43000000
n	305	152	153	295
Pretreatment/baseline HCV RNA (IU/mL)				
<=800,000	61 (20%)	22 (14%)	25 (16%)	62 (21%)
> 800,000	244 (80%)	130 (86%)	128 (84%)	233 (79%)
n	305	152	153	295
Cirrhosis status pretreatment[a]				
CIRRHOTIC	79 (25%)	45 (29%)	46 (30%)	88 (28%)
NONCIRRHOTIC	237 (75%)	110 (71%)	109 (70%)	223 (72%)
n	316	155	155	311
Months from Liver Biopsy to Treatment				
Mean	11.51	12.74	12.57	12.19
SD	11.307	11.261	11.345	11.467
SEM	0.638	0.904	0.914	0.650
Median	8.76	10.97	11.50	9.72
Min-Max	0.0 - 66.3	0.0 - 49.4	0.0 - 53.2	0.0 - 75.6
n	314	155	154	311
Pretreatment/baseline ALT (U/L)				
Mean	65.0	68.6	67.8	69.4
SD	46.36	46.08	46.67	52.25
SEM	2.61	3.69	3.74	2.95
Median	52.3	52.2	55.4	54.9
Min-Max	12 - 328	15 - 266	14 - 287	10 - 380
n	315	156	156	313
Pretreatment/baseline ALT Quotient				
(1) 0 - 1	44 (14%)	29 (19%)	23 (15%)	38 (12%)
(2) >1 - 3	217 (69%)	86 (55%)	104 (67%)	213 (68%)
(3) >3	54 (17%)	41 (26%)	29 (19%)	62 (20%)
n	315	156	156	313
Steatosis score				
NONE	92 (32%)	43 (30%)	47 (33%)	84 (29%)
UP TO 5% OF HEPATOCYTES	117 (40%)	66 (47%)	61 (43%)	135 (46%)
6% - 33% OF HEPATOCYTES	53 (18%)	21 (15%)	23 (16%)	49 (17%)
34% - 66% OF HEPATOCYTES	23 (8%)	11 (8%)	11 (8%)	19 (7%)
67% - 100% OF HEPATOCYTES	5 (2%)	-	1 (<1%)	4 (1%)
n	290	141	143	291

[a] As judged by the local pathologist based on pretreatment liver biopsy results.
Note: n represents number of patients contributing to summary statistics. Percentages based on n.
DM11 05DEC2007:12:52:03

Previous PEG-IFN alfa-2b and Ribavirin Therapy

The median starting dose of previous PEG-IFN alfa-2b therapy was the same (1.5 µg/kg weekly) and the median durations of previous PEG-IFN alfa-2b therapy were comparable (190 to 201 days) in the four treatment groups. The median starting dose of previous ribavirin therapy was the same (1000 mg daily) and median durations of previous ribavirin were comparable (190 to 200 days) in the four treatment groups. A total of 15 patients had either a previous ribavirin starting dose of <800 mg daily or had not received previous PEG-IFN alfa-2b and ribavirin combination therapy. Overall the prior treatment attempt appears to have been initiated with overall acceptable dose intensity.

Patient disposition

A total of 950 patients were randomly assigned in a ratio of 2:1:1:2 to groups A, B, C, and D, respectively. A total of eight randomised patients (three in the two 72-week treatment groups and five in the two 48-week treatment groups) did not receive study drug. Five of the eight patients withdrew consent after being randomised, one patient violated study entry criteria, and two patients had other protocol violations. Among the remaining 942 patients, a similar percentage of patients in each group

completed the first 12 weeks (94% to 96%) and 24 weeks (88% to 92%) of treatment indicating that high dose induction is not too poorly tolerated. The most frequent reason for withdrawal was adverse events (Table 2).

A similar percentage of patients in each group completed 48 weeks of treatment (67% to 72%). The most common reason for premature withdrawal between weeks 25 and 48 in all treatment groups was "insufficient therapeutic response" (13% to 17%). The protocol instructed investigators to consider treatment discontinuation for patients who did not demonstrate evidence of virological response by week 24.

Overall the percentage of patients who completed their scheduled treatment was lower in the two 72-week treatment groups (57% and 58%) than in the two 48-week treatment groups (72%). Between weeks 49 and 72, only patients in the two 72-week treatment groups were still on study treatment. During this period, an additional 10% to 11% of patients in the two treatment groups prematurely withdrew from treatment; the most common reasons patients withdrew between weeks 49 and 72 were adverse events and insufficient therapeutic response.

The percentage of patients who completed 12 weeks of follow-up (94% to 95%) and 24 weeks of follow-up (80% to 84%) according to the actual end of treatment was similar across the four treatment groups. The percentage of patients who completed 24 weeks of follow-up after the scheduled end of treatment was 59% to 62% in the two 72-week treatment groups and 74% to 75% in the two 48-week treatment groups.

Table 2: *Summary of Reasons over Time that Patients Did Not Complete the scheduled Treatment in study MV17150*

	PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 72 Weeks (N=318)	PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 48 Weeks (N=158)	PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 72 Weeks (N=158)	PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 48 Weeks (N=316)
Patients randomized	318 (100%)	158 (100%)	158 (100%)	316 (100%)
Patients who received study drug	317 (>99%)	156 (99%)	156 (99%)	313 (>99%)
Patients randomized but never dosed	1 (<1%)	2 (1%)	2 (1%)	3 (<1%)
Violation of Selection Criteria at Entry				1 (<1%)
Other Protocol Violation	1 (<1%)		1 (<1%)	
Withdrew Consent		2 (1%)	1 (<1%)	2 (<1%)
Patients who completed 12 weeks of treatment	299 (94%)	148 (94%)	149 (94%)	304 (96%)
Patients who withdrew during week 1 to week 12	18 (6%)	8 (5%)	7 (4%)	9 (3%)
Adverse Event/Intercurrent Illness	7 (2%)	3 (2%)	4 (3%)	7 (2%)
Failure to Return	4 (1%)	1 (<1%)		
Violation of Selection Criteria at Entry				1 (<1%)
Other Protocol Violation	1 (<1%)	1 (<1%)		
Withdrew Consent	1 (<1%)		1 (<1%)	
Refused Treatment/Did Not Cooperate	3 (<1%)	3 (2%)	1 (<1%)	1 (<1%)
Administrative/Other	2 (<1%)		1 (<1%)	
Patients who completed 24 weeks of treatment	279 (88%)	142 (90%)	140 (89%)	292 (92%)
Patients who withdrew during week 13 to week 24	20 (6%)	6 (4%)	9 (6%)	12 (4%)
Adverse Event/Intercurrent Illness	7 (2%)	2 (1%)	5 (3%)	4 (1%)
Insufficient Therapeutic Response	4 (1%)	3 (2%)	3 (2%)	4 (1%)
Failure to Return	1 (<1%)			1 (<1%)
Violation of Selection Criteria at Entry	1 (<1%)			
Withdrew Consent	3 (<1%)			1 (<1%)
Refused Treatment/Did Not Cooperate	3 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Administrative/Other	1 (<1%)			1 (<1%)
Patients who completed 48 weeks of treatment	214 (67%)	114 (72%)	109 (69%)	229 (72%)
Patients who withdrew during week 25 to week 48	65 (20%)	28 (18%)	31 (20%)	63 (20%)
Adverse Event/Intercurrent Illness	10 (3%)	1 (<1%)	4 (3%)	9 (3%)
Death		1 (<1%)		
Insufficient Therapeutic Response	50 (16%)	21 (13%)	27 (17%)	47 (15%)
Failure to Return		1 (<1%)		2 (<1%)
Other Protocol Violation	1 (<1%)			
Withdrew Consent	1 (<1%)	1 (<1%)		1 (<1%)
Refused Treatment/Did Not Cooperate	2 (<1%)	2 (1%)		3 (<1%)
Administrative/Other	1 (<1%)	1 (<1%)		1 (<1%)
Patients who completed 72 weeks of treatment	182 (57%)		91 (58%)	
Patients who withdrew during week 49 to week 72	32 (10%)		18 (11%)	
Adverse Event/Intercurrent Illness	13 (4%)		5 (3%)	
Insufficient Therapeutic Response	10 (3%)		8 (5%)	
Failure to Return			2 (1%)	
Other Protocol Violation	1 (<1%)			
Withdrew Consent	1 (<1%)		1 (<1%)	
Refused Treatment/Did Not Cooperate	5 (2%)		2 (1%)	
Administrative/Other	2 (<1%)			
Patients who completed 24 weeks of follow-up	254 (80%)	131 (83%)	131 (83%)	266 (84%)

Note: If one component of the combination treatment (PEG-IFN alfa-2a and Ribavirin) was discontinued earlier than the other, then the reason for withdrawal refers to the study drug discontinued last.

Program : $PROD/cdl0303r/mv17150/tdisp02.sas / Output : $PROD/cdl0303r/mv17150/reports/tdisp02_r.lst
12JUL2007 22:48

Primary Efficacy Parameters

Treatment with the 360 µg induction dose of PEG-IFN alfa-2a for 12 weeks followed by 180 µg for 60 weeks in combination with 1000/1200 mg of ribavirin for 72 weeks (group A) was significantly more effective than treatment for 48 weeks with 180 µg of PEG-IFN alfa-2a and 1000/1200 mg of ribavirin (group D). In the analysis based on all patients treated (intent-to-treat population), 16% of patients in group A achieved a sustained virological response compared with 9% of patients in group D, a difference that was statistically significant (odds ratio of 2.00; 95% confidence interval (CI) of 1.21 to 3.31, and a p value of 0.006; Table 3). The sustained virological response appeared to be consistently better in group A than in group D across the randomization strata formed by geographical region, HCV genotype, and cirrhosis status (p-value of 0.211 using Breslow and Day's test).

Table 3: *Sustained Virological Response: Group A versus Group D*

PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 72 Weeks (N=317)	PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 48 Weeks (N=313)	Odds Ratio (95% CI) (a)	P Value (b)	Treatment-by-Stratum Interaction P Value (c)
52 (16%)	27 (9%)	2.00 (1.21, 3.31)	0.0060	0.2114

Note: Sustained virological response is defined as a single last HCV RNA measurement that is not detectable (<50 IU/mL) >= follow-up week 20 (>= study day of last dose of study medication + 140).
a: The odds ratio is the ratio of the odds of a response in treatment group A to the odds of a response in treatment group D.
b: Assessed by Cochran-Mantel-Haenszel test stratified by region, HCV genotype and histological diagnosis stage.
c: Breslow and Day's test for homogeneity of the odds ratio across strata.

Comparisons of Sustained Virological Response: Pooled Results
In order to investigate whether the longer treatment duration of 72 weeks was superior to 48 weeks, the data from groups A and C were pooled and compared with the pooled data from groups B and D. Similarly, data from groups A and B were pooled and compared with the pooled data from groups C and D in order to investigate whether the PEG-IFN alfa-2a induction dose of 360 µg was superior to 180 µg.

In the analysis based on all patients treated, sustained virological response according to the actual treatment period was 16% for the pooled groups receiving 72 weeks treatment, which was statistically significantly higher than the sustained virological response of 8% for the pooled groups receiving 48 weeks of treatment. The odds ratio of the comparison was 2.22 with a 95% CI of 1.40 to 3.52) and a p value of 0.001. See Table 4.

Sustained virological response assessed according to the actual treatment period in the population of all patients treated was 13% in the pooled group receiving the 360 µg PEGIFN alfa-2a induction dose compared with 10% in the pooled group receiving 180 µg of PEG-IFN alfa-2a, a difference that was not statistically significant (Table 4). The odds ratio for the comparison was 0.98 (95% CI = 0.63, 1.51 and p value = 0.923). The lack of a significant difference in sustained virological response between the pooled induction groups and the pooled non-induction groups indicated that induction dosing was not the driver for the difference observed between groups A and D.

Table 4: Pooled Treatment Comparisons, ITT

	Groups A & C 72 weeks N = 473	Groups B & D 48 weeks N = 469	Groups A & B 360/180 µg N = 473	Groups C & D 180 µg N = 469	P Value
72 weeks vs 48 weeks	16%	8%	-	-	0.0006[a]
Induction vs noninducton	-	-	13%	10%	0.9228[a]

[a]Comparison of odds ratio using the Cochran-Mantel-Haenszel test.

Pair wise Treatment Comparisons

72 weeks of treatment versus 48 weeks of treatment

Results support those presented for the primary efficacy analysis showing that sustained virological response was higher in patients treated for 72 weeks than in those who received 48 weeks of treatment.

Group A versus group B

Sustained virological response in group A assessed according to the actual treatment period (16%) was significantly higher than the sustained virological response of 7% in group B. The odds ratio of this comparison was 2.77 with a 95% CI of 1.36 to 5.67 and a p value of 0.0036 (see Table 5).

Group B versus group C

Sustained virological response in group B assessed according to the actual treatment period (7%) was significantly lower than the sustained virological response of 14% in group C. The odds ratio of this comparison was 0.49 with a 95% CI of 0.23 to 1.03 and a p value of 0.049 (see Table 5).

Group C versus group D

Sustained virological response in group C assessed according to the actual treatment period (14%) was higher than the sustained virological response of 9% in group D, with an odds ratio of this comparison of 1.80 (95% CI: 0.97 to 3.32). However, the p value for this comparison (0.060) did not reach the statistically significant level of 0.05 (Table 5). Although the sustained virological response in group C was not statistically higher than that in group D, the study was not powered to detect a significant difference for this pair wise comparison. A significant difference was also noted when comparing the standard analysis population in groups C and D who had received a PEG-IFN alfa-2b starting dose of ≥ 1.25 µg/kg.

Table 5: *Pair wise Treatment Comparisons, ITT*

	Group A 360/180 µg 72 weeks N = 317	Group B 360/180 µg 48 weeks N = 156	Group C 180 µg 72 weeks N = 156	Group D 180 µg 48 weeks N = 313	Odds Ratio (95% CI)	p Value[a]
A vs D	16%	-	-	9%	2.00 (1.21, 3.31)	0.006
A vs B	16%	7%	-	-	2.77 (1.36, 5.67)	0.004
C vs D	-	-	14%	9%	1.80 (0.97, 3.32)	0.060
B vs C	-	7%	14%	-	0.49 (0.23, 1.03)	0.049
A vs C	16%	-	14%	-	1.11 (0.64, 1.93)	0.714
B vs D	-	7%	-	9%	0.79 (0.38, 1.64)	0.530

[a] Comparison of odds ratio using the Cochran-Mantel-Haenszel test.

Overall the results of the efficacy analysis indicate that duration of therapy (72 vs. 48 weeks) is of importance while high-dose induction seems not to be associated with improved treatment outcome.

Secondary Efficacy Parameters

Virological response

A summary of virological response (undetectable virus) assessed at various time points during the trial for all patients treated is provided in Table 6. The proportion of patients achieving viral suppression (HCV RNA < 50 IU/ml) at week 12 was highest in group A (24%) and lowest in group D (11%) and similar in groups B (14%) and C (16%). Exploratory logistic regression analyses on the probability of virological response (undetectable virus) at week 12 did not identify any imbalance in baseline demographic or disease characteristics or in on-treatment factors (such as cumulative PEG-IFN alfa-2a and ribavirin dose during the first 12 weeks) among the treatment groups that might explain the differences in virological response observed between groups A and B or between groups C and D.

Although the data are not conclusive, high dose induction does not seem to result in a higher early (week 12) response rate.

Table 6: Summary of Virological Response over Time

	PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 72 Weeks (N=317)	PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 48 Weeks (N=156)	PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 72 Weeks (N=156)	PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 48 Weeks (N=313)
Week 12	75 (24%)	22 (14%)	25 (16%)	35 (11%)
Week 24	103 (32%)	50 (32%)	45 (29%)	86 (27%)
Week 48	103 (32%)	51 (33%)	49 (31%)	81 (26%)
Week 72	91 (29%)		44 (28%)	
End-of-treatment (a)	93 (29%)	52 (33%)	46 (29%)	85 (27%)
End-of-treatment (b)	99 (31%)	52 (33%)	48 (31%)	88 (28%)
End-of-follow-up (c)	51 (16%)	11 (7%)	21 (13%)	27 (9%)
End-of-follow-up (d)	52 (16%)	11 (7%)	22 (14%)	27 (9%)

Note: Virological response is defined as undetectable HCV RNA (<50 IU/mL). Patients without HCV RNA measurements at a study week are considered nonresponders at that study week.
(a) End-of-treatment virological response according to scheduled treatment period.
(b) End-of-treatment virological response according to actual treatment period.
(c) Sustained virological response according to scheduled treatment period.
(d) Sustained virological response according to actual treatment period.

Exploratory analyses

Best Response to Previous PEG-IFN alfa-2b and Ribavirin Combination Therapy

This analysis was retrospectively carried out in response to a request by the CHMP after completion of the study. The best HCV RNA response to previous treatment with PEG-IFN alfa-2b plus ribavirin combination therapy was determined based on HCV RNA measurements performed during previous treatment, which were collected on the CRF for study MV17150. The best response was calculated by determining the difference between the previous baseline HCV RNA value and the best (lowest) HCV RNA result between the start of previous treatment and the end of previous treatment plus 28 days. The last quantitative HCV RNA result within 1 year of previous treatment was used as the previous baseline value for HCV RNA.

Appropriate quantitative HCV RNA data that could be used to calculate the best response to previous PEG-IFN alfa-2b plus ribavirin combination therapy were available for 53% of the patients. The main reasons that the best previous response could not be determined for the remaining patients were (1) the availability of only qualitative rather than quantitative HCV RNA test results during previous treatment or (2) baseline HCV RNA values before previous treatment were measured outside the 1-year pretreatment time window.

Table 7: *Best Response to Previous Combination Therapy with PEGIFN alfa-2b and Ribavirin in Patients with Available Data*

Treatment Group	N	Best Response to Previous Combination Therapy[a]	
		≥ 2-$\log_{10}$ Decrease from Baseline[b]	<2-$\log_{10}$ Decrease from Baseline
PEG-IFN alfa-2a 360/180 µg + Ribavirin 1000/1200 mg 72 weeks (Group A)	142	37 (26%)	105 (74%)
PEG-IFN alfa-2a 360/180 µg + Ribavirin 1000/1200 mg 48 weeks (Group B)	69	20 (29%)	49 (71%)
PEG-IFN alfa-2a 180 µg + Ribavirin 1000/1200 mg 72 weeks (Group C)	69	20 (29%)	49 (71%)
PEG-IFN alfa-2a 180 µg + Ribavirin 1000/1200 mg 48 weeks (Group D)	141	28 (20%)	113 (80%)

[a] Best response to previous combination therapy with PEG-IFN alfa-2b plus ribavirin calculated using best HCV RNA result between study day 2 and end of treatment + 28 days during previous treatment. Baseline time window for previous combination therapy was study day -365 to study day 1 of previous treatment.
[b] Includes patients with unquantifiable HCV RNA as their best response to previous treatment.

In patients for whom the necessary HCV RNA results were available, the best HCV RNA response to previous treatment has been categorized as either (1) at least a 2-log10 RNA or (2) less than a 2-log10 decrease from baseline in HCV RNA. The best previous HCV RNA response was at least a 2-log10 decrease from baseline in a similar percentage of patients across the four treatment groups, 26% in group A, 29% in group B, 29% in group C, and 20% in group D. See table 7. The majority of patients in the four treatment groups had a best previous HCV RNA response of less than a 2-log10 decrease from baseline.

Impact of Best response on HCV RNA at week 12
In patients whose best response to previous treatment was ≥ 2-log10 decrease, a higher percentage achieved viral suppression at week 12 in the two groups treated with the 360 µg induction dose of PEG-IFN alfa-2a than in the two groups treated with the 180-µg dose of PEG-IFN alfa-2a. A total of 43% of patients in group A and 35% of patients in group B achieved viral suppression at week 12 of treatment compared with 10% of patients in group C and 14% of patients in group D (See Table 8).

In contrast, in patients whose best previous response was <2-log10 decrease, no clear pattern was seen and the 360 µg induction dose did not appear to have an impact on the proportion of these patients who achieved viral suppression at week 12.

Table 8: *Viral Response at Week 12 by Best Previous Response*

	PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 72 Weeks (N=254)		PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 48 Weeks (N=132)		PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 72 Weeks (N=141)		PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 48 Weeks (N=271)	
	N	Wk12 VR(a)	N	Wk12 VR(a)	N	Wk12 VR(a)	N	Wk12 VR(a)
All Patients	254	58 (23%)	132	18 (14%)	141	22 (16%)	271	29 (11%)
Best previous response(b)								
At least 2 log drop from baseline(c)	97	16 (43%)	20	7 (35%)	20	2 (10%)	28	4 (14%)
Less than a 2 log drop from baseline	105	14 (13%)	49	2 (4%)	49	9 (18%)	113	11 (10%)
Unknown	112	28 (25%)	63	9 (14%)	72	11 (15%)	130	14 (11%)

(a) HCV RNA undetectable at week 12 (study day 72 to 99).
(b) Best response to previous PEG-IFN alfa-2b + ribavirin combination therapy calculated using the best response between study day 2 and end of treatment + 28 days. Baseline time window for previous combination therapy was study day -365 to 1.
(c) Includes patients with unquantifiable HCV RNA.

Impact of Best Response on Sustained Virological Response

A similar exploratory analysis of the relationship between best previous response and sustained virological response was performed (Table 9). The results showed that in patients whose best response to previous treatment was at least a 2-log10 decrease, a higher percentage achieved a sustained virological response when they were treated with the 360 µg induction PEG-IFN alfa-2a dose plus ribavirin (35% in group A and 30% in group B) then when they were treated with the 180-µg dose of PEG-IFN alfa- 2a plus ribavirin (5% in group C and 7% in group D).

In contrast, in patients whose best previous response was <2-log10 decrease the pattern was different and the proportion of patients who achieved a sustained virological response appeared to be higher in patients in the two 72-week treatment groups (11% in group A and 18% in group C) than in the two 48-week treatment groups (0% in group B and 9% in group D).

Table 9: Sustained Virological Response by Best Previous Response

	PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 72 Weeks (N=254)		PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 48 Weeks (N=182)		PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 72 Weeks (N=141)		PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 48 Weeks (N=271)	
	N	SVR(a)	N	SVR(a)	N	SVR(a)	N	SVR(a)
All Patients	254	40 (16%)	182	10 (5%)	141	19 (13%)	271	19 (7%)
Best previous response(b)								
At least 2 log drop from baseline(c)	37	13 (35%)	20	6 (30%)	20	1 (5%)	28	2 (7%)
Not at least 2 log drop from baseline	105	12 (11%)	49	0 (0%)	49	9 (18%)	113	10 (9%)
Unknown	112	15 (13%)	63	4 (6%)	72	9 (13%)	130	7 (5%)

Note:
(a) Sustained virological response is defined as a single last HCV RNA measurement that is not detectable (<50 IU/mL) ≥ follow-up week 20 (≥ study day of last dose of study medication + 140).
(b) Best response to previous PEG-IFN alfa-2b + ribavirin combination therapy calculated using the best response between study day 2 and end of treatment + 28 days. Baseline time window for previous combination therapy was study day -365 to 1.
(c) Includes patients with unquantifiable HCV RNA.

Sustained Virological Response According to the Actual Treatment Period by Factors Predictive of SVR

HCV genotype, baseline viral load, and cirrhosis status are known important predictors for sustained virological response in treatment-naïve patients. These three factors were also found in multiple logistic regression analyses to be important predictors for sustained virological response in the present study in nonresponders. Therefore, sustained virological responses have been summarized in the subgroups of patients with HCV genotype 1 or genotype non-1 infection, with baseline viral load ≤ 800,000 or >800,000 IU/ml, and with cirrhosis or without cirrhosis.

Sustained virological response in all four treatment groups was very low (4% to 7%) in patients with transition to cirrhosis or cirrhosis (Table 10).

The majority of patients were infected with HCV genotype 1 (91%), and only a small number of patients were infected with HCV genotype 2 or 3 (3%).

Table 10: *SVR according to actual treatment time by HCV Genotype, baseline viral load, and histological diagnosis*

	PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 72 Weeks (N=317)		PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 48 Weeks (N=156)		PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 72 Weeks (N=156)		PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 48 Weeks (N=313)	
	N	SVR	N	SVR	N	SVR	N	SVR
All Patients	317	52 (16%)	156	11 (7%)	156	22 (14%)	313	27 (9%)
Genotype 1	288	42 (15%)	142	10 (7%)	142	18 (13%)	284	21 (7%)
Genotype Non-1	29	10 (34%)	14	1 (7%)	14	4 (29%)	29	6 (21%)
HCV RNA <=800,000 IU/mL	61	22 (36%)	22	2 (9%)	25	5 (20%)	62	9 (15%)
HCV RNA > 800,000 IU/mL	244	29 (12%)	130	9 (7%)	128	17 (13%)	233	16 (7%)
Baseline Viral Load Missing	12	1 (8%)	4	0 (0%)	3	0 (0%)	18	2 (11%)
Cirrhosis	79	3 (4%)	45	2 (4%)	46	3 (7%)	88	4 (5%)
Noncirrhosis	237	49 (21%)	110	8 (7%)	109	19 (17%)	223	23 (10%)
Hist. Diag. Missing	1	0 (0%)	1	1 (100%)	1	0 (0%)	2	0 (0%)

Note: Sustained virological response is defined as a single last HCV RNA measurement that is not detectable (<50 IU/mL) >= follow-up week 20 (>= study day of last dose of study medication + 140).
Histological Diagnosis (cirrhosis vs noncirrhosis) was based on pretreatment liver biopsy as judged by the local pathologist.

Predictive Values of Various Degrees of Virological Responses at Week 12 on Sustained Virological Response

In patients who failed to achieve full viral suppression at week 12, the negative predictive value for not achieving a sustained virological response was high and ranged from 94% to 98% in the four treatment groups. In contrast, as shown in table 11 the ability to predict whether a patient would achieve a sustained virological response if they achieved viral suppression at week 12 was 53% and 68% in the two groups receiving 72 weeks of treatment (57% when the two 72 week groups are pooled), and 36% and 34% in the two groups receiving 48 weeks of treatment (35% when the two 48 week groups are pooled). These analyses underline the importance of achieving full suppression at week 12 in order to attain sustained response.

Table 11: *Positive Predictive Values of Various Degrees of Virological Responses at Week 12 on Sustained Virological Response*

	PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 72 Weeks (N=317)		PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 48 Weeks (N=156)		PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 72 Weeks (N=156)		PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 48 Weeks (N=313)	
	N	SVR	N	SVR	N	SVR	N	SVR
All Patients	317	52 (16%)	156	11 (7%)	156	22 (14%)	313	27 (9%)
HCV RNA Response at Week 12 (a)								
Undetectable	75	40 (53%)	22	8 (36%)	25	17 (68%)	35	12 (34%)
Detectable but not quantifiable	66	9 (14%)	35	2 (6%)	14	1 (7%)	44	11 (25%)
Quantifiable >=2 log drop from baseline	55	2 (4%)	34	0 (0%)	37	2 (5%)	51	3 (6%)
Quantifiable 1-2 log drop from baseline	43	0 (0%)	28	0 (0%)	32	1 (3%)	68	0 (0%)
Quantifiable not >=1 log drop from baseline	47	0 (0%)	22	0 (0%)	36	0 (0%)	81	1 (1%)
Missing or not assessable (b)	31	1 (3%)	15	1 (7%)	12	1 (8%)	34	0 (0%)

Note: Baseline HCV RNA: Last valid quantitative HCV RNA result at or prior to baseline (<=study day 1).
(a) HCV RNA at week 12: Last valid HCV RNA result in week 12 time window (>=study day 72 and <=study day 99).
(b) No HCV RNA result at week 12 or
no baseline HCV RNA result and HCV RNA at week 12 neither 'undetectable' nor 'detectable but not quantifiable'.

Sustained Virological Response in Patients by Baseline Covariates According to Virological Response at Week 12

A multiple logistic regression analysis of independent baseline predictors of non response at week 12 was carried out to identify covariates that would be sufficiently predictive to exclude patients with a low likelihood of week 12 response. The baseline covariates were: infection with HCV genotype 1, the presence of cirrhosis or bridging fibrosis, older age, and high baseline HCV RNA viral load. Complete virus suppression at week 12, however was shown to be the strongest predictor of SVR, irrespective of whether baseline prognostic factors were favorable or unfavorable as can be seen in Table 12.

Table 12: *Sustained Virological Response in Patients by Baseline Covariates According to Virological Response at Week 12*

	72 Weeks		**48 Weeks**	
	VR at Wk 12	Non-VR at Wk 12	VR at Wk 12	Non-VR at Wk 12
Cirrhosis Status				
No cirrhosis or bridging fibrosis	59%	6%	34%	5%
Cirrhosis or bridging fibrosis	46%	0%	50%	3%
Age				
≤ 40 years	54%	12%	42%	5%
>40 years	58%	3%	33%	4%
Baseline HCV RNA				
≤ 800,000 IU/mL	63%	9%	38%	4%
>800,000 IU/mL	54%	4%	32%	5%

Note: VR = virological response, defined as HCV RNA undetectable (<50 IU/mL).

Supportive studies – Non-responders

HALT-C

The HALT-C trial was a study conducted by the US National Institutes of Health that was designed to determine whether prolonged low-dose maintenance monotherapy with PEG-IFN alfa-2a altered histological and clinical outcomes in a broad population of CHC patients with advanced fibrosis or cirrhosis (Ishak score of 3 to 6) who had failed to eradicate the virus with previous IFN-alfa-based treatment for a minimum of 12 weeks. Although the majority of patients had received previous treatment with IFN alfa monotherapy or IFN alfa and ribavirin combination therapy, some of the

patients were nonresponders to previous PEG-IFN alfa monotherapy or PEG-IFN alfa plus ribavirin combination therapy.

Before randomisation into the maintenance phase of the study, patients were enrolled into a lead-in phase during which all patients were treated with PEG-IFN alfa-2a (180 μg weekly) and ribavirin (1000/1200 mg daily) combination therapy for 24 weeks. Patients who had detectable virus at week 20 were entered into the maintenance phase of the study and randomised either to low-dose (90 μg) maintenance PEG-IFN alfa-2a monotherapy or to observation for a 3.5-year period. Patients with no detectable virus at week 20 remained on PEG-IFN alfa-2a plus ribavirin combination therapy for a total of 48 weeks and were then followed for an additional 24 weeks to assess sustained virological response. These patients were not randomised to the low-dose maintenance phase unless they experienced a virological breakthrough during the 48 weeks of treatment or relapsed after the end of treatment.

*This submission of the HALT-C study is based on data from the following three papers***:**

1. Shiffman *et al.* (2004)[2] reported on the first 604 patients enrolled in the lead-in phase of the study.
2. Everson *et al.* (2006)[3] reported on 1046 patients who had HCV RNA assessments at week 20 and week 72 and analyzed the results in four subgroups of patients subdivided by increasing liver disease severity. The four subgroups were group A, which consisted of 559 patients with bridging fibrosis (Ishak score of 3 or 4) and platelet counts >125,000/mm3; group B, which consisted of 96 patients with bridging fibrosis and platelet counts ≤125,000/mm3; group C, which consisted of 198 patients with cirrhosis (Ishak score of 5 or 6) and platelet counts >125,000/mm3; and group D, which consisted of 195 patients with cirrhosis and platelet counts ≤125,000/mm3.
3. Shiffman *et al.* (2007)[4] reported on 936 patients infected with genotype 1 who had HCV RNA assessments at week 20 and week 72, which was a subgroup of the 1046 patients described in the publication by Everson *et al.*

Baseline characteristics
The baseline characteristics for the three papers are presented in table 13 hereafter: Most of the patients were Caucasian, and most were men. HCV genotype 1 predominates.

[2] Shiffman ML, DiBisceglie AM, Lindsay KL, et al. Peginterferon alfa- 2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. *Gastroenterology.* 2004;126:1015-1023.

[3] Everson G, Hoefs JC, Seeff LB, et al. Impact of disease severity on outcome of antiviral therapy for chronic hepatitis C - lessons from the HALT-C Trial. *Hepatology.* 2006; 44:1675- 1684.

[4] Shiffman ML, Ghany MG, Morgan TR, et al. Impact of reducing peginterferon alfa-2a and ribavirin dose during retreatment in patients with chronic hepatitis C. *Gastroenterology*. 2007; 132:103-112.

Table 13*: demographic and Baseline Disease Characteristics in HALT-C Study*

	Shiffman et al 2004 (N = 604)	Everson et al 2006[a] (N = 1046)	Shiffman et al 2007 (N = 936)
Mean age, y	49.9	49.9	50
Males	438 (73%)	757 (72%)	673 (72%)
Race and Ethnicity			
Caucasian	466 (77%)	771 (74%)	693 (74%)
Black	84 (14%)	164 (16%)	157 (17%)
Hispanic	39 (6%)	83 (8%)	66 (7%)
Other	15 (3%)	28 (3%)	20 (2%)
Mean BMI, kg/m^2	29.7	29.7	NA
HCV genotype			
1	539 (89%)	936 (89%)	936 (100%)
2 and 3	57 (9%)	93 (9%)	0
2	31 (5%)	45 (4%)	0
3	26 (4%)	48 (5%)	0
Mean HCV RNA, log_{10} IU/mL	6.46	6.43	6.4
Cirrhosis (Ishak score = 5 or 6)	233 (39%)	391 (37%)	355 (38%)
Previous Treatment			
IFN alfa	219 (36%)	255 (24%)	NA
IFN alfa + ribavirin	385 (64%)	692 (66%)	NA
PEG-IFN alfa	0	38 (4%)	NA
PEG-IFN alfa + ribavirin	0	61 (6%)	NA

Note: NA = not available in publication.
[a] Data are from the Everson publication and from an updated publication data set of the HALT-C study.

Results HALT-C

Sustained Virological Response in HALT-C
The sustained virological responses reported in the three HALT-C publications for the patients in the lead-in phase of the study are provided in Table 14.

Overall and by Disease Severity
In the cohort consisting of the first 604 patients enrolled in the lead-in phase of the study, 18% of the patients achieved a sustained virological response (Table 13). In patients with fibrosis in this cohort, 23% of patients achieved a sustained virological response, while in patients with cirrhosis, only 11% of patients achieved a sustained virological response.

The results were very similar in the larger cohort consisting of the 1046 patients from the lead-in phase of the study who had HCV RNA assessments at week 20 and week 72. A total of 17% of these patients achieved a sustained virological response (Table 13). In patients with fibrosis in this cohort, 22% of patients achieved a sustained virological response, while in patients with cirrhosis, only 10% of patients achieved a sustained virological response.

The results of an analysis of sustained virological response by increasing disease severity were provided in the Everson publication. In this analysis, the proportion of patients who achieved a sustained virological response was found to decrease with increasing disease severity and ranged from 23% in the group with less severe disease (fibrosis and platelet count >125,000/mm3) to 9% in the group with the most severe disease (cirrhosis and platelet count ≤125,000/mm3) (Table 13).

The decrease in sustained virological response with increasing disease severity was independent of age, percentage African-Americans, HCV genotype, HCV RNA viral load, and type of previous therapy.

Table 14: Sustained Virological Response in HALT-C Study

	Shiffman et al 2004			Everson et al 2006[a]			Shiffman et al 2007		
	N	N	SVR	N	N	SVR	N	N	SVR
Overall Population	604	NA	18%	1046	180	17%			
HCV Genotype									
1	539	NA	14%	936	131	14%	936	131	14%
2 and 3	57	34	60%	93	47	51%			
2	31	20	65%	45	25	56%			
3	26	14	54%	48	22	46%			
Previous Treatment									
IFN alfa	219	NA	28%	255	70	27%			
IFN alfa + ribavirin	385	NA	12%	692	90	13%			
PEG-IFN alfa	0			38	13	34%			
PEG-IFN alfa + ribavirin	0			61	7	11%			
Race and Ethnicity									
Caucasian	466	NA	20%	771	147	19%			
Black	84	NA	6%	164	13	8%			
Hispanic	39	NA	18%	83	15	18%			
Cirrhosis Status									
Fibrosis	371	NA	23%	655	142	22%			
Cirrhosis	233	NA	11%	391	38	10%			
Disease Severity									
Fibrotic, Plt >125,000/mm^3				559	NA	23%			
Fibrotic, Plt ≤125,000/mm^3				96	NA	17%			
Cirrhotic, Plt >125,000/mm^3				198	NA	10%			
Cirrhotic, Plt ≤125,000/mm^3				193	NA	9%			

Note: NA = not available in publication, Plt = platelet count.
[a] Data are from the Everson publication and from an updated publication data set of the HALT-C study.

Relapser Patients

Study WV16143

Study WV16143 was an open-label, multicenter, uncontrolled re-treatment trial in 64 HCV patients who had initially been randomised to and treated for 24 weeks with 180 µg of PEG-IFN alfa-2a and 800 or 1000/1200 mg of ribavirin combination therapy in the phase III registration study NV15942 and had relapsed after the end of treatment. In study WV16143, these patients were re-treated for 48 weeks with PEG-IFN alfa-2a and ribavirin combination therapy and then followed for 24 weeks to assess sustained virological response.

Demographic and Baseline Disease Characteristics in Study WV16143

Most of the patients were Caucasian, and most were men. The majority of the patients (70%) were infected with HCV genotype 1, and 22% (14 patients) were infected with genotype 2 or 3. Approximately 31% had transition to cirrhosis or cirrhosis.

Results Study WV16143

A total of 55% of patients who had relapsed after 24 weeks of treatment with PEG-IFN alfa-2a (180 µg) plus ribavirin (800 or 1000/1200 mg) combination therapy and were retreated for 48 weeks with the combination of PEG-IFN alfa-2a and ribavirin achieved a sustained virological response. In patients infected with HCV genotype 2 or 3, 64% (9 of 14) of the patients achieved a sustained virological response after re-treatment for 48 weeks (Table 15).

In this re-treatment study, 55% of patients with genotype 1 infection achieved sustained virological response. However, it should be noted that these genotype 1 patients may have received suboptimal previous treatment in terms of treatment duration and ribavirin dose in the initial study, NV15942, since 24 weeks of treatment and 800 mg of ribavirin is not the standard of care for patients with genotype 1 infection.

Table 15: *Sustained Virological Response in Study WV16143*

	PEG-IFN alfa-2a + Ribavirin		
	N	N	SVR
Overall	64	35	55%
HCV Genotype			
1	45	23	51%
2	6	4	67%
3	8	5	63%

Kaiser et al study

This was an academic study with 120 patients who had relapsed after 48 weeks of combination treatment with PEG-IFN alfa plus ribavirin were re-treated for 72 weeks with the combination of either PEG-IFN alfa-2a (180 µg) once weekly plus weight-based ribavirin daily (60 patients) or consensus IFN (9 µg) daily plus weight-based ribavirin daily (60 patients).

Demographic and Baseline Disease Characteristics

The majority of the patients were men, and most of the patients were infected with HCV genotype 1. Approximately two thirds of the patients had been previously treated with PEG-IFN alfa-2b plus ribavirin and one third had been previously treated with PEG-IFN alfa-2a plus ribavirin

Results Kaiser et al study[5]

Overall sustained virological response was achieved by 51% (54/107) of the patients who had previously relapsed after treatment with PEG-IFN alfa and ribavirin combination therapy and were re-treated for 72 weeks with 180 µg of PEG-IFN alfa-2a in combination with weight-based ribavirin.

The incremental benefit over 48 weeks of re-treatment could not be determined because 48 weeks of re-treatment was not studied. However, there was a high positive predictive value for sustained virological response if patients achieved viral suppression (undetectable HCV RNA) at week 12. In total, 43% of these relapser patients (46 of 107 patients) achieved viral suppression at week 12 (HCV RNA <15 IU/ml), and 93% of the patients who achieved viral suppression at week 12 also achieved a sustained virological response (43 of 46 patients) with 72 weeks of re-treatment.

Discussion on Clinical Efficacy

Non-responders

Efficacy data presented in study MV17150 support the benefit of PEG-IFN plus weight adjusted ribavirin in patients non-responding to PEG-IFN alfa 2b and weight adjusted ribavirin. The results from HALT-C study are compatible with the results reported in the pivotal study.

With respect to pivotal study MV17150, prolonged therapy from 48 to 72 weeks is associated with improved efficacy whereas induction with high-dose pegylated IFN did not improve treatment outcome.

However the proportion of patients responding to a new treatment course with PEG-IFN alfa-2a plus ribavirin as defined by sustained virological response (SVR) at the end of follow-up was modest: 16% and 14% in the 72 week treatment arms respectively. Due to toxic effects associated with PEG-IFN plus ribavirin treatment it is important to define early predictive factors of response to treatment in order to avoid unsuccessful therapy and toxic effects in a large majority of patients that would be included in the extended therapeutic indication. In a multiple logistic regression analysis of study MV17150, independent baseline predictors of non-response at week 12 included infection with HCV genotype 1, the presence of cirrhosis or bridging fibrosis, older age, and high baseline HCV RNA viral load. Complete virus suppression at week 12, however, was clearly shown to be the strongest predictor

[5] Data are derived from an abstract (AASLD Annual Meeting, 2008, abstract 1860).

of SVR, irrespective of whether baseline prognostic factors were favourable or unfavourable, providing a treatment stopping rule.

The CHMP had concerns that the definition criteria for non-responders may be too broad and that data was lacking on the duration of proviso response. It is a concern whether the response to a new treatment course with PEG-IFN plus ribavirin can be related with previous treatment response. Indeed, analysis of sustained virological response by best previous response supports this possibility but yields conflicting results with the global data of the pivotal study. Furthermore the CHMP requested a stratification of patients according to different non-responder criteria, best previous response and duration of previous treatment to provide some key to define such markers of response to re-treatment

Regarding the definition criteria for non-responders the MAH highlighted that the study excluded patients who achieved undetectable levels of virus. Furthermore patients failing an initially adequate course of treatment were excluded if their previous non-response was based solely on treatment with less potent therapy, that is, treatment with IFN alfa, IFN alfa plus ribavirin, or PEG-IFN alfa monotherapy. The study did include patients with treatment intolerance, but the percentage was low, ranging from 0.3% to 3.2% across the four treatment arms. Four patients were reported to have achieved undetectable HCV RNA levels on previous therapy. These four patients were included in the intent-to-treat analysis but are considered protocol violators and were excluded from the standard population (per protocol analysis).

To further investigate the effect of previous response on the achievement of a sustained virological response after re-treatment, and as the initial analysis of sustained virological response by best previous response yields potentially conflicting results with the global data of the study an additional multiple logistic regression analysis was conducted. The best previous response (≥ 2 $\log_{10}$ vs <2 $\log_{10}$ decrease from baseline in HCV RNA) was tested as a prognostic factor for sustained virological response. Looking at all patients pooled, a best previous response of ≥ 2 $\log_{10}$ decrease from baseline was found to be an independent predictor for achieving a sustained virological response in addition to other factors identified in the previous analysis with more complete data (body weight, HCV RNA level at baseline, and treatment duration). However, when this analysis was conducted looking separately at patients assigned to 48 weeks and 72 weeks of treatment, best previous response was predictive only in patients assigned to 48 weeks and not in patients assigned to 72 weeks.

The CHMP considered the definition of non-responders as acceptable, but highlighted that there was remaining heterogeneity. In order to properly assess the benefit/risk balance, there is a need to separate between factors predictive of week 12 response and factors predictive of sustained response and that data should be reported in the SPC in a way that facilitates the benefit/risk assessment.

Regarding the effect of the previous duration of PEG-IFN alfa-2b and the effect of the previous duration of ribavirin, both as continuous variables in weeks, were examined in a multiple logistic regression model for the probability of a sustained virological response after re-treatment in study MV17150. In the model assessing all parameters, duration of previous treatment of PEG-IFN alfa-2b (odds ratio =1.04, p value = 0.56) and duration of previous treatment of ribavirin (odds ratio = 0.961, p value = 0.55) were not significant.

Concerning the CHMP request for stratification of patients according to different non-responder criteria, best previous response and duration of previous treatment the MAH considered that such an analysis was not feasible in a study that collects non responder status based on historical data. The CHMP accepted the position of the MAH taking into account that data is provided in the SPC in a manner that facilitates the assessment of the benefit risk balance to allow prescribers to separate between factors predictive of week 12 response and factors predictive of SVR.

Relapsers

Conceptually, these data supported by single arm studies in relapse patients have been provided to support a second course of therapy for a prolonged period of time in relapse patients. However in study WV16143 that re-treated patients for 48 weeks, a short course of first line IFN therapy of 24 weeks was administered and cannot be considered as the standard of treatment. Although the Kaiser results, which includes predominantly genotype 1 patients, shows that relapsers from a previous course of 48 weeks of PEG-IFN alfa plus ribavirin show clear benefit from re-treatment for 72 weeks (with a positive predictive value of 93% for those patients who achieved viral suppression at week 12), it is not possible to evaluate the benefit/risk relationship for 72 weeks of re-treatment compared with 48 weeks of re-treatment. Even though logical, the added benefit of prolonged therapy from 48 weeks to 72 weeks remains quantitatively undetermined, formally making a benefit/risk assessment impossible. Overall the MAH no longer proposes the inclusion of data on relapsing patients in the SPC. This approach is endorsed by the CHMP.

Clinical safety

The safety data to support this variation are provided from the pivotal study (MV17150). Supporting safety data are provided from the HALT-C study and from three studies in 411 treatment-naïve patients treated with PEG-IFN alfa-2a plus ribavirin for 72 weeks.

The three studies are outlined hereafter:

- Study M78014 was an open-label, randomised, active-controlled, parallel-group, multicenter, phase III study that compared the efficacy and safety of 48 weeks vs 72 weeks of treatment with PEG-IFN alfa-2a plus ribavirin in 225 treatment-naïve CHC patients infected with HCV genotype 1**.**
- Study M78019 was a multicenter, randomised parallel-group, phase III study comparing the safety and efficacy of 48 weeks vs 72 weeks of treatment with PEG-IFN alfa-2a plus ribavirin in 162 treatment-naïve CHC patients who did not have an early virological response at week 4.
- The Dynamically Individualized Treatment of Hepatitis C Infection and Correlates of Viral/ Host Dynamics (DITTO-HCV) study was a phase III, open label, randomised, multicenter study using combination therapy with PEG-IFN alfa-2a plus ribavirin that compared a dynamically individualized treatment schedule based on early virological response versus the standard of care. A total of 270 treatment-naïve patients were treated for 48 weeks and 24 patients were treated for 72 weeks.

Study MV17150

Patient exposure

The total safety population, defined as all patients who received at least one dose of study medication and had at least one follow-up assessment, in study MV17150 was 942 patients. Of the total safety population, 473 patients (50%) received combination therapy for 72 weeks.

Adverse events

Nearly all patients (≥ 96%) in each of the four treatment groups reported at least one AE. The frequency of severe AEs was higher in the two groups receiving 72 weeks of treatment (24% in groups A and C) than in the two groups receiving 48 weeks of treatment (16% in group B and 20% in group D). Overall, a total of 9 patients among the four treatment groups experienced life-threatening AEs.

Serious adverse events and deaths

Deaths

Five patients died during this study. One patient in group B died from a ruptured cerebral aneurysm, 2 patients in group C died (one from metastatic esophageal adenocarcinoma and the other from malignant hepatic neoplasm), and 2 patients in group D died (one from an esophageal variceal

hemorrhage and the other from a thermal burn). One of the 5 deaths occurred during study treatment (ruptured cerebral aneurysm), and all the deaths were considered by the investigator as being unrelated to study treatment.

Serious adverse events

The frequency of severe AEs was higher in the two groups receiving 72 weeks of treatment (24% in groups A and C) than in the two groups receiving 48 weeks of treatment (16% in group B and 20% in group D). A total of 9 patients experienced life-threatening AEs (1 patient each in groups A and B; 3 patients in group C; 4 patients in group D). Between 4% and 5% of patients in groups A, C, and D and 1% of patients in group B experienced serious AEs that were considered by the investigator to be related to study treatment. Serious infections, serious blood and lymphatic disorders and serious gastrointestinal disorders were the most common types of serious AEs reported. No apparent differences in the frequency or types of treatment- related serious AEs were observed among the four treatment groups.

Discontinuations and dose modifications due to AE Adverse Events or Laboratory Abnormalities Leading to Premature Withdrawal from Treatment

The percentage of patients who were prematurely withdrawn from PEG-IFN alfa-2a treatment for AEs or laboratory abnormalities was higher in the two groups receiving 72 weeks of treatment (12%) than in the two groups receiving 48 weeks of treatment (4% and 6%;). A similar trend was seen in the percentage of patients who were prematurely withdrawn from ribavirin treatment for AEs or laboratory abnormalities (13% in the two groups receiving 72 weeks of treatment and 6% and 7% in the two groups receiving 48 weeks of treatment), since the protocol specified that patients discontinuing PEG-IFN alfa-2a therapy also had to stop treatment with ribavirin.

During the first 12 weeks of treatment, the percentage of patients prematurely withdrawn from PEG-IFN alfa-2a treatment for AEs or laboratory abnormalities was the same (2%), irrespective of the PEG-IFN alfa-2a induction dose (180 or 360 μg). No differences were observed in the types of AEs or laboratory abnormalities leading to premature withdrawal during this treatment period.

The most frequent type of AEs leading to premature discontinuation of PEG-IFN alfa-2a treatment were general disorders and administration site conditions, which led to withdrawal from PEG-IFN alfa-2a treatment in 1% to 2% of patients in the four treatment groups; infections and infestations (<1% to 2% of patients); and blood and lymphatic system disorders (0% to 3% of patients).

The most frequent type of AEs leading to premature discontinuation of ribavirin treatment was blood and lymphatic system disorders, which led to withdrawal from ribavirin treatment in 1% to 3% of patients in the four treatment groups. The major difference between premature discontinuation of PEG-IFN alfa-2a and ribavirin treatment for safety reasons was that anaemia was the most important reason for ribavirin treatment discontinuation (12 patients) but not for discontinuation of PEG-IFN alfa-2a treatment (3 patients).

Dose modification

Dose modifications of PEG-IFN alfa-2a for AEs or laboratory abnormalities occurred in a comparable percentage of patients across the four treatment groups (18% to 26%). Across all four treatment groups, laboratory abnormalities (16% to 22%), mainly neutropenia (12% to 16%) and less frequently thrombocytopenia (3% to 7%), were the main reasons for dose modification of PEG-IFN alfa-2a. Dose modifications of ribavirin also occurred in a comparable percentage of patients in the four treatment groups (25% to 32%). Across the four treatment groups, dose modification of ribavirin occurred more frequently because of laboratory abnormalities (15% to 22%) than because of AEs (9% to 15%). Anaemia was the main laboratory abnormality leading to ribavirin dose modifications in all groups (15% to 21%).

Exploratory Analysis of Adverse Events per Patient Year

In order to examine whether patients exposed to 72 weeks of treatment experienced an additional safety burden compared to patients exposed to 48 weeks of treatment, an exploratory analysis was

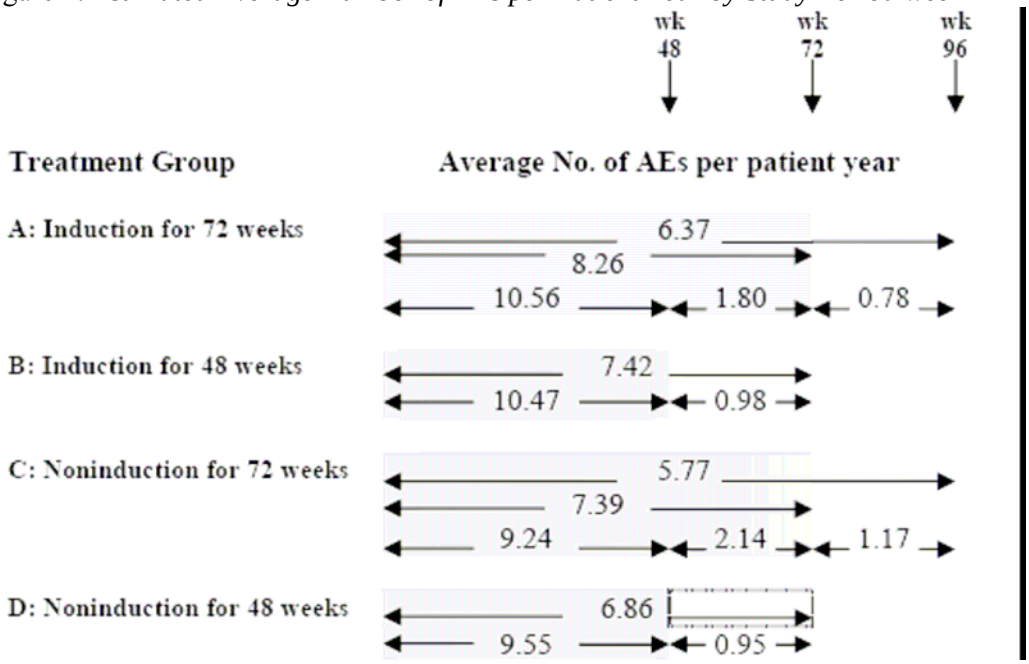
performed to examine the total number of AEs each patient experienced across the four treatment groups adjusted for the length of exposure and follow-up period.

Short comings with this analysis relate to:
- Multiple episodes of the same AE preferred term were counted only once for each patient.
- Approximately two thirds of the AEs had a date of onset during the first 12 weeks of treatment.
- The rate of AEs per patient year during the study period (treatment and follow-up) was lower than the rate of AEs per patient year during the treatment period.

.
Therefore, the rate of AEs per patient year was calculated for the four treatment groups for the following three separate time periods:
- During the first 48 weeks of treatment for all four treatment groups.
- During treatment weeks 48 to 72 for the two 72-week treatment groups.
- During the treatment-free follow-up period.

The results of this exploratory analysis are shown graphically in Figure 2.

Figure 2: *Estimated Average Number of AEs per Patient Year by Study Period week*



Note: Scheduled treatment period is shaded; scheduled follow-up period is unshaded. Multiple episodes of the same AE preferred term were counted only once for each patient.

The rate of AEs per patient year during treatment weeks 48 to 72 was substantially lower than the rate during the first 48 weeks of treatment (reduced from 9.24 to 2.14 per patient year in the non-induction 72-week treatment arm). The rate of AEs per patient year during the treatment-free follow-up period was further reduced compared with the rate during treatment weeks 48 to 72 (reduced from 2.14 to 1.17 per patient year in the non-induction 72-week treatment arm). The rate of AEs per patient year during the treatment-free follow-up period for the non-induction 72-week treatment arm was similar to the rate for the non-induction 48-week treatment arm (1.17 vs 0.95 per patient year, respectively).

The results of this exploratory analysis indicate that extending treatment duration in a patient for another half a year from 48 weeks to 72 weeks will lead to the occurrence of approximately 1 new AE (2.14 per patient year).

Exploratory analysis of the average number of adverse events per patient on treatment day

In this analysis the average number of adverse events per patient on each treatment day was calculated over time. If a patient has repeated episodes of a particular adverse event, only the most

severe episode, or the episode with the strongest causal relationship to study drug, is usually counted. In this analysis adverse events were counted on each treatment day that the adverse event was present. The average number of adverse events per patient on a treatment day increased during the first 12 weeks and then reached a plateau for the remainder of the treatment period whether the total treatment duration was 48 weeks or 72 weeks. The peak safety burden experienced in both the 48 week and 72 week treatment groups was slightly more than four adverse events per patient per treatment day and remained constant after week 48 in the 72 week treatment groups.

The frequency of treatment days with serious adverse events in relation to all treatment days was determined. The ratios of the average number of days per patient with serious adverse events to days on treatment were 0.015 and 0.013 for patients treated for 48 weeks and 72 weeks, respectively, suggesting that the frequency of AEs per time period is considered stable over 72 weeks.

Of the patients assigned to 72 weeks of treatment who remained on treatment at week 48 (323 patients), 5.6% (18 patients) discontinued treatment for adverse events or laboratory abnormalities between weeks 49 and 72. Many of the safety reasons for discontinuation during weeks 49 to 72 were typical of the reasons for discontinuation during the first 48 weeks.

Frequency of all serious and irreversible life-threatening adverse events
In order to quantify the frequency of all serious and irreversible adverse events that were life-threatening and/or persisting and thus potentially irreversible, the MAH analyzed safety data pooled from study MV17150 and 11 previous, randomised, multicenter, prospective, well-controlled clinical studies in treatment-naïve CHC patients treated with PEG-IFN alfa-2a plus ribavirin combination therapy for 48 weeks.

Prospectively, 50 adverse event MedDRA preferred terms were selected from this database that were considered by the MAH to be medically not only serious adverse events but were also considered either likely to be life-threatening. Of the 6180 patients exposed to PEG-IFN alfa-2a, the most frequently reported of these rarely observed serious adverse events were suicide attempt (14 patients, 0.2%), suicidal ideation (13 patients, 0.2%), overdose (9 patients, 0.1%), and sarcoidosis (7 patients, 0.1%); all these rare serious adverse events are currently included as labeled events in the Pegasys SPC. All the other selected serious adverse events were reported at an incidence of < 0.1% (ie, ≤ 5 patients).

Overall, of the 114 serious adverse events that were considered by the MAH to be potentially life-threatening and/or persisting, 83 events (73%) were reported during the first 36 weeks of treatment

Given the rarity of all these serious adverse events, it was not possible to identify any trend that would suggest with any assurance that these events are likely to be seen more frequently when treatment is extended from 48 to 72 weeks.

Supportive Safety Information from Studies Using PEG-IFN alfa-2a and Ribavirin Combination Therapy

Studies Using PEG-IFN alfa-2a and Ribavirin Combination Therapy for 72 Weeks in CHC treatment-naïve Patients
Supporting safety data are provided from three studies in treatment-naïve patients treated with PEG-IFN alfa-2a plus ribavirin for 72 weeks. The studies include two MAH sponsored studies (M78014 and M78019) in 387 patients treated with PEG-IFN alfa-2a (180 µg/week) and ribavirin (800 mg/day) and limited safety information from a third published study, DITTO-HCV, in which 24 patients treated with the same dose of PEG-IFN alfa-2a but a higher dose of ribavirin (1000/1200 mg/day).

Studies M78014 and M78019
The types and frequencies of common AEs experienced by nonresponder patients treated with PEG-IFN alfa-2a plus ribavirin in the pivotal study MV17150 were similar to those observed in the two MAH sponsored studies in treatment-naïve patients treated with PEG-IFN alfa-2a plus ribavirin for 72

weeks. Also, the number and spectrum of AEs that occurred in both of these studies were typical for a CHC patient population treated with PEG-IFN alfa and ribavirin combination therapy.

Even though there were two deaths in the non-responder patients assigned to 72 weeks of treatment in study MV17150, and none in these studies in treatment-naïve patients, the deaths in study MV17150 were assessed as unrelated to the study treatment.

Serious AEs overall were reported in a similar percentage of patients in the two studies with treatment-naïve patients and in study MV17150 in nonresponders.

The frequency of premature withdrawals for safety reasons was similar in non-responder patients and the treatment-naïve patients, approximately 12% of patients. Dose modification of PEG-IFN alfa-2a for AEs was lower in non-responder patients than in treatment-naïve patients. Ribavirin dose modification for AEs was similar in non-responder patients and in treatment-naive patients in study M78014 but higher in treatment-naive patients in study M78019.

Overall as study MV17150 only included patients treated previously with PEG-IFN alfa-2b and ribavirin and specifically excluded patients who had discontinued previous treatment for a haematological toxicity, the frequencies of anaemia, neutropenia, and thrombocytopenia were higher in the studies with treatment-naïve patients even though the dose of ribavirin was lower.

DITTO-HCV study
The DITTO-HCV study compared an individualized versus standard treatment in treatment-naïve CHC patients. A total of 270 patients were treated with PEG-IFN alfa-2a (180 µg/week) and ribavirin (1000/1200 mg/day) for the first 6 weeks and then classified as rapid, slow, flat or null responders and treatment was individualized and consisted of PEG-IFN alfa-2a monotherapy for either 48 or 24 weeks, triple therapy with histamine or prolonged combination therapy (72 weeks) or high dose PEG-IFN alfa-2a (360 µg/week) plus ribavirin. A total of 24 patients were treated with PEG-IFN alfa-2a (180 µg/week) and ribavirin (1000/1200 mg/d) for 72 weeks, and safety information is limited to AEs of special interest. The overall safety results from the 24 patients treated for 72 weeks in the DITTO-HCV study were similar to MV17150 and no new safety concerns were identified in this study.

Safety Profile in HALT-C Study during the First 20 Weeks of PEG-IFN alfa-2a plus Ribavirin Combination Therapy in Non-responder Patients with Advanced Fibrosis or Cirrhosis

The HALT-C study in non-responder patients treated with PEG-IFN alfa-2a (180 µg/week) plus ribavirin (1000-1200 mg/day) combination therapy for 48 weeks also provided limited safety data. As the efficacy from the lead-in phase of the trial was used as supporting data for the purposes of this filing, the safety data from the lead-in phase, provided by the NIH, was reviewed to determine if any additional safety signals were seen.

The HALT-C lead-in phase study population included 1145 CHC patients who were predominantly male (72%), Caucasian (74%), and genotype 1 (89%), with a mean age of 50 years. The majority of the patients had liver cirrhosis (62%, Ishak score of 5 or 6). Patients with a baseline platelet count as low as 50,000/mm^3 were allowed into this trial.

The safety review of the HALT-C lead-in phase included AEs reported in weeks 1 to 20, haematologic laboratory abnormalities, and deaths. Based on this review, the only notable safety finding was the frequency of haematologic laboratory abnormalities observed during the first 20 weeks of the trial: haemoglobin levels <10 g/dl occurred in 26% of the patients absolute neutrophil counts <750/mm3 occurred in 30% of the patients and platelet count <50,000/mm3 occurred in 13% of the patients. The frequency of these haematologic laboratory abnormalities was higher than that observed in study MV17150 and was consistent with treatment of a patient population containing a higher proportion of patients with advanced fibrosis and cirrhosis who entered the study with lower baseline platelet counts.

Discussion Clinical Safety

Seventy-two weeks of PEG-IFN plus weight adjusted ribavirin therapy constitutes a major burden of toxicity to the patient due to prevalent and sustained tolerability problems. At least one serious adverse event related to treatment was recorded for all patients in the pivotal trial. Extension of treatment to 72 weeks increased the number of adverse events**.** Of note is the risk for serious and irreversible adverse reactions such as pneumonitis (some times fatal), autoimmune disorders such as Thrombotic thrombocytopenic purpura (TTP) and aplastic anaemia. Overall the most frequently reported types of adverse events were those already known to associate with IFN-PEG and ribavirin therapy.

To show whether there was an unacceptable excess of adverse events associated to the 72-week regimen, as compared with 48 weeks, the MAH has performed a number of post-hoc analysis. The analyses addressing frequency of all serious events shows that the percentage of adverse events considered to be potentially life-threatening and/or persisting is 1.7% (103/114). In addition, it is shown that most serious adverse events occur in the first 36 weeks of therapy.

However in this analysis the mean duration of exposure in the data base was not reported but it is probable that the results are mainly driven for patients treated during 48 weeks or less as they are supposed to be the majority in the database that has been used for the analysis. In addition, the analyses assumes that the rate of adverse events is constant over time. Furthermore patients that interrupted the treatment due to haematological adverse events were excluded from the trial. The results are therefore biased in this regard, at least for patients enrolled in trial MV17150.

As such although the results of this analysis are reassuring they are of limited value. As a consequence, the MAH will enrol patients who failed previous therapy in an observational study to specifically collect SAE's in order to provide further assurance of the safety of the extended treatment duration.

Risk Management plan

The CHMP agreed that an EU-Risk management plan would not be required for Pegasys for the extension of indication of the treatment of patients who failed previous treatment with pegylated interferon alfa and ribavirin combination therapy. The CHMP took into account that the population to be covered by the extension of indication have already been exposed to therapy with PEG-INF.

BENEFIT RISK ASSESSMENT

Benefit

In patients with Chronic Hepatitis C being non-responders to PEG-IFN 2b plus ribavirin, prolonged therapy from 48 to 72 weeks at retreatment with PEG-IFN 2a plus weight adjusted ribavirin results in an increased sustained viral response rate (SVR) from about 8% to about 15%. SVR in practice means cure of the viral disease even though there is a remaining risk for complications related to cirrhosis. Treatment for 48 weeks is licensed for patients infected with virus genotype 1 and patients relapsing after treatment with interferon and ribavirin, but not for non-responding patients.

If treatment is optimised in accordance with current clinical guidelines and therapy is stopped if virus is still detectable at week 12, the SVR will be about 12% and one in four patients would actually undergo treatment beyond the 12 week stopping point. This may be compared with about 8% using the same approach if treatment is administered for 48 weeks (8% is based on the assumption that viral response rate at week 12 is the same in the comparison 48 vs. 72 weeks, and a positive predictive value of 35% for 48 weeks of therapy, instead of 50% for 72 weeks).

In principle, SVR varies in line with what would be expected based on known risk factors, but the very poor SVR in patients with cirrhosis (about 3-4% if all patients are treated for 72 weeks) should be noticed.

There is a likely benefit of prolonged therapy at time of retreatment also in relapse patients however, submitted single arm study data are not sufficient to estimate the add-on benefit of the 72-week

regimen in patients infected with virus genotype 1. Furthermore in study WV16143 where patients were re-treated for 48 weeks, suboptimal first-line therapy was administered. As such no data on relapsers has been included in the SPC and the MAH no longer requests the extension of indication to relapsing patients.

Risk

Seventy-two weeks of PEG-IFN plus weight adjusted ribavirin therapy constitutes a major burden of toxicity to the patient due to prevalent and sustained tolerability problems. Post-hoc analyses addressing frequency of all serious events show that the percentage of adverse events considered to be potentially life-threatening and/or persisting is 1.7% (103/114). In addition, it is shown that most serious adverse events occur in the first 36 weeks of therapy. The results of the analysis are reassuring but of limited value due to bias. As such the MAH will include non-responder patients in observational studies in order to provide reassurance that prolonged therapy is not associated with an unacceptable burden of toxicity.

Conclusion

Non-responding patients: Overall four out of five patients will be treated for 12 weeks without any benefit and one in five treated for 72 weeks will have a chance of around 50% of being cured from the viral disease. However, outcome varies according to well known prognostic factors. An individualised approach is therefore needed. These patients are all treatment experienced and are thus knowledgeable about adverse reactions to be expected; at least the meaning of 3 months of therapy without benefit. Extending time on therapy is a major tolerability issue. However it is possible to inform about the benefit 72 weeks of therapy.

There is a risk for serious and irreversible adverse reactions such as pneumonitis (some times fatal), autoimmune disorders such as TTP and aplastic anaemia. The risk for suicide is also a reality, but probably less so in these treatment-experienced patients. Altogether the risk of these events is considered acceptably low at least in patients with a reasonable chance of virological cure

Unfortunately the outcome in patients with cirrhosis, i.e. the group of patients with more urgent need for therapy, is very poor, probably less than 2% SVR if treatment is stopped at week 12 in non-responders. Hardly ever is benefit/risk likely to be positive in this patients group. However, this should be left to the treating physician and the patient.

Even though the sustained viral response rate is low in non-responders to a proper course of PEG-IFN and ribavirin it cannot be stated that benefit – risk is negative in the individual patient willing to take the problems associated with retreatment with PEG-IFN plus ribavirin. If retreatment is considered, the aim should be for 72 weeks of therapy and the week 12 stopping criteria should be adhered to.

Relapse patients: Conceptually, there is support for the notion to retreat relapse patients. However the data provided from the WV16143 single arm study that re-treated patients for 72 weeks used suboptimal first-line therapy in Genotype 1 patients and the added benefit of going from 48 to 72 weeks in patients infected with HCV genotype 1 could not be estimated from the single arm Kaiser study that re-treated patients for 48 weeks. As such the MAH no longer requests the extension of the indication to relapsing patients. This position is endorsed by the CHMP.