

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICAL PRODUCT

Rebetol 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 200 mg of ribavirin.

Excipient: each hard capsule contains 40 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

White, opaque and imprinted with blue ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rebetol is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults, children 3 years of age and older and adolescents and must only be used as part of a combination regimen with peginterferon alpha-2b or interferon alpha-2b. Rebetol monotherapy must not be used.

There is no safety or efficacy information on the use of Rebetol with other forms of interferon (i.e., not alpha-2b).

Naïve patients

Adult patients: Rebetol is indicated, in combination with interferon alpha-2b or peginterferon alpha-2b, for the treatment of adult patients with chronic hepatitis C, not previously treated, without liver decompensation with elevated alanine aminotransferase (ALT), who are positive for hepatitis C viral ribonucleic acid (HCV-RNA). In combination with peginterferon alpha-2b also patients with compensated cirrhosis and/or clinically stable HIV co-infection are included (see section 4.4).

Children 3 years of age and older and adolescents: Rebetol is indicated, in a combination regimen with peginterferon alpha-2b or interferon alpha-2b, for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding to not to defer treatment until sobriety, it is important to consider that the combination therapy induced a growth inhibition. The reversibility of growth inhibition is uncertain.

The decision to treat should be made on a case by case basis (see section 4.4).

Previously treated patients

Adult patients: Rebetol is indicated, in combination with interferon alpha-2b, for the treatment of adult patients with chronic hepatitis C, who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed. Rebetol is indicated, in combination with peginterferon alpha-2b, for the treatment of adult patients with chronic hepatitis C, who have failed previous treatment with interferon alpha (pegylated or non-pegylated) alone or in combination with ribavirin (see section 5.1).

4.2 Posology and method of administration

Rebetol should be initiated, and monitored, by a physician experienced in the management of chronic hepatitis C.

Rebetol must be used in combination with either peginterferon alpha-2b or interferon alpha-2b.

Please refer also to the peginterferon alpha-2b or interferon alpha-2b Summary of Product Characteristics (SPC) for prescribing information particular to that product.

Dose to be administered

The dose of Rebetol is based on patient body weight. Rebetol capsules are to be administered orally each day in two divided doses (morning and evening) with food.

Adult patients:

The dose of Rebetol is based on patient body weight (Table 1).

Rebetol must be used in combination with either peginterferon alpha-2b (1.5 micrograms/kg/week) or interferon alpha-2b (3 million international units [MIU] three times a week). The choice of combination regimen is based on the characteristics of the patient. The regimen administered should be selected based on the anticipated efficacy and safety of the combination treatment for an individual patient (see section 5.1).

Table 1. Rebetol dose based on body weight for HCV monoinfected or HCV/HIV coinfected patients and whatever the genotype			
Patient weight (kg)	Daily Rebetol dose	Number of 200 mg capsules	
< 65	800 mg	4 ^a	
65 – 80	1,000 mg	5 ^a	
81 – 105	1,200 mg	6 ^a	
> 105	1,400 mg	7 ^a	

^a 2 morning, 2 evening
^b 2 morning, 3 evening
^c 3 morning, 3 evening
^d 3 morning, 4 evening

Rebetol capsules in combination with peginterferon alpha-2b:

Duration of treatment – Naïve patients

Predictability of sustained virological response: Patients infected with virus genotype 1 who fail to achieve undetectable HCV-RNA or demonstrate adequate virological response at week 4 or 12 are highly unlikely to become sustained virological responders and should be evaluated for discontinuation (see also section 5.1).

Genotype 1: Patients who have undetectable HCV-RNA at treatment week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).

Patients with detectable but \geq 2 log decrease in HCV-RNA level from baseline at treatment week 12 should be reassessed at treatment week 24 and, if HCV-RNA is undetectable, a total of 48 weeks of therapy, i.e., a total of 48 weeks.

However, if HCV-RNA is still detectable at treatment week 24, discontinuation of therapy should be considered.

In the subset of patients with genotype 1 infection and low viral load (< 600,000 IU/ml) who become HCV-RNA negative at treatment week 4 and remain HCV-RNA negative at week 24, the treatment could either be stopped after this 24 week treatment course or pursued for an additional 24 weeks (i.e., overall 48 weeks treatment duration). However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1).

Genotype 2 or 3: It is recommended that all patients be treated for 24 weeks, except for HCV/HIV co-infected patients who should receive 48 weeks of treatment.

Genotype 4: In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a duration of treatment as for genotype 1.

Duration of treatment – HCV/HIV co-infected patients
The recommended duration of Rebetol weight-based dosing (see Table 1) for HCV/HIV co-infected patients is 48 weeks, regardless of genotype.

Predictability of response and non-response in HCV/HIV Co-infection
Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV-RNA, has been shown to be predictive for sustained response. The negative predictive value for sustained response in HCV/HIV co-infected patients treated with Rebetol in combination with peginterferon alpha-2b was 99 % (67/68; Study 1) (see section 5.1). A positive predictive value of 50 % (52/104; Study 1) was observed for HCV/HIV co-infected patients receiving combination therapy.

Duration of treatment – Retreatment
Predictability of sustained virological response: All patients, irrespective of genotype, who have demonstrated serum HCV-RNA below the limits of detection at week 12 should receive 48 weeks of therapy. Retreated patients who fail to achieve virological response (i.e. HCV-RNA below the limits of detection) at week 12 are unlikely to become sustained virological responders after 48 weeks of therapy (see also section 5.1).

Retreatment duration greater than 48 weeks in non-responder patients with genotype 1 has not been studied with pegylated interferon alpha-2b and ribavirin combination therapy.

Rebetol capsules in combination with interferon alpha-2b:

Based on the results of clinical trials, it is recommended that patients be treated for at least six months. During those clinical trials in which patients were treated for one year, patients who failed to show a virological response after six months of treatment (HCV-RNA below lower limit of detection) were unlikely to become sustained virological responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Genotype 1: Treatment should be continued for another six month period (i.e., a total of one year) in patients who exhibit negative HCV-RNA after six months of treatment.

Genotypes Non-1: The decision to extend therapy to one year in patients with negative HCV-RNA after six months of treatment should be based on other prognostic factors (e.g., age > 40 years, male gender, bridging fibrosis).

Children 3 years of age and older and adolescents:
Note: For patients who weigh < 47 kg, or are unable to swallow capsules, please refer to the SPC for ribavirin 40 mg/ml oral solution.

Dosing for children and adolescent patients is determined by body weight for Rebetol and by body surface area for peginterferon alpha-2b and interferon alpha-2b.

Dose to be administered for the combination therapy with peginterferon alpha-2b:
The recommended dose of peginterferon alpha-2b is 60 µg/m²/week subcutaneously in combination with Rebetol 15 mg/kg/day (Table 2).

Dose to be administered for the combination therapy with interferon alpha-2b:
In clinical studies performed in this population ribavirin and interferon alpha-2b were used in doses of 15 mg/kg/day and 3 million international units (MIU)/m² three times a week respectively (Table 2).

Table 2 Rebetol dose based on body weight when used in combination with interferon alpha-2b or peginterferon alpha-2b in children and adolescents

Patient weight (kg)	Daily Rebetol dose	Number of 200 mg capsules
47 – 49	600 mg	3 capsules*
50 – 65	800 mg	4 capsules*
> 65	Refer to adult dosing table (Table 1)	

* 1 morning, 2 evening
* 2 morning, 2 evening

Duration of treatment in children and adolescents
Genotype 1: The recommended duration of treatment is 1 year. By extrapolation from clinical data on combination therapy with standard interferon in paediatric patients (negative predictive value 96 % for interferon alpha-2b/Rebetol), patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders. Therefore, it is recommended that children and adolescent patients receiving interferon alpha-2b (pegylated or non-pegylated)/Rebetol combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 log10 compared to pretreatment, or if they have detectable HCV-RNA at treatment week 24.

Genotype 2 or 3: The recommended duration of treatment is 24 weeks.

Genotype 4: Only 5 children and adolescents with Genotype 4 were treated in the peginterferon alpha-2b/Rebetol clinical trial. The recommended duration of treatment is 1 year. It is recommended that children and adolescent patients receiving peginterferon alpha-2b/Rebetol combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 log10 compared to pretreatment, or if they have detectable HCV-RNA at treatment week 24.

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during therapy with Rebetol and peginterferon alpha-2b or interferon alpha-2b, modify the dosages of each product if appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification (see Dosage modification guidelines, Table 3). As adherence might be of importance for outcome of therapy, the dose should be kept as close as possible to the recommended standard dose. The potential negative impact of ribavirin dose reduction on efficacy results could not be ruled out.

Laboratory values	Reduce only Rebetol daily dose (see note 1) if:	Reduce only peginterferon alpha-2b or interferon alpha-2b dose (see note 2) if:	Discontinue combination therapy when the below test value is reported:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Adults: Haemoglobin	< 2 g/dl decrease in haemoglobin during any 4 week period during treatment (permanent dose reduction)	-	< 12 g/dl after 4 weeks dose reduction
In patients with history of stable cardiac disease	-	-	-
Children and adolescents: not applicable (see section 4.4)	-	-	-
Leukocytes	-	< 1.5 x 10 ⁹ /l	< 1.0 x 10 ⁹ /l
Neutrophils	-	< 0.75 x 10 ⁹ /l	< 0.5 x 10 ⁹ /l
Platelets	-	< 50 x 10 ⁹ /l (adults) < 70 x 10 ⁹ /l (children and adolescents)	< 25 x 10 ⁹ /l (adults) < 50 x 10 ⁹ /l (children and adolescents)
Bilirubin – Direct	-	-	2.5 x ULN ^a
Bilirubin – Indirect	-	-	> 4 mg/dl (adults) > 5 mg/dl (for > 4 weeks) (children and adolescents treated with peginterferon alpha-2b) or > 4 mg/dl (for > 4 weeks) (children and adolescents treated with peginterferon alpha-2b)
Serum Creatinine	-	-	> 2.0 mg/dl
Creatinine Clearance	-	-	If CrCl < 50 ml/minute
Alanine aminotransferase (ALT)	-	-	2 x baseline and > 10 x ULN ^a or
or Aspartate aminotransferase (AST)	-	-	2 x baseline and > 10 x ULN ^a

Upper limit of normal
^a Refer to SPC for pegylated interferon alpha-2b and interferon alpha-2b for dose modification and discontinuation

Note 1: In adult patients, 1st dose reduction of Rebetol is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of Rebetol is by an additional 200 mg/day. Patients whose dose of Rebetol is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

In children and adolescent patients treated with Rebetol plus peginterferon alpha-2b, 1st dose reduction of Rebetol is to 12 mg/kg/day, 2nd dose reduction of Rebetol is to 8 mg/kg/day.

In children and adolescent patients treated with Rebetol plus interferon alpha-2b, reduce Rebetol dose to 7.5 mg/kg/day.

Note 2: In adult patients treated with Rebetol plus peginterferon alpha-2b, 1st dose reduction of peginterferon alpha-2b is to 1 µg/kg/week. If needed, 2nd dose reduction of peginterferon alpha-2b is to 0.5 µg/kg/week.

In children and adolescent patients treated with Rebetol plus peginterferon alpha-2b, 1st dose reduction of peginterferon alpha-2b is to 40 µg/m²/week, 2nd dose reduction of peginterferon alpha-2b is to 20 µg/m²/week.

In adult patients and children and adolescent patients treated with Rebetol plus interferon alpha-2b, reduce the interferon alpha-2b dose by one-half dose.

Special populations

Use in renal impairment: The pharmacokinetics of ribavirin are altered in patients with renal dysfunction due to reduction of apparent creatinine clearance in these patients (see section 5.2).

Therefore, it is recommended that renal function be evaluated in all patients prior to initiation of Rebetol. Patients with creatinine clearance < 50 ml/minute must not be treated with Rebetol (see section 4.3). Subjects with impaired renal function should be carefully monitored with respect to the development of anaemia. If serum creatinine rises to > 2.0 mg/dl (Table 3), Rebetol and peginterferon alpha-2b/interferon alpha-2b must be discontinued.

Use in hepatic impairment: No pharmacokinetic interaction appears between ribavirin and hepatic function (see section 5.2). Therefore, no dose adjustment of Rebetol is required in patients with hepatic impairment. The use of ribavirin is contraindicated in patients with severe hepatic impairment or decompensated cirrhosis (see section 4.3).

Use in the elderly (≥ 65 years of age): There does not appear to be a significant age-related effect on the pharmacokinetics of ribavirin. However, as in younger patients, renal function must be determined prior to administration of Rebetol (see section 5.2).

Use in patients under the age of 18 years: Rebetol may be used in combination with peginterferon alpha-2b or interferon alpha-2b in children 3 years of age and older and adolescents. The selection of formulation is based on individual characteristics of the patient. Safety and effectiveness of Rebetol with other forms of interferon (i.e. not alpha-2b) in these patients have not been evaluated.

Patients co-infected with HCV/HIV: Patients taking nucleoside reverse transcriptase inhibitor (NRTI) treatment in association with ribavirin and interferon alpha-2b or peginterferon alpha-2b may be at increased risk of mitochondrial toxicity, lactic acidosis and hepatic decompensation (see section 4.4).

Please refer also to the relevant product information for antiretroviral medicinal products.

4.3 Contraindications

- Hypersensitivity to the active substance and to any of the excipients.

- Pregnant women (see sections 4.4, 4.6 and 5.3). Rebetol must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.

- Lactation.

- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease, in the previous six months (see section 4.4).

- Patients with severe, debilitating medical conditions.

- Patients with chronic renal failure, patients with creatinine clearance < 50 ml/minute and/or on haemodialysis.

- Severe hepatic impairment (Child-Pugh Classification B or C) or decompensated cirrhosis of the liver.

- Haemoglobinopathies (e.g., thalassemia, sickle-cell anaemia).

- Initiation of peginterferon alpha-2b is contraindicated in HCV/HIV patients with cirrhosis and a Child-Pugh score ≥ 6.

Children and adolescents:

- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation, or suicide attempt.

- Performance in combination with peginterferon alpha-2b and interferon alpha-2b:

- Autoimmune hepatitis; or history of autoimmune disease.

4.4 Special warnings and precautions for use

Psychiatric and Central Nervous System (CNS):

Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Rebetol combination therapy with peginterferon alpha-2b or interferon alpha-2b, and even after treatment discontinuation mainly during the 6-month follow-up period. Among children and adolescents, treated with Rebetol in combination with interferon alpha-2b, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % versus 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse reactions (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorder, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with Rebetol and peginterferon alpha-2b or interferon alpha-2b be discontinued, and the patient followed, with psychiatric intervention as appropriate.

Patients with existence of, or history of severe psychiatric conditions:

If treatment with Rebetol in combination with peginterferon alpha-2b or interferon alpha-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.

- The use of Rebetol and interferon alpha-2b or peginterferon alpha-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).

Patients with substance use/abuse:

HCV infected patients having a co-occurring substance use disorder (alcohol, cannabis, etc.) are at an increased risk of developing psychiatric disorders or exacerbation of already existing psychiatric disorders when treated with alpha interferon. If treatment with alpha interferon is judged necessary in these patients, the presence of psychiatric co-morbidities and the potential for other substance use should be carefully assessed and adequately managed before initiating therapy. If necessary, an inter-disciplinary approach including a mental health care provider or addiction specialist should be considered to evaluate, treat and follow the patient. Patients should be closely monitored during therapy and even after treatment discontinuation. Early intervention for re-emergence or development of psychiatric disorders and substance use is recommended.

Growth and development (children and adolescents):

During the course of interferon (standard and pegylated)/ribavirin therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination of interferon/ribavirin are indicative of substantial growth inhibition. The mean weight gain in children > 15 years, percentage decrease in height percentile as compared to baseline) in 21 % of children despite being offered treatment for more than 5 years.

Case by case benefit/risk assessment in children:

The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).

- It is important to consider that the combination therapy induced a growth inhibition, the reversibility of which is uncertain. - This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

Based on results of clinical trials, the use of ribavirin as monotherapy is not effective and Rebetol must not be used alone. The safety and efficacy of this combination have been established only using Ribavirin capsules together with peginterferon alpha-2b or interferon alpha-2b solution for injection.

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

Haemolysis: A decrease in haemoglobin levels to < 10 g/dl was observed in up to 14 % of adult patients and 7 % of children and adolescents treated with Rebetol in combination with peginterferon alpha-2b or interferon alpha-2b in clinical trials. Although ribavirin has no direct haemolytic effects, anaemia associated with Rebetol may result in deterioration of cardiac function, or exacerbation of the symptoms of coronary disease, or both. Thus, Rebetol must be administered with caution to patients with pre-existing cardiac disease (see section 4.3). Cardiac status must be assessed before start of therapy and monitored clinically during therapy; if any deterioration occurs, therapy must be stopped (see section 4.2).

Cardiovascular: Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities have electrocardiograms taken at the start and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of therapy. There are no data in children or adolescents with a history of cardiac disease.

Acute hypersensitivity: If an acute hypersensitivity reaction (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) develops, Rebetol must be discontinued immediately and appropriate medical therapy instituted. Transient rashes do not necessitate interruption of treatment.

Ocular changes: Ribavirin is used in combination therapy with alpha interferons. Retinopathy including retinal haemorrhages, retinal exudates, retinopathy, optic neuropathy and/or retinal artery or vein thrombosis may result in loss of vision have been reported in rare instances with combination therapy with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of decrease or loss of vision must have a prompt and complete eye examination.

Patients with pre-existing ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during combination therapy with alpha interferons. Combination therapy with alpha interferons should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Liver function: Any patient developing significant liver function abnormalities during treatment must be monitored closely. Discontinue treatment in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Potential to exacerbate immunosuppression: Pancytopenia and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the administration of a peginterferon and ribavirin concomitantly with azathioprine. This myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone (see section 4.5).

Thyroid supplemental monitoring specific for children and adolescents:

Approximately 12 to 21 % of children treated with Rebetol and interferon alpha-2b (pegylated and nonpegylated) developed increase in thyroid stimulating hormone (TSH). Among approximately 4 % had a transient decrease below the lower limit of normal. Prior to initiation of interferon alpha-2b therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Interferon alpha-2b (pegylated and non-pegylated) therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with Rebetol and interferon alpha-2b and during treatment with Rebetol and peginterferon alpha-2b has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

HCV/HIV Co-infection:

Mitochondrial toxicity and lactic acidosis:

Caution should be taken in HIV-positive subjects co-infected with HCV who receive nucleoside reverse transcriptase inhibitor (NRTI) treatment (especially ddI and d4T) and associated interferon alpha-2b/ribavirin treatment. In the HIV-positive population receiving an NRTI regimen, physicians should carefully monitor markers of mitochondrial toxicity and lactic acidosis when ribavirin is administered. In particular:

- co-administration of Rebetol and didanosine is not recommended due to the risk of mitochondrial toxicity (see section 4.5).

- co-administration of Rebetol and stavudine should be avoided to limit the risk of overlapping mitochondrial toxicity.

Hepatic decompensation in HCV/HIV co-infected patients with advanced cirrhosis:

Co-infected patients with advanced cirrhosis receiving highly active anti-retroviral therapy (HAART) may be at increased risk of hepatic decompensation and death. Addition treatment with alpha interferons alone or in combination with ribavirin may increase the risk in this patient subset. Other baseline factors in co-infected patients that may be associated with a higher risk of hepatic decompensation include treatment with didanosine and elevated bilirubin serum concentrations.

Co-infected patients receiving both antiretroviral (ARV) and anti-hepatitis treatment should be closely monitored, assessing their Child-Pugh score during treatment. Patients progressing to hepatic decompensation should have their anti-hepatitis treatment immediately discontinued and the ARV treatment reassessed.

Haematological abnormalities in HCV/HIV co-infected patients:

HCV/HIV co-infected patients receiving peginterferon alpha-2b/ribavirin treatment and HAART may be at increased risk to develop haematological abnormalities (as neutropenia, thrombocytopenia and anaemia) compared to HCV mono-infected patients. Although, the majority of them could be managed by dose reduction, close monitoring of haematological parameters should be undertaken in this population of patients (see section 4.2 and below "Laboratory tests" and section 4.8).

Patients treated with ribavirin and zidovudine are at increased risk of developing anaemia; therefore, the concomitant use of ribavirin with zidovudine is not recommended (see section 4.5).

Patients with low CD4 counts:

In patients co-infected with HCV/HIV, limited efficacy and safety data (N = 25) are available in subjects with CD

Reported adverse reactions listed in **Table 5** are based on experience from the two multicentre children and adolescents clinical trials using Rebetal with interferon alfa-2b or peginterferon alfa-2b. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥ 1/10); common (≥ 1/10 to < 1/10), and uncommon (≥ 1/100 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Adverse Reactions
Infections and infestations	
Very common:	Viral infection, pharyngitis
Common:	Bacterial infection, fungal infection, pulmonary infection, nasopharyngitis, pharyngitis streptococcal, sinusitis, tooth abscess, influenza, oral herpes, herpes simplex, urinary tract infection, vaginitis, gastroenteritis
Uncommon:	Pneumonia, ascariasis, enterobiasis, herpes zoster, cellulitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common:	Neoplasm unspecified
Blood and lymphatic system disorders	
Very common:	Anaemia, neutropenia
Common:	Thrombocytopenia, lymphadenopathy
Endocrine disorders	
Very Common:	Hypothyroidism
Common:	Hyperthyroidism, virilism
Metabolism and nutrition disorders	
Very common:	Anorexia, increased appetite, decreased appetite
Common:	Hyperglycaemia, hyperuricaemia,
Psychiatric disorders	
Very common:	Depression, emotional lability, insomnia
Common:	Suicidal ideation, aggression, confusion, affect lability, behaviour disorder, agitation, somnambulism, anxiety, mood altered, restlessness, nervousness, sleep disorder, abnormal dreaming, apathy
Uncommon:	Abnormal behaviour, depressed mood, emotional disorder, fear, nightmare
Nervous system disorders	
Very common:	Headache, dizziness
Common:	Hyperkinesia, tremor, dysphonia, paresthaesia, hyperaesthesia, hyperaesthesia, concentration impaired, comolence, disturbance in attention, poor quality of sleep
Uncommon:	Neuralgia, lethargy, psychomotor hyperactivity
Eye disorders	
Common:	Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder
Uncommon:	Conjunctival haemorrhage, eye pruritis, keratitis, vision blurred, photophobia
Ear and labyrinth disorders	
Common:	Vertigo
Cardiac disorders	
Common:	Palpitation, tachycardia
Vascular disorders	
Common:	Pallor, flushing
Uncommon:	Hypotension,
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhoea, sneezing, pharyngolaryngeal pain
Uncommon:	Wheezing, nasal discomfort
Gastro-intestinal disorders	
Very common:	Abdominal pain, abdominal pain upper, vomiting , diarrhoea, nausea
Common:	Mouth ulceration, stomatitis ulcerative, stomatitis, aphthous stomatitis, dyspepsia, cheilitis, glossitis, gastroesophageal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder, stomatal discomfort, oral pain
Uncommon:	Gingivitis
Hepatobiliary disorders	
Common:	Hepatic function abnormal
Uncommon:	Hepatomegaly
Skin and subcutaneous tissue disorders	
Very common:	Alopecia, rash
Common:	Pruritus, photosensitivity reaction, maculopapular rash, eczema, hyperhidrosis, acne, skin disorder, nail disorder, skin discoloration, dry skin, erythema, bruise
Uncommon:	Pigmentation disorder, dermatitis atopica, skin exfoliation
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia, myalgia, musculoskeletal pain
Common:	Pain in extremity, back pain, muscle contracture
Renal and urinary disorders	
Common:	Enuresis, micturition disorder, urinary incontinence, proteinuria
Reproductive system and breast disorders	
Common:	Female: amenorrhoea, menorrhagia, menstrual disorder, vaginal disorder, Male: testicular pain
Uncommon:	Female: dysmenorrhoea
General disorders and administration site conditions	
Very common:	Injection site inflammation, injection site reaction, injection site erythema, injection site pain, fatigue, rigors, pyrexia, influenza-like illness, asthenia, malaise, irritability
Common:	Chest pain, oedema, pain, injection site pruritus, injection site rash, injection site dryness, feeling cold
Uncommon:	Chest discomfort, facial pain, injection site induration
Investigations	
Very common:	Growth rate decrease (height and/or weight decrease for age)
Common:	Blood thyroid stimulating hormone increased, thyroglobulin increased
Injury, poisoning and procedural complications	
Common:	Skin laceration
Uncommon:	Contusion
P1.5/R Rebetal (800 mg) + peginterferon alfa-2b (1.5 micrograms/kg)	
P0.5/R Rebetal (1,000/1,200 mg) + peginterferon alfa-2b (1.5 to 0.5 microgram/kg)	
I/R Rebetal (1,000/1,200 mg) + interferon alfa-2b (3 MIU)	

Most of the changes in laboratory values in the Rebetal/peginterferon alfa-2b clinical trial were mild or moderate. Decreases in haemoglobin, white blood cells, platelets, neutrophils and increase in bilirubin may require dose reduction or permanent discontinuation from therapy (see section 4.2). While changes in laboratory values were observed in some patients treated with Rebetal used in combination with peginterferon alfa-2b in the clinical trial, values returned to baseline levels within a few weeks after the end of therapy.

4.9 Overdose

In clinical trials with Rebetal used in combination with peginterferon alfa-2b or interferon alfa-2b, the maximum overdose reported was a total dose of 10 g of Rebetal (50 x 200 mg capsules) and 39 MIU of interferon alfa-2b (13 subcutaneous injections of 3 MIU each) taken in one day by a patient in an attempt at suicide. The patient was observed for two days in the emergency room, during which time no adverse reaction from the overdose was noted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotheapeutic group: Direct acting antivirals, nucleosides and nucleotides (excl. reverse transcriptase inhibitors). ATC code: J05A B04.

Ribavirin (Rebetol) is a synthetic nucleoside analogue which has shown *in vitro* activity against some RNA and DNA viruses. The mechanism by which Rebetol in combination with peginterferon alfa-2b or interferon alfa-2b exerts its effects against HCV is unknown. Oral formulations of Rebetol monotherapy have been investigated as therapy for chronic hepatitis C in several clinical trials. Results of these investigations showed that Rebetol monotherapy had no effect on eliminating hepatitis virus (HCV-RNA) or improving hepatic histology after 6 to 12 months of therapy and 6 months of follow-up.

Rebetol clinical trials in adults

The use of Rebetal in combination treatment with peginterferon alfa-2b or interferon alfa-2b was evaluated in a number of clinical trials. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

Naïve patients

Three trials examined the use of interferon in naïve patients, two with Rebetal + interferon alfa-2b (C95-132 and I95-143) and one with Rebetal + peginterferon alfa-2b (C198-580). In all cases the treatment was for one year with a follow-up of six months. The sustained response at the end of follow-up was significantly increased by the addition of Rebetal to interferon alfa-2b (41 % vs 16 %, p < 0.001).

In clinical trials C95-132 and I95-143, Rebetal + interferon alfa-2b combination therapy proved to be significantly more effective than interferon alfa-2b monotherapy (a doubling in sustained response). Combination therapy also decreased the relapse rate. This was true for all HCV genotypes, particularly Genotype 1, in which the relapse rate was reduced by 30 % compared with interferon alfa-2b monotherapy.

In clinical trial C198-580, 1,530 naïve patients were treated for one year with one of the following combination regimens: • Rebetal (800 mg/day) + peginterferon alfa-2b (1.5 micrograms/kg/week) (n = 511). • Rebetal (1,000/1,200 mg/day) + peginterferon alfa-2b (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) (n = 514). • Rebetal (1,000/1,200 mg/day) + interferon alfa-2b (3 MIU three times a week) (n = 505).

In this trial, the combination of Rebetal and peginterferon alfa-2b (1.5 micrograms/kg/week) was significantly more effective than the combination of Rebetal and Interferon alfa-2b, particularly in patients infected with Genotype 1. Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of Rebetal administered in combination with peginterferon alfa-2b or interferon alfa-2b. In those patients that received > 10.6 mg/kg Rebetal (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg Rebetal (Table 6), while response rates in patients that received > 13.2 mg/kg Rebetal were even higher.

Table 6 Sustained response rates with Rebetal + peginterferon alfa-2b (mg/kg), genotype and viral load)					
HCV Genotype	Rebetol dose (mg/kg)	(mg/kg)	P 1.5/R P 0.5/R	I/R	
All Genotypes	All	54%	47%	47%	
	≤ 10.6	50%	41%	27%	
	> 10.6	61%	48%	47%	
Genotype 1	All	42%	34%	33%	
	≤ 10.6	38%	25%	20%	
	> 10.6	48%	34%	34%	
Genotype 1 ≤ 600,000 IU/ml	All	73%	51%	45%	
	≤ 10.6	74%	25%	33%	
	> 10.6	71%	52%	45%	
Genotype 1 > 600,000 IU/ml	All	30%	27%	17%	
	≤ 10.6	27%	25%	17%	
	> 10.6	82%	80%	79%	
Genotype 2/3	All	79%	73%	50%	
	≤ 10.6	79%	73%	50%	
	> 10.6	88%	80%	80%	
P1.5/R Rebetal (800 mg) + peginterferon alfa-2b (1.5 micrograms/kg)					
P0.5/R Rebetal (1,000/1,200 mg) + peginterferon alfa-2b (1.5 to 0.5 microgram/kg)					
I/R Rebetal (1,000/1,200 mg) + interferon alfa-2b (3 MIU)					

In a separate trial, 224 patients with genotype 2 or 3 received peginterferon alfa-2b, 1.5 microgram/kg subcutaneously, once weekly, in combination with ribavirin 800 mg -1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose) (Table 7). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

Table 7 Virologic Response at End of Treatment, Sustained Virologic Response and Relapse by HCV Genotype and Viral Load*				
	Rebetol 800-1,400 mg/day plus peginterferon alfa-2b 1.5 µg/kg once weekly	End of Treatment Response	Sustained Virologic Response	Relapse
All Subjects	94 % (211/224)	81 % (182/224)	12 % (27/224)	
HCV 2 ≤ 600,000 IU/ml	100 % (42/42)	93 % (39/42)	7 % (3/42)	
> 600,000 IU/ml	100 % (20/20)	95 % (19/20)	5 % (1/20)	
Uncommon	100 % (22/22)	91 % (20/22)	9 % (2/22)	
HCV 3 ≤ 600,000 IU/ml	93 % (169/182)	79 % (143/182)	14 % (24/166)	
> 600,000 IU/ml	93 % (92/99)	86 % (85/99)	8 % (7/91)	
Uncommon	93 % (77/83)	70 % (58/83)	23 % (17/75)	

* Any subject with an undetectable HCV-RNA level at the follow-up week 12 visit and missing data at the follow up week 24 visit was considered a sustained responder. Any subject with missing data in and after the follow-up week 12 window was considered to be a non-responder at week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %. In a non-comparative trial, 235 patients with genotype 1 and low viral load (< 600,000 IU/ml) received peginterferon alfa-2b, 1.5 microgram/kg subcutaneously, once weekly, in combination with weight adjusted Rebetal. The overall sustained response rate after a 24-week treatment duration was 30 %. For one percent of subjects (97/235) had nondetectable plasma HCV-RNA levels at week 4 and week 24 of therapy. In this subgroup, there was a 92 % (89/97) sustained virologic response rate. The high sustained response rate in this subgroup of patients was identified in an interim analysis (n=49) and prospectively confirmed (n=48). Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (11/11) and with a lower risk of relapse (0/11) as compared to 7/96 following 24 weeks of treatment).

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two peginterferon alfa-2b/Rebetol regimens [peginterferon alfa-2b 1.5 µg/kg and 1 µg/kg subcutaneously once weekly both in combination with Rebetal 800 to 1,400 mg p.o. daily (in two divided doses) or Rebetal 180 µg subcutaneously once weekly with Rebetal 1,000 to 1,200 mg p.o. daily (in two divided doses)] in 3,070 treatment-naïve adults with chronic hepatitis C genotype 1. Response to the treatment was measured by Sustained Virologic Response (SVR) which is defined as undetectable HCV-RNA at 24 weeks post-treatment (see Table 8).

Treatment group	% (number) of patients		
	peginterferon alfa-2b 1.5 µg/kg + Rebetal (n/N)	peginterferon alfa-2b 1 µg/kg + Rebetal (n/N)	peginterferon alfa-2a 180 µg + ribavirin (n/N)
Undetectable HCV-RNA at treatment week 12	40 (4077/1,019)	36 (3667/1,016)	45 (4667/1,035)
End of treatment response*	53 (5427/1,019)	49 (5007/1,016)	64 (6677/1,035)
Relapse*	24 (123/523)	20 (95/475)	32 (193/612)
SVR*	40 (4067/1,019)	38 (3867/1,016)	41 (4237/1,035)
SVR in patients with undetectable HCV-RNA at treatment week 12	81 (328/407)	83 (303/366)	74 (344/466)

*HCV-RNA PCR assay, with a lower limit of quantitation of 27 IU/ml

Lack of early virologic response by treatment week 12 (detectable HCV-RNA with a < 2 log10 reduction from baseline) was a criterion for discontinuation of treatment.

In all three treatment groups, sustained virologic response rates were similar. In patients of African American origin (which is known to be a poor prognostic factor for HCV eradication), treatment with peginterferon alfa-2b (1.5 µg/kg)/Rebetol combination therapy resulted in a higher sustained virologic response rate compared to peginterferon alfa-2b 1 µg/kg dose. At the peginterferon alfa-2b 1.5 µg/kg plus Rebetal dose, sustained virologic response rates were lower in patients with cirrhosis, in patients with normal ALT levels, in patients with a baseline viral load > 600,000 IU/ml and in patients > 40 years old. Caucasian patients had a higher sustained virologic response rate compared to the African Americans. Among patients with undetectable HCV-RNA at the end of treatment, the relapse rate was 24 %.

Predictability of sustained virological response in naïve patients

Virological response by week 12 is defined as at least 2-log viral load decrease or undetectable levels of HCV-RNA. Virological response by week 4 is defined as at least 1-log viral load decrease or undetectable levels of HCV-RNA. These time points (treatment week 4 and treatment week 12) have been shown to be predictive for sustained response (Table 9).

Table 9 Predictive Value of In-Treatment Virologic Response while on peginterferon alfa-2b 1.5 µg/kg/Rebetol 800-1,400 mg Combination Therapy					
	Negative		Positive		
	No Response At Treatment Week	No Sustained Response	Predictive Value	Response At Treatment Week	No Sustained Response
Genotype 1*					
By Week 4***				116	107
(n=950)					92% (107/116)
HCV-RNA negative	834	539	65% (539/834)	73	392
HCV-RNA negative or ≥ 1 log decrease in viral load	220	210	95% (210/220)	73	340
By Week 12***					
(n=915)					
HCV-RNA negative	508	433	85% (433/508)	407	328
HCV-RNA negative Or ≥ 1 log decrease in viral load	206	205	91% (205/206)	709	402
Genotype 2, 3**					
By Week 12					
(n=215)					
HCV-RNA negative Or ≥ 2 log decrease in viral load	2	1	50% (1/2)	213	177
					83% (177/213)

*Genotype 1 receive 48 weeks treatment

**Genotype 2, 3 receive 24 weeks treatment

***The presented results are from a single point of time. A patient may be missing or have had a different result for week 4 or week 12. † These criteria were used in the protocol: If week 12 HCV-RNA is positive and < 2 log10 decrease from baseline, patients to stop therapy. If week 12 HCV-RNA is positive and decreased ≥ 2 log10 from baseline, then retest HCV-RNA at week 24 and if positive, patients to stop therapy.

HCV/HIV co-infected patients Two trials have been conducted in patients co-infected with HIV and HCV. The response to treatment in both of these trials is presented in Table 10. Study 1 (IRBIAVC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either Rebetal (800 mg/day) plus peginterferon alfa-2b (1.5 µg/kg/week) or Rebetal (800 mg/day) plus interferon alfa-2b (3 MIU TIW) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either Rebetal (800-1,200 mg/day based on weight) plus peginterferon alfa-2b (100 or 150 µg/kg based on weight) or Rebetal (800-1,200 mg/day based on weight) plus interferon alfa-2b (3 MIU TIW). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load > 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6 month follow-up period.

Table 10 Sustained virological response based on genotype after Rebetal in combination with peginterferon alfa-2b in HCV/HIV co-infected patients						
	Study 11			Study 22		
	Rebetal (800 mg/day) Peginterferon alfa-2b (1.5 µg/kg/ week)	Rebetal (800 mg/day) + interferon alfa-2b (3 MIU TIW)	p value a	Rebetal (800- 1,200 mg/day) + peginterferon alfa-2b (100 or 150c µg/week)	Rebetal (800- 1,200 mg/day) a + interferon alfa-2b (3 MIU TIW)	p value b
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: p value based on Cochran-Mantel-Haenszel Chi square test.

b: p value based on chi-square test.

c: subjects < 75 kg received 100 µg/kg peginterferon alfa-2b and subjects ≥ 75 kg received 150 µg/kg peginterferon alfa-2b.

d: Rebetal dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

1 Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.

2 Laguno M, Murrillas J, Blanco JJ, et al. AIDS 2004; 18(13): F27-F36.

Histological response

Liver biopsies were obtained before and after treatment in Study 1 and were available for 210 of the 412 subjects (51 %). Both the Metavir score and Ishak grade decreased among subjects treated with Rebetal in combination with peginterferon alfa-2b. This decline was significant among responders (-0.3 for Metavir and -1.2 for Ishak) and stable (-0.1 for Metavir and -0.2 for Ishak) among nonresponders. In terms of activity, about one-third of sustained responders showed improvement and none showed worsening. There was no improvement in terms of fibrosis observed in this study. Steatosis was significantly improved in patients infected with HCV Genotype 3.

Previously treated patients

-Retreatment of prior treatment failures (relapse and non-responder patients) with peginterferon alfa- 2b in combination with Rebetal:

In a non-comparative trial, 2,293 patients with moderate to severe fibrosis who failed previous treatment with combination alfa-2b, interferon/ribavirin were retreated with peginterferon alfa-2b, 1.5 microgram/kg subcutaneously, once weekly, in combination with weight adjusted Rebetal. Failure to prior therapy was defined as relapse or non-response (HCV-RNA positive at the end of a minimum of 12 weeks of treatment). Patients who were HCV-RNA negative at Treatment week 12 continued treatment for 48 weeks and were followed for 24 weeks post-treatment. Response week 12 was defined as undetectable HCVRNA after 12 weeks of treatment. Sustained Virologic Response (SVR) is defined as undetectable HCV-RNA at 24 weeks post-treatment (Table 11).

Table 11 Rates of response to retreatment in prior treatment failures

	Patients with undetectable HCV-RNA at treatment week 12 and SVR upon retreatment				Overall Population*
	interferon alpha/ribavirin		peginterferon alpha/ribavirin		
	Response week 12 % (n/N)	SVR % (n/N) 99% CI	Response week 12 % (n/N)	SVR % (n/N) 99% CI	SVR % (n/N) 99% CI
Overall	38.6 (549/1,423)	59.4 (326/549) 54.0-64.8	31.5 (272/863)	50.4 (137/272) 42.6, 58.2	21.7 (497/2,293) 19.5, 23.9
Prior Response					
Relapse	67.7 (203/300)	59.6 (121/203) 50.7, 68.5	58.1 (200/344)	52.5 (105/200) 43.4, 61.6	37.7 (243/645) 32.8, 42.6
Genotype 1/4	59.7 (129/216)	51.3 (66/129) 39.8, 62.5	48.6 (122/251)	44.3 (54/122) 32.7, 55.8	28.6 (134/468) 23.3, 34.0
Genotype 2/3	88.9 (72/81)	73.6 (53/72) (60.2, 87.0)	83.7 (77/92)	64.9 (50/77) 50.9, 78.9	61.3 (106/173) 51.7, 70.8
NR	28.6 (258/903)	57.0 (147/258) 49.0, 64.9	12.4 (59/476)	24.1 (26/59) 17.4, 30.7	13.6 (188/1,385) 11.2, 15.9
Genotype 1/4	23.0 (182/790)	51.6 (94/182) 42.1, 61.2	9.9 (44/446)	38.6 (17/44) 19.7, 57.5	9.9 (123/1,242) 7.7, 12.1
Genotype 2/3	67.9 (74/109)	70.3 (52/74) 56.6, 84.0	53.6 (15/28)	60.0 (9/15) 27.4, 92.6	46.0 (63/137) 35.0, 57.0

Genotype 1	30.2 (343/1,135)	51.3 (176/343) 44.4, 58.3	23.0 (162/704)	42.6 (69/162) 32.6, 52.6	14.6 (270/1,846) 12.5, 16.7
2/3	77.1 (185/240)	73.0 (135/185) 64.6, 81.4	75.6 (96/127)	63.5 (61/96) 50.9, 76.2 55.3	203/367 48.6, 62.0
4	42.5 (17/40)	70.6 (12/17) 42.1, 99.1	44.4 (12/27)	50.0 (6/12) 12.8, 87.2	28.4 (19/67) 14.2, 42.5
METAVIR Fibrosis score					
F2	46.0 (193/420)	66.8 (129/193) 58.1, 75.6	33.6 (78/232)	57.7 (45/78) 43.3, 72.1	29.2 (191/653) 24.7, 33.8
F3	38.0 (163/429)	62.6 (102/163) 52.8, 72.3	32.4 (78/241)	51.3 (40/78) 36.7, 65.9	21.9 (147/672) 17.8, 26.0
F4	33.6 (192/572)	49.5 (95/192) 40.2, 58.8	29.7 (116/390)	44.8 (52/116) 32.9, 56.7	16.5 (159/966) 13.4, 19.5
Baseline Viral Load					
<VL <600,000 (U/ml)	32.4 (280/864)	56.1 (157/280) 48.4, 63.7	26.5 (152/573)	41.4 (63/152) 31.2, 51.7	16.6 (239/1,441) 14.1, 19.1
<VL <600,000 (U/ml)	48.3 (269/557)	62.8 (169/269) 55.2, 70.4	41.0 (118/288)	61.0 (77/118) 49.5, 72.6	30.2 (256/848) 26.1, 34.2