ANRS HC 23 COAT IFN STUDY

A multicentre, randomised, open-label study comparing the tolerability and viral reduction of the combination of IFN α-2b XL + Ribavirin versus peg IFN α-2b + Ribavirin in patients with chronic hepatitis C, genotype 1 or 4.

SUMMARY OF FINAL REPORT

DECEMBER 2013

Name of Sponsor/Company: INSERM-ANRS 101 rue de Tolbiac 75013 PARIS FRANCE	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product: • IFN α-2bXL 27 MIU • IFN α-2bXL 36 MIU • Viraferon PEG • Ribavirin	**Volume:**	
Name of Active Ingredient: • IFN α-2b • Ribavirin	**Page:**	

Title of Study:
A multicentre, randomised, open-label study comparing the tolerability and viral reduction of the combination of IFN α-2b XL + ribavirin versus peg IFN α-2b + ribavirin in patients with chronic hepatitis C, genotype 1 or 4.

Investigators:
Coordinating investigator: Prof. Christian TREPO

22 participating investigators

Study centre(s): Cf. Page 4
18 centres in France

4 centres in Romania

Publications:
Trepo C, Maynard-Muet M, Pradat P, et al. Interim report on efficacy results of a new sustained release interferon-alpha-2b (IFN alpha-2bXL) compared with Pegylated IFN-alpha-2b during a 3-month course of combined therapy with ribavirin in hepatitis C patients (Phase 2 study: ANRS HC23 COAT-IFN). Hepatology. 2012; 56:1013A-A.

Trepo C, Maynard-Muet M, Pradat P, et al. Intermediate analysis of a phase IIA study of a new sustained release interferon-alpha-2b (IFN-alpha-2bXL) confirms improved safety profile versus marketed pegylated IFN-alpha-2b during a 3-month course of combined therapy with weight-based ribavirin. Hepatology. 2011; 54:1440A-A.

Studied period (years):	**Phase of development:**
date of first enrolment : 10 March 2010 **date of last completed :** 26 June 2013	Phase IIa

Objectives:

The primary objective was to evaluate the antiviral activity (assessed by viral load decrease at week 4 and week 12), of repeated weekly injections for 12 weeks of IFN α-2b XL 27 MIU/week, IFN α-2b XL 36 MIU/week and the commercial reference product (peg IFN α-2b 1.5µg/kg/week) in combination with ribavirin in patients with chronic hepatitis C virus, including naive patients and those who did not respond to previous treatment with pegylated interferon plus ribavirin.

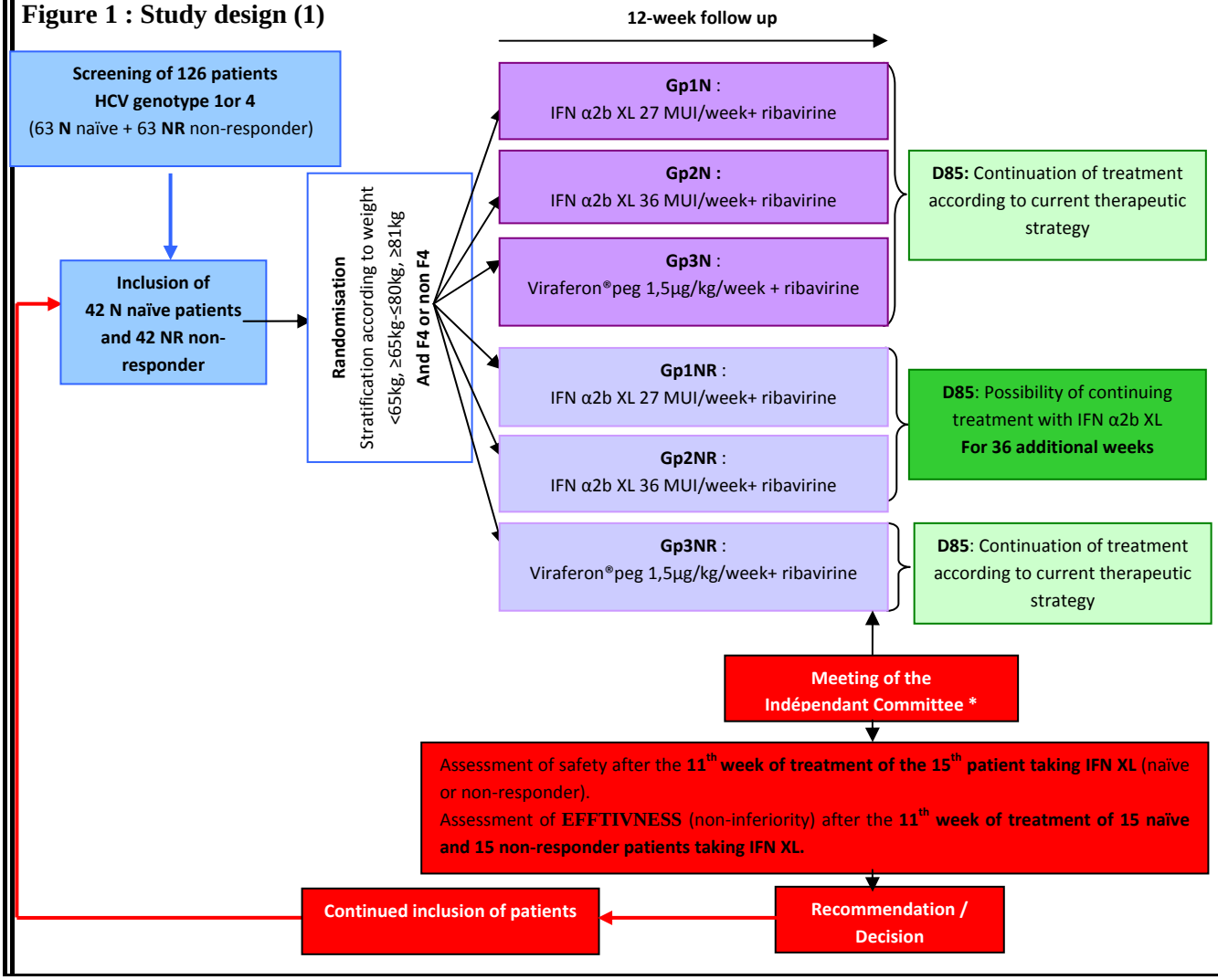
Secondary objectives include the assessment of clinical and biological tolerability.

Methodology:

Randomised, three-parallel-arm, comparative, open-label, multicentre, European (France and Romania) study, comparing three treatment regimens during 12 weeks :

- **Group 1** : IFN α-2bXL 27 MIU + Ribavirin
- **Group 2** : IFN α-2bXL 36 MIU + Ribavirin
- **Group 3** : Viraferon PEG + Ribavirin

Figure 1 : Study design (1)



Number of patients (planned and analysed):

84 patients were planned and enrolled (42 N naïve and 42 NR non-responder patients). **55 patients in France and 29 patients in Romania**. 56% were males, 79% had genotype 1 (21% genotype 4) and median age was 49.5 years (range 24-68). 15% were F4 (4, 4 and 5 in each treatment arm, respectively).

Centre's List

071 - Lyon	321 - Montpellier
016 - Nîmes	323 - Grenoble
090 - Tourcoing	327 - Créteil
300 - Clichy	329 - Saint Antoine
302 - Cochin	333 - Villejuif
304 - Pessac	335 - Besançon
305 - Marseille	357 - Poitiers
306 - Nice	901 - Hristea
307 - La Pitié	902 - Motoc
308 - Orléans	903 - Voiculescu
358 - Lille	904 - Sparchez

Number of patients per treatment arm according to patient' status at enrolment:

	IFN XL 27 MIU	IFN XL 36 MIU	Viraferon Peg	Total
Naive patients	14	14	14	**42**
Non-responder patients	14	14	14	**42**
Total	28	28	28	**84**

Diagnosis and main criteria for inclusion:

Main inclusion criteria

- Patient with chronic hepatitis C genotype 1 or 4, naïve or non-responsive to previous treatment with pegylated interferon α + ribavirin, non-responders being defined as patients with sensitivity to IFN with a viral load reduction of at least 1 log during treatment with pegylated interferon-α + ribavirin for at least 3 months, but without

- either a reduction of ≥ 2 log at the end of a 12-week treatment at a proper dosage taken according to plan

- or an undetectable viral load at the end of a 12-month treatment at a proper dosage taken according to plan
  - Between 18 and 65 years of age, and with a body weight between 45 and 100 kg
  - Laboratory and haematologic tests allow for treatment with interferon and ribavirin and show neither advanced liver disease nor impaired kidney, thyroid or immune system function
  - No hepatitis B or HIV-related infection
  - Patient has health insurance coverage
  - Patient has signed the consent form before undergoing any procedure specific to the study

Main exclusion criteria

- Women who are pregnant or nursing or likely to become pregnant during the study
- Absolute contraindication to interferon α or ribavirin
- Treatment with interferon or ribavirin within 3 months prior to inclusion
- History of organ transplantation
- Severe systemic infection, poorly controlled diabetes, certain cancers, liver disease associated with hepatitis
- Recent general anaesthesia or blood transfusion

Test product, dose and mode of administration:

- Group 1 : IFN α-2bXL 27 MIU/week, powder and solvent for solution for injection in combination with ribavirin
- Group 2 : IFN α-2bXL 36 MIU/week, powder and solvent for solution for injection in combination with ribavirin

Duration of treatment:

12 weeks + 36 complementary weeks in previously non-responder patients achieving EVR (early virological response defined as viral load reduction of at least 2 log at the end of week 12).

Reference therapy, dose and mode of administration:

- Group 3 : Pegylated IFN α-2b 1.5 µg/kg/week in combination with ribavirin (Viraferon®PEG)

Name of Finished Product: • IFN α-2bXL 27 MIU • IFN α-2bXL 36 MIU • Viraferon PEG • Ribavirin	**Volume:**
Name of Active Ingredient: • IFN α-2b • Ribavirin	**Page:**

Criteria for evaluation:

EFFICACY:

Efficacy was assessed **as viral load reduction at the end of week 4 and week 12.** Viral load was measured using real-time PCR with a threshold of 15 IU/mL.

Efficacy was also assessed giving **the percentage of patients with early viral response (EVR) (viral load reduction of at least 2 log) at the end of week 12, and the percentage of patients with complete early viral response (cEVR**) (viral load < 15 IU/mL) at the end of week 12. The percentage of patients with rapid viral response (viral load < 15 IU/mL) at week 4 was also calculated.

IL28b polymorphism

Since IL28b polymorphism is known to be associated with virological response to PEG-IFN/ribavirin therapy, the objective was to study the IL28b allele distribution in the different treatment groups. A skewed distribution of these alleles could indeed impact and bias virological response.

IP-10 level

Similarly, it has been shown that high pre-treatment serum levels of interferon-gamma-inducible protein 10 kDa (IP-10) are associated with nonresponse or virologic relapse after PEG-IFN/ribavirin combination therapy and a level above 600 pg/mL was suggested as being associated with lower response rate. The IP-10 level in each treatment group was thus assessed to see whether a confounding effect could be observed.

SAFETY:

- Biological tolerance was assessed by studying the following parameters: hemoglobin, neutrophils, and platelets. For each patient and for each of these parameters, the maximal decrease (difference between baseline value and nadir) was calculated. Biological tolerance also included assessment of **ANTI-IFN-α AND ANTI-POLYMER ANTIBODY LEVELS.**

- Tolerance at the injection site was measured using a specific form recording presence/absence of erythema, pain, induration, burning sensation, itching, and nodular infiltration.

- Clinical safety was also assessed through recording of all adverse events throughout the study period. For each event, the grade (ANRS scale) and level of imputability were recorded.

COMPLIANCE, PERCEIVED TOXICITY AND QUALITY OF LIFE :

Compliance, perceived toxicity and quality of life will be assessed using quality of life questionnaires administered to patients.

PHARMACOKINETIC PARAMETERS

Serum concentrations of IFNα -2b will be analysed following the first week administration. An ELISA assay (Enzyme-Linked ImmunoSorbent Assay), validated for recombinant Interferon α-2b, will be used to measure serum levels of interferon. The following parameters will be analysed during the 7 days following injection on Day 1: **Cmax, tmax, tlag, ke, t1/2, AUC0-t, AUC0-∞.**In addition, residual serum levels of IFNα-2b will be measured before the injections on Days 8, 15, 22, 29,36, 50, 64, 78 and 85.

Statistical methods:

Quantitative variables were compared between the three treatments arms using the non-parametric Kruskal-Wallis test and qualitative parameters using the Fisher exact test. Quantitative data are presented as means +/- standard deviation and qualitative data as the number and percentage of patients. Analyses were performed using SPSS for Windows or R. A p value below 0.05 was considered as statistically significant.

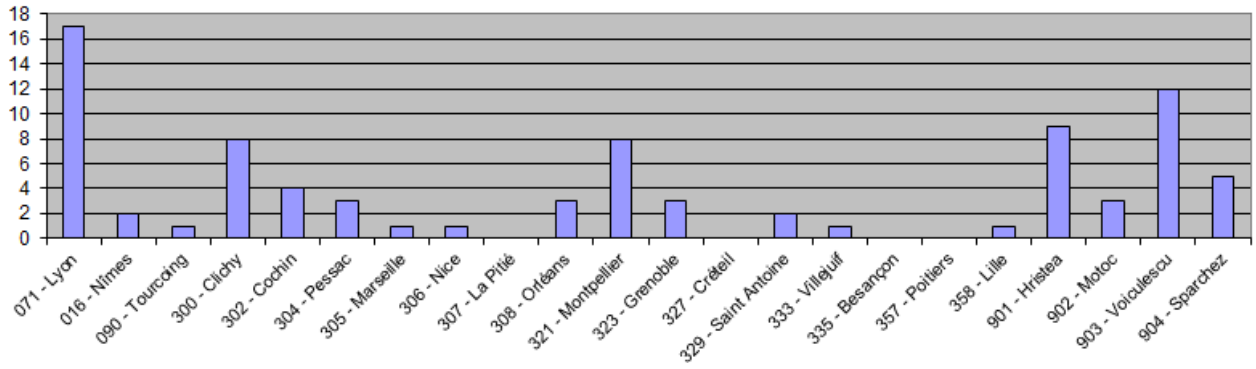
SUMMARY - CONCLUSIONS

Inclusions
84 patients were included between March 2010 and June 2012

Number of patients per centre
84 patients were enrolled in 14 active centres in France and 4 centres in Romania : 55 patients in France and 29 in Romania.

Number of patients per centre

84 patients were enrolled in 18 centres in France and 4 centres in Romania.



Deviations
None of the reported deviations had an impact on patients' safety (Cf. appendix 1).

Patients' characteristics

Naive patients

	IFN XL 27 MIU (n=14)	IFN XL 36 MIU (n=14)	Viraferon Peg (n=14)	p
Male gender, n *(%)*	11 *(78.6)*	6 *(42.9)*	7 *(50)*	0.150
Genotype 1, n *(%)*	10 *(71.4)*	12 *(85.7)*	11 *(78.6)*	0.892
Age (years) (Mean ± SD)	44.9 ± 7.7	52.9 ± 5.3	49.4 ± 10.1	0.049
Known duration of infection (years)	7.9 ± 7.1	8.3 ± 7.8	9.9 ± 10.1	0.934
Weight (kg)	75.4 ± 16.1	72.2 ± 13.0	76.6 ± 16.9	0.731
BMI ($kg.m^{-2}$)	24.8 ± 4.1	25.8 ± 3.6	27.0 ± 3.8	0.732
Cirrhosis (F4), n *(%)*	2 *(14.3)*	2 *(14.3)*	2 *(14.3)*	1

Among naive patients, those in the IFN XL 27 arm were slightly younger than those in the IFN XL 36 arm.

Non-responder patients

	IFN XL 27 MIU (n=14)	IFN XL 36 MIU (n=14)	Viraferon Peg (n=14)	p
Male gender, n *(%)*	9 *(64.3)*	7 *(50.0)*	7 *(50.0)*	0.792
Genotype 1, n *(%)*	11 *(78.6)*	12 *(85.7)*	10 *(71.4)*	0.892
Age (years) (Mean ± SD)	51.9 ± 9.0	46.7 ± 10.8	51.8 ± 8.1	0.416
Known duration of infection (years)	9.0 ± 6.5	7.6 ± 7.2	8.8 ± 8.4	0.733
Weight (kg)	74.5 ± 11.6	75.3 ± 13.7	72.9 ± 12.8	0.984
BMI ($kg.m^{-2}$)	25.5 ± 2.4	27.0 ± 4.4	26.0 ± 4.2	0.312
Cirrhosis (F4), n *(%)*	2 *(14.3)*	2 *(14.3)*	3 *(21.4)*	1

EFFICACY RESULTS:

Naive patients (n=42)

Nb of patients with F4	IFN XL 27 MIU (n=14) *2*	IFN XL 36 MIU (n=14) *2*	Viraferon Peg (n=14) *2*	p
VL decrease at W4 (Log ± SD)	1.4 ± 1.6	1.4 ± 1.4	2.4 ± 1.9	0.223
VL decrease at W12 (Log ± SD)	3.3 ± 2.8	2.3 ± 2.2	4.2 ± 2.6	0.104
RVR* [n *(%)*]	0	1 *(7.1)*	2 *(14.3)*	0.761
EVR† [n *(%)*]	8 *(57.1)*	6 *(42.9)*	10 *(71.4)*	0.371
cEVR†† [n *(%)*]	6 *(42.9)*	3 *(21.4)*	9 *(64.3)*	0.086

**RVR=rapid virologic response defined as HCV RNA level below the detection threshold of 15 IU/mL at W4*

† HCV RNA decrease ≥2 log IU/mL at W12

†† cEVR defined as HCV RNA level below the detection threshold of 15 IU/mL at W12

Non-responder patients (n=42)

Nb of patients with F4	IFN XL 27 MIU (n=14) *2*	IFN XL 36 MIU (n=14) *2*	Viraferon Peg (n=14) *3*	p
VL decrease at W4 (Log ± SD)	0.6 ± 0.5	0.6 ± 0.4	0.7 ± 0.6	0.943
VL decrease at W12 (Log ± SD)	0.7 ± 0.9	0.8 ± 0.7	1.2 ± 1.0	0.246
RVR* [n *(%)*]	0	0	0	1
EVR† [n *(%)*]	1 *(7.1)*	1 *(7.1)*	1 *(7.1)*	1
cEVR†† [n *(%)*]	0	0	0	1

**RVR=rapid virologic response defined as HCV RNA level below the detection threshold of 15 IU/mL at W4*

†HCV RNA decrease ≥2 log IU/mL at W12 ††cEVR defined as HCV RNA level below the detection threshold of 15 IU/mL at W12

Antiviral activity was similar for IFNα-2bXL 27 MIU, IFNα-2bXL 36 MIU and Viraferon PEG with a mean viral decrease at W12 for naive patients of 3.3 log, 2.3 log and 4.2 log, respectively (p=0.104). The corresponding figures for non-responders were 0.7 log, 0.8 log and 1.2 log (p=0.246). In naive patients, cEVR was obtained in 6 patients receiving IFN α-2bXL 27 MIU, 3 patients receiving IFN α-2bXL 36 MIU, and 9 patients receiving Viraferon PEG (p=0.086) whereas EVR was obtained in 8, 6 and 10 patients, respectively (p=0.371).

Among non-responder patients, none achieved cEVR whereas 3 patients achieved EVR (one in each treatment arm; p=1).

IL28b polymorphism

Since IL28b polymorphism is known to be associated with virological response to PEG-IFN/ribavirin therapy, the objective was to study the IL28b allele distribution in the different treatment groups. A skewed distribution of these alleles could indeed impact and bias virological response.

A specific genetic consent was obtained for 47 patients (56%). Among them, 10 (21%) were C/C, 29 (62%) were C/T, and 8 (17%) were T/T. The substantial proportion of missing information did not allow us to assess the overall allele distribution in the different treatment arms and the potential impact.

IP-10 level

It has been shown that high pre-treatment serum levels of interferon-gamma-inducible protein 10 kDa (IP-10) are associated with nonresponse or virologic relapse after PEG-IFN/ribavirin combination therapy and a level above 600 pg/mL was suggested as being associated with lower response rate. The IP-10 level in each treatment group was thus assessed to see whether a confounding effect could be observed.

	IFN XL 27 MIU	IFN XL 36 MIU	Viraferon Peg	p
Naive patients	N=13	N=14	N=14	
Median IP-10 level (pg/mL)	157.0	99.5	73.3	0.587
Nb of pts with IP-10>600 pg/mL	0	2	2	0.357
Non-responder patients	N=14	N=14	N=14	
Median IP-10 level (pg/mL)	141	238	146	0.475
Nb of pts with IP-10>600 pg/mL	0	4	1	0.052

Among naive patients, the median IP-10 level seems higher in the IFN XL 27 MIU group compared with IFN XL 36 MIU and Viraferon Peg although this difference does not reach statistical significance. It is therefore reasonable to conclude that IP-10 level distribution did not strongly impact our results.

SAFETY RESULTS:

Biological criteria

Nb of patients with F4	IFN XL 27 MIU (n=28) *4*	IFN XL 36 MIU (n=28) *4*	Viraferon Peg (n=28) *5*	p
Hemoglobin decrease (g/dL)	2.8 ± 1.5	2.5 ± 1.2	2.6 ± 1.2	0.675
Patients with Hb<10g/dL during FU	2 *(7.1)*	3 *(10.7)*	5 *(17.9)*	0.544
PNN decrease (10^9/L)	1.24 ± 1.23	2.17 ± 1.97	1.58 ± 0.69	0.096
Patients with PNN<0.75.10^9/L during FU	2 *(7.1)*	1 *(3.6)*	2 *(7.1)*	1
Platelets decrease (10^9/L)	34 ± 27	42 ± 35	52 ± 40	0.253
Patients with platelets <100.10^9/L during FU	2 *(7.1)*	3 *(10.7)*	5 *(17.9)*	0.544

Tolerance at injection site

	IFN XL 27 MIU (n=28)	IFN XL 36 MIU (n=28)	Viraferon Peg (n=28)	p
Erythema	15	16	22	0.132
Pain	5	9	2	0.066
Induration	4	8	1	0.038
Burning sensation	2	6	1	0.134
Itching	2	6	5	0.408
Nodular infiltration	1	1	0	1

Severity of erythema

	IFN XL 27 MIU (n=28)	IFN XL 36 MIU (n=28)	Viraferon Peg (n=28)	p
Erythema, n *(%)*	15 *(53.6)*	16 *(57.1)*	22 *(78.6)*	0.132
Mild, n *(%)*	7 *(46.7)*	8 *(50.0)*	15 *(68.2)*	
Moderate, n *(%)*	6 *(40.0)*	6 *(37.5)*	6 *(27.3)*	
Severe, n *(%)*	2 *(13.3)*	2 *(12.5)*	1 *(4.5)*	

Most frequently encountered adverse events (n>10)

Most frequently encountered adverse events were Flu-like syndrome (83% of all cases) followed by asthenia (68%) and sleep disorder (32%). No clear-cut difference appeared between treatment arms except a possible over-risk of irritability in the PEG-IFN group.

Among biological abnormalities, four patients developed severe leucopenia (ANRS grade 3), one, two, and one in each treatment arm respectively.

	IFN XL 27 MIU (n=28)	IFN XL 36 MIU (n=28)	Viraferon Peg (n=28)	p
Flu-like syndrome *Grade 1/2/3/4**	24 *15/9/0/0*	23 *14/8/0/0***	23 *14/7/2/0*	1
Asthenia *Grade 1/2/3/4*	19 *15/4/0/0*	16 *6/8/1/0***	22 *14/7/1/0*	0.252
Sleep disorder *Grade 1/2/3/4*	11 *7/4/0/0*	10 *6/3/1/0*	6 *5/1/0/0*	0.337
Leucopenia *Grade 1/2/3/4*	6 *1/4/1/0*	7 *1/4/2/0*	10 *1/8/1/0*	0.557
Nausea *Grade 1/2/3/4*	8 *7/1/0/0*	9 *9/0/0/0*	6 *3/3/0/0*	0.749
Prurit *Grade 1/2/3/4*	9 *7/2/0/0*	9 *8/0/1/0*	5 *4/1/0/0*	0.418
Dyspnea *Grade 1/2/3/4*	6 *4/2/0/0*	4 *3/1/0/0*	9 *7/2/0/0*	0.316
Loss of appetite *Grade 1/2/3/4*	4 *3/1/0/0*	6 *4/2/0/0*	6 *3/3/0/0*	0.829
Dizziness *Grade 1/2/3/4*	2 *1/1/0/0*	9 *7/1/1/0*	4 *2/2/0/0*	0.065
Diarrhea *Grade 1/2/3/4*	4 *4/0/0/0*	5 *3/2/0/0*	5 *3/2/0/0*	1
Joint pains *Grade 1/2/3/4*	4 *3/1/0/0*	3 *3/0/0/0*	6 *5/1/0/0*	0.651

Anemia *Grade 1/2/3/4*	3 *2/1/0/0*	3 *3/0/0/0*	6 *5/1/0/0*	0.574
Irritability *Grade 1/2/3/4*	2 *1/1/0/0*	2 *1/1/0/0*	8 *5/3/0/0*	0.046
Dry skin *Grade 1/2/3/4*	2 *1/1/0/0*	4 *3/1/0/0*	6 *4/2/0/0*	0.370
Depression *Grade 1/2/3/4*	4 *3/1/0/0*	3 *0/2/1/0*	4 *3/0/1/0*	1

**Grade 1=mild; 2=moderate; 3=severe; 4=life threatening*

***One patient with unspecified grade*

Overall and mean number of adverse events (AE)

	IFN XL 27 MIU (n=28)	IFN XL 36 MIU (n=28)	Viraferon Peg (n=28)	p
Overall number of AE	177	202	200	
Number of AE/patient	6.3	7.2	7.1	0.462

The total number of adverse events seems slightly lower with IFNα-2bXL 27 MIU than with IFNα-2bXL 36 MIU or Viraferon PEG, although this difference does not reach statistical significance.

Serious adverse events

The list of serious adverse events is given in Appendix 2.

ANTI-IFN-α ANTIBODY LEVELS

Only 4 patients presented significant anti-IFNα antibody level and 7 patients presented low amounts.

ANTI-POLYMER ANTIBODY LEVELS

No patients had significant anti-polymer antibody level. No significant evolution of this level was observed after the beginning of treatment.
Only 2 patients presented significant increase of anti-polymer antibody level at day 85 but the titre remained low.

COMPLIANCE, PERCEIVED TOXICITY, QUALITY OF LIFE

Health questionnaires were used to evaluate perceived toxicity of treatment (self-reported symptoms), depressive symptoms, and quality of life (including functional impact of fatigue). Patients' adherence to treatment was also assessed.

The study of health questionnaires aimed at:
- describing the changes observed in these patient-reported outcomes (PROs) during follow-up in treatment groups
- analyzing the effect of treatment group on each outcome
- identifying other potential correlates of PROs (among socio-demographic and behavioral variables)
- analyzing the relationship between adherence to treatment and viral response at W12

Comparison of treatment groups

- No significant differences were found between experimental treatment groups (Gp1 and Gp2) and the standard treatment group (Gp3) for all patient-reported outcomes (PROs) considered, including:

- number of self-reported symptoms
- number of self-reported symptoms causing discomfort
- depressive symptoms (CES-D)
- physical quality of life (PCS)
- mental quality of life (MCS)
- functional impact of fatigue (FIS)
- adherence to HCV treatment.

- Higher values for MCS were observed in Gp1 than in Gp3 in the univariate analysis.

- Lower values for MCS were observed in Gp2 than in Gp1.

- No significant differences were found between experimental drug treatment groups (Gp1 and Gp2) and the standard treatment group (Gp3) for the number of self-reported symptoms and the number of self-reported symptoms causing discomfort after excluding from the analysis the data corresponding to visits with low or medium adherence to HCV treatment.

Changes with time in PROs

- The number of self-reported symptoms, the number of self-reported symptoms causing discomfort, CES-D score and perceived functional impact of fatigue significantly increased during the follow-up.

- Adherence to HCV treatment significantly decreased during the follow-up (44 patients classified as highly adherent at Day 29 versus 31 patients at Day 85).

Potential correlates of PROs

- History of IFN therapy was not found to be significantly associated with any PRO.
- Gender, age, BMI, tobacco use and alcohol consumption were not found to be significantly associated with the number of self-reported symptoms, the number of self-reported symptoms causing discomfort, the presence of depressive symptoms, physical and mental quality of life, perceived functional impact of fatigue.
- Women and alcohol abusers tended to report high adherence less frequently than the other patients (not significant at the 0.05 level).
- Age, BMI and tobacco use were not found to be significantly associated with high adherence to HCV treatment.
- High adherence during the follow-up was not significantly associated with viral response at W12 (p=0.08).

PHARMACOKINETIC PARAMETERS

The aim of this study was to determine the concentrations of interferon alpha-2b and pegylated interferon alpha-2b in human serum samples collected. Validated ECLIA analytical methods for the determination of interferon alpha-2b and pegylated interferon alpha-2b in human serum were used for the analysis of human serum samples from ANRS HC23 COAT IFN. The pre-study and in-study validation criteria were met for a successful analysis of the study samples.

Baseline samples (Visit 1, Day 1 – pre-dose) and last visit samples (Visit 16, Day 85 – V16) were analysed spiked to control potential interference of individual matrices in the detection of the analytes (interferon alpha-2b or pegylated interferon alpha-2b). Among patients for which results were available, interferences were observed in some cases and were especially marked for patients 005_R901, 007_R901 and 018_R903.

CONCLUSION

No clear-cut difference is observed between the three treatment arms in terms of viral efficacy as assessed by viral load decrease at week 4 and week 12 or by the proportion of patients with RVR, EVR and cEVR.

Due to a substantial proportion of patients without IL28b information, IL28b allele distribution in the different treatment groups could not be adequately assessed.

Results on IP-10 level distribution suggest no strong impact or bias on the efficacy results.

Regarding compliance, perceived toxicity and quality of life analysis, no significant differences were found between experimental drug treatment groups (Gp1 and Gp2) and the standard drug treatment group (Gp3) for all patient-reported outcomes (PROs) considered

Safety data report no difference in terms of biological tolerance (hemoglobin, PNN, platelets), tolerance at injection site (except a possible overrisk of pain and induration in patients receiving IFNα-2bXL 36 MIU) and occurrence of adverse events (except an increased risk of irritability in patients receiving PEG-IFN) between study treatment groups.

Date of the report: 18/12/2013

APPENDIX 1 ANRS HC23 COAT IFN STUDY : DEVIATIONS FROM INCLUSION CRITERIA (Authorized by the study coordinator Pr Ch Trepo or the medical project manager Dr M Maynard)				
PATIENT	**CRITERIA**	**DATE OF REQUEST**	**DETAILS**	**DATE OF AUTHORIZATION**
071 004 DIJX	Biological results	25/05/2010	AST results non interpretable at V0. Use of a recent result (18/03/2010) to validate pre-inclusion visit.	25/05/2010
071-005-KWVJ	Age	27/09/2010	The patient was born on 25/05/1942. She was 68 years old at pre-inclusion.	27/09/2010
071-007-RVSN	Naive definition	25/02/2011	The patient received a 17 day long treatment by Peg IFN+Ribavirin from 01 to 17th March 2006. Ribavirin cessation on 26/03/2006. Patient considered as treatment naive.	28/02/2011
071-009-IEMV	Biological results/Non-Responder definition	31/03/2011	Leucocytes <4000/mm3 (3520/mm3). Treatment by Viraferon PEG+Ribavirin from 18/11/2004 to 22/12/2005. Viral load decrease < 1 log (-0.63 log)	04/04/2011
071-010-UXXL	Age	11/07/2011	The patient was born on 01/02/1945. She was 66 years old at pre-inclusion.	15/10/2012
071-016-VNSJ	Naive definition	29/09/2011	The patient received several lines of therapy. Standard alpha-IFN monotherapy (6 months), standard alpha IFN + ribavirin (1 month), ribavirin as maintenance therapy. These treatments were initiated in the 90s and were of short duration. The patient was considered as naive for this study.	29/09/2011
071-017-QAXD	Weight/biological results/associated pathology	14/09/2011	Weight at 113 kg (agreement from Flamel). Hemoglobin at 12.4 g/dl (instead of 13). Moderate to severe Hemophilia A.	16/09/2011

071-018-YDKT	Biological results	02/09/2011	Leucocytes at 2680/mm3 (>4000); PNN at 940/mm3 (>1500)	07/09/2011
071-020-KOIG	Non-Responder definition	24/05/2012	Viral load decrease > 2 log during a previous 3 month course of treatment	29/05/2012
071-022-WUBM	Naive definition	13/12/2012	The patient received Ribavirin monotherapy from 21/04/2005 to November 2011. She was considered as naive for this study	13/12/2012
071-024-XKFK	Biological results	02/03/2012	Glucose above normal range	06/03/2012
300-002-ROCS	Non-Responder definition	28/12/2011	Viral load decrease <1 log during previous treatment	09/01/2012
300-002-ROCS	ECG	08/03/2011	ECG not done at V0*	18/02/2013
300-006-UUGF	Non-Responder definition	27/06/2012	Viral load decrease <1 log during previous treatment	05/07/2012
300-006-UUGF	ECG	27/06/2012	ECG not done at V0*	05/07/2012
300-008-GDJJ	Non-Responder definition	02/10/2012	Received only one month of Viraferon PEG + Ribavirin therapy (<3months)	02/10/2012
300-008-GDJJ	Biological results	_	CBC, fibrinogen, anti-TSH receptor, HIV, anti-thyroglobulin and anti-thyroperoxidase not done at V0*	17/12/2012
305-001-DEDA	Biological results	06/12/2010	Anti-smooth muscle antibodies at 1/160 (threshold at 1/320). Non clinically significant.	06/12/2010
306-001-OAVX	Associated pathology	16/11/2011	Papillary thyroidian carcinoma on 16/11/2008. D1 on 11/04/2011	24/11/2011
308-001-NRCA	Biological results	15/06/2010	Hemoglobin <12g/l (11.4g/l)	15/06/2010
308-002-YKQR	Biological results	09/09/2010	Fibroscan at 12.3 KPa (max 12 KPa)	17/09/2010

APPENDIX 2: SERIOUS ADVERSE EVENT

Patient ID	Death	Probable cause of death	Life threatening	Hospitalisation	Date of seriousness onset	Main diagnosis	Description	Outcome except death
071-007-RVSN	No		No	Yes	23/03/2011	Diabetes glycaemia of 3g.	Prolongation of hospitalisation due to diabetes	4
323-002-AVUQ	No		No	Yes	13/10/2011	Malaise	Epigastralgia, malaise without loss of consciousness	5
071-012-YUCW	No		No	Yes	05/03/2012	Adjustement of insuline dose	Adjustement of insuline dose	5
071-013-XCKP	No		No	Yes	11/10/2011	Syncope	Syncope	2
903-013-CJFR	No		No	Yes	14/06/2012	Headache, poyleuropathy	Patient have frontal headache, fotophobia, vertigo, equilibrum disorders, phosphenes, vomiting	2
903-013-CJFR	No		No	Yes	13/06/2012	Vertigo	Vertigo since 13/06/2012, progressively measuring which determined hospitalization on 20/07/2012. Blood tests (biochemistry, hemoleuco : normal)	2
071-011-TYFK	No		No	Yes	04/05/2011	Hematemesis and melena	Episode of hematemesis and melena	5
071-017-QAXD	No		No	Yes	19/10/2011	Drug intolerance	Fatigue, effort dyspnea, fever	5
302-001-NLQG	Yes	Motor cycling accident	No	No	06/01/2012	Death	Death	
903-011-RAGE	No		Yes	No	ND/07/2012	Suicidal ideation	Suicidal ideation	5
903-019-DLCO	No		No	Yes	07/09/2012	Right tight abscess	Right tight abscess	5

071-012-YUCW	No		No	Yes	12/03/2012	Acute pyelonephritis	Acute pyelonephritis	5
302-004-TYIY	No		No	Yes	09/01/2012	Splenic lymphoma	Splenic lymphoma	5

1: unknown; 2: recovering; 3: worsening; 4: stable; 5: recovered

PRINCIPAL OR COORDINATING
INVESTIGATOR(S) SIGNATURE(S)
OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER

STUDY TITLE: A multicentre, randomised, open-label study comparing the tolerability and viral reduction of the combination of IFN α-2b XL + ribavirin versus peg IFN α-2b + ribavirin in patients with chronic hepatitis C, genotype 1 or 4.

STUDY AUTHOR(S): Pr Christian Trepo, PI.

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

INVESTIGATOR: **Christian TREPO** SIGNATURE :

SPONSOR : **Pr. Jean-François DELFRAISSY** SIGNATURE :
Directeur de **l'ANRS**

DATE: December 18, 2013