CLINICAL TRIAL PROTOCOL WITH DRUGS

Open-label Phase III Study to Evaluate the Efficacy and Safety of Boceprevir Treatment in Patients co-infected with HIV and HCV (genotype 1), who have failed previous treatment with peginterferon and ribavirin

Protocol Code: BOC-HIV

Version / Date: 1.0, dated 18 September 2012.
EudraCT number: 2012-003984-23
ClinicalTrials.gov ID: NCT01718301

SPONSOR: Fundació Clínic per a la Recerca Biomèdica Principal Investigator and coordinator of the study:
Dr. Josep Mallolas Masferrer.
Head of HIV Day Hospital.
Infectious Diseases Service.
Hospital Clínic de Barcelona.
Spain.

Phone: +34 932274747 / +34-649914304.
Email: mallolas@clinic.ub.es

CONFIDENTIAL

1. SUMMARY

1.0. Type of application:

Open-label, phase III, prospective, multicenter study.

1.1. Identification of the developer:

Fundació Clínic per a la Recerca Biomèdica
Manager: Ms. Pastora Martínez Samper
C. Roselló, 143
08036 Barcelona

1.2. Title of the clinical trial:

Phase III open-label study to evaluate the efficacy and safety of boceprevir treatment in patients co-infected with HIV and HCV (genotype 1), who have failed prior treatment with peginterferon and ribavirin.

Version / Date: 1.0, dated 18 September 2012.

1.3. Protocol code: BOC-HIV

EudraCT number: 2012-003984-23

1.4. Principal Investigator and Study Coordinator: Dr. Josep Mallolas Masferrer

Collaborating researchers: Dr. Montserrat Laguno Centeno.

1.5. Centres in which the trial is planned to be carried out:

The centres where the trial is planned to be carried out are detailed in the document *"List of participating centres and researchers".*

1.6. Clinical Research Ethics Committees that have approved the trial:

The trial has been presented to all the CEICs corresponding to the participating centers, and the CEIC of the Hospital Clínic de Barcelona has also been assigned as a reference CEIC.

1.7. Name and qualification of the person responsible for monitoring:

Dr. Anna Cruceta.
Clinical Trials Unit.
CTU Clinic. Clinical Pharmacology Service.
(Hospital Clínic de Barcelona).
Head of the CTU: Dr Joan Albert Arnaiz

1.8. Study drug information:

Boceprevir: The drug has final approval by the Ministry of Health. As stated in its technical sheet (see annexes).

1.9. Phase of the clinical trial: Phase III.

1.10. Objectives:

1.10.1. Main objective:

The primary objective of this study is to evaluate the safety and efficacy of response-guided therapy with boceprevir 800 mg three times daily orally (o.v.) in combination with peginterferon (alpha-2b or alpha-2a) and ribavirin in genotype 1 HIV- and HCV-infected patients in whom prior HCV treatment with ribavirin-associated pegylated interferon had failed.

1.10.2. Secondary objectives:

- To define predictors of sustained virologic response (SVR), such as epidemiological factors, disease characteristics, clinical status of HIV infection, and response during treatment, especially at weeks 4, 8, 12, and at the end of treatment.

- To determine the percentage of patients with undetectable HCV RNA at treatment weeks (ST) 4, 8, and 12 and at the end of treatment.

- Evaluate virologic response based on baseline characteristics

- To investigate HCV resistance following virological failure with a regimen containing boceprevir (BOC). Blood samples should be obtained at baseline, at the time of virological failure (VF) (VF: two consecutive samples with signs of HCV replication after HCV was undetectable – below the lower limit of detection – or HCV RNA rebound equal to or greater than one logarithmic unit with respect to the RNA nadir) and six months after virological failure. The evaluation of resistance will be carried out in a single center (coordinating center: Hospital Clínic, Barcelona) by means of population sequencing of the genome that encodes the HCV protease.

1.11. Design:

Open-label, Phase III, prospective, multicenter study.

1.12. Disease under study:

HCV (hepatitis C virus) co-infection (genotype 1 (subtype a or b)) + HIV (acquired immunodeficiency virus)

1.13. Assessment variables:

1.13.1. Main

- **Primary efficacy endpoint:** achievement of SVR (sustained virologic response, defined as an undetectable plasma HCV RNA at follow-up week (SS) 24. If SS24 data are not available in a patient and the HCV RNA in SS12 is undetectable, SVR will be considered to be present.

1.13.2. Secondary

- Percentage of patients with virologic response (HCV RNA undetectable at weeks 4, 8, or 12) in those who achieve SVR.
- Percentage of patients with HCV RNA undetectable in SS12.

- Percentage of patients with undetectable HCV RNA 72 weeks after randomization.

- To investigate the resistances that appear after virological failure. Blood samples will be obtained at baseline, at the time of virological failure (VF) (VF defined as two consecutive samples with detectable HCV-RNA after the HCV-RNA is undetectable – below the lower limit of detection – or HCV-RNA rebound equal to or greater than one logarithmic unit with respect to the RNA nadir) and six months after virological failure. The evaluation of resistance will be carried out in a single center (coordinating center: Hospital Clínic, Barcelona) by means of population sequencing of the genome encoding the HCV protease

- Safety

1.14. Study population and total number of patients:

Adult patients with well-controlled chronic HIV infection and chronic hepatitis with genotype 1 C virus (subtype a or b), who have failed previous treatment with pegylated interferon associated with ribavirin.

A total of 128 patients will be included.

1.15. Duration of treatment:

The approximate expected duration for the inclusion of patients is 12 months, and the duration of treatment and follow-up of the included patients will be extended by a maximum of 72 weeks.

1.16. Schedule and expected completion date:

The study is expected to begin, once the permits have been obtained, in March 2013. The recruitment period will be 12 months. Patients will be followed for 6 months after the end of treatment. The study is expected to be completed in November 2015.

2. INDEX

Annexes and documents:

List of participating centres and researchers, version 1.0 dated 18 September 2012.

3. General Information

3.1 Identification of the test

Title:
Phase III open-label study to evaluate the efficacy and safety of boceprevir treatment in patients co-infected with HIV and HCV (genotype 1) who have failed prior treatment with peginterferon and ribavirin.
Open-label, Phase III, prospective, multicenter study.

Version / Date: 1.0 (18-09-2012)
EudraCT number: 2012-003984-23

3.2 Identification of the promoter

Fundació Clinic per a la Recerca Biomèdica.
C/ Rossello 143
08036 Barcelona

3.3 Identification of the promoter's representative

Manager: Dr. Pastora Martínez Samper Fundació
Clinic per a la Recerca biomedica.
C/ Rossello 143 08036
Barcelona
e-mail: PMARTIN2@clinic.ub.es

3.4 Identification of researchers of the promoting entity

Hospital Clínic
Principal Investigator and Study Coordinator:
Dr. Josep Mallolas Masferrer
Infectious Diseases Service. mallolas@clinic.ub.es

Collaborating researchers:
Dr. Montserrat Laguno Centeno, Infectious Diseases Service mlaguno@clinic.ub.es

3.5 Identification of principal investigators from participating centres

The identification of the principal investigators as well as the centers participating in the trial are detailed in the document *"List of centers and principal investigators".*

3.6 Identification of researchers from other services involved

Microbiology: Dr. Josep Costa
Pharmacy: Anna Estafell and Begoña Gómez
Biostatistician: Iñaki Pérez
Nurse: Amparo Tricas
Laboratory Technician: Pilar Callau

3.7 Information on the laboratories or technical departments involved

Daily clinical evaluation of patients enrolled in the study, routine blood/urine laboratory determinations, and viral determinations (HCV and HIV), will be performed in the corresponding services at each center participating in the study.

Determinations of HCV mutations that confer resistance to boceprevir in patients with virological failure will be carried out centrally in the Microbiology Laboratory of the Hospital Clínic de Barcelona.

3.8 Monitoring

CTU (clinical Trial Unit).
Responsible for monitoring:
Dr. Anna Cruceta. acruceta@clinic.ub.es
Tel 932275400 ext 4380 fax 932279877

Head of the CTU:
Dr. Joan Albert Arnaiz.
Clinical Pharmacology Service.
Hospital Clínic de Barcelona

4. Justification

Currently, the standard of care for chronic hepatitis C virus (HCV) in patients with concurrent HIV and HCV infection is peginterferon plus ribavirin for 48 weeks. Although the sustained virologic response rate (SVR) has improved markedly in recent years, in most studies it remains below 50%-55%.

As a result, more than 50% of patients who fail treatment have no treatment options and will develop progressive liver fibrosis. In fact, end-stage liver disease is the main cause of morbidity and mortality in patients co-infected with HIV and HCV, and its incidence is higher in patients without SVR to treatment with peginterferon plus ribavirin.

New approaches are needed to try to improve response in these patients. Recently, excellent results have been presented with a triple therapy based on peginterferon, ribavirin and the new HCV protease inhibitors telaprevir and boceprevir in patients with HCV monoinfection.

Although triple therapy achieves a higher rate of SVR, it is also true that the use of three drugs can be more toxic and will be more expensive. Preliminary data suggest that response-guided therapy (TGR) (32 weeks of triple therapy) in patients with HCV monoinfection can achieve the same virological outcomes as standard triple therapy (44 weeks) but with lower toxicity and lower cost. This point will be investigated in the present study.

Of the patients in whom previous treatment with peginterferon plus ribavirin has failed, the most difficult subgroup to rescue is those with no viral response. There are currently doubts about what the response to triple therapy will be in patients with a zero viral response to dual therapy and whether 44 weeks of treatment will be necessary in this subgroup of patients or whether the TGR approach can be applied. Information on this field is not available in patients with co-infection with HCV and HIV, and we believe that our study can provide valuable information on this important topic.
Results from a phase II, double-blind, comparative study of boceprevir and placebo in patients with controlled HIV co-infection who had not received HCV treatment have recently been published. Efficacy and safety results were similar to those previously described in patients with HCV monoinfection. The overall sustained viral response was 61% in patients treated with boceprevir, compared with no more than 39% in those treated with peginterferon/ribavirin. Although the efficacy data are encouraging, response-guided therapy has not been formally investigated.

Several studies are underway to evaluate the efficacy and safety of HCV protease inhibitor triple therapy in HIV-HCV co-infected patients previously treated with peginterferon and ribavirin, but response-guided therapy has not been evaluated so far. The main hypothesis of this proposal is that response-guided triple therapy with boceprevir could obtain better SVR than classic treatment with peginterferon plus ribavirin.

4.1 Identification of the investigational medicinal product

Generic name: Boceprevir
Trade name: Victrelis®
Composition: boceprevir 200 mg.
Pharmaceutical form: hard gelatin capsules.

Generic name: Peginterferon (alpha-2b or alpha-2a)
Trade name: Pegintron® or Pegasys®
Composition: peginterferon alfa-2b 80-150mcg or peginterferon alfa-2a: 180 micrograms
Pharmaceutical form: solution for injection

Generic name: Ribavirin Trade name: Ribavirin Teva®.
Composition: ribavirin: 200 mg
Dosage form: hard capsule

4.2 Investigational Drug Information

Boceprevir: The drug has final approval by the Ministry of Health. Date of first authorisation 18/07/2011.

4.3 Treatment Regimen

PEG-IFN alfa-2a or 2b and ribavirin will be provided by each hospital and will be administered in accordance with the approved technical data sheets.

BOC (Boceprevir). Provided by the study sponsor.

Description:

BOC is supplied in 200 mg capsules. Each capsule contains 200 mg of BOC, sodium lauryl sulfate, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, pregelatinized starch, and magnesium stearate packaged in number 0 hard gelatin capsules. Each capsule contains approximately 56 mg of lactose monohydrate. In people with lactase deficiency, the clinical manifestations of lactose intolerance require 3 to 5 g of lactose (4 to 7 times the total amount of BOC capsules) to appear.

Route of administration: oral
Dosage: total daily 2400 mg, (12 capsules).

Storage: keep in the fridge at a temperature between 2ºC and 8ºC. The products of the study must be stored in a safe place with limited access and in the storage conditions specified on the supply label.

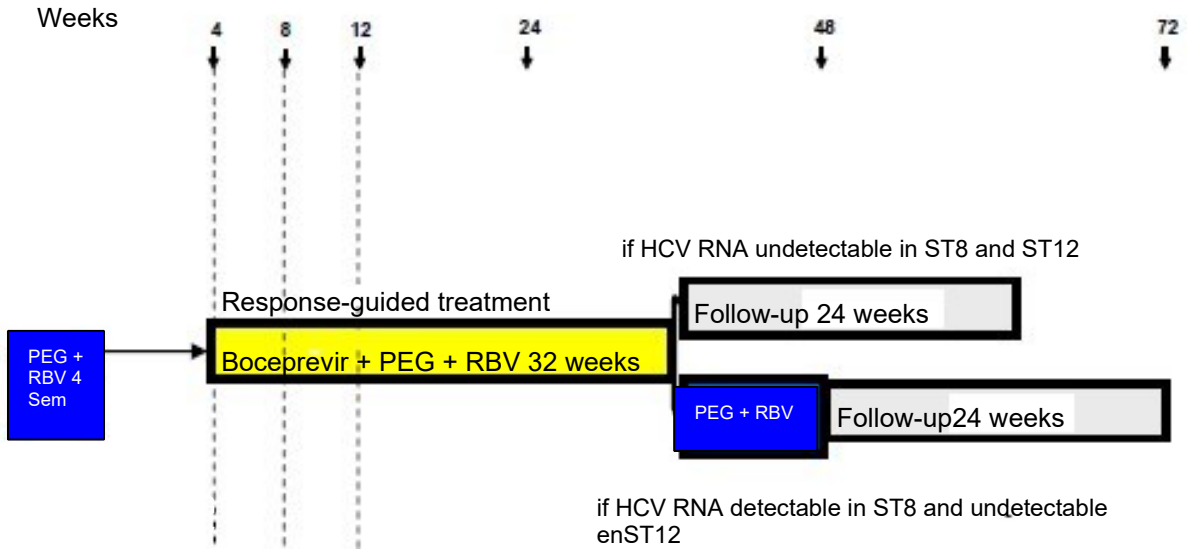
Dosage Schedule:

Boceprevir is administered three times a day using a dosing schedule of 4 capsules every 8 hours. Actual times of dose administration may be modified to fit the patient's schedule, although 7- to 9-hour

intervals between administrations should be maintained. All doses of boceprevir will be given with food (a small snack is sufficient).

Study period and treatment:

All patients will receive an initial 4 weeks of bitherapy with Peg-Interferon and ribavirin (PR).
-If there is a decrease in HCV RNA greater than 1 logarithm with respect to baseline HCV-RNA, the patient will be included in the treatment scheme detailed below.



-If the RNA drop is ≤ 1 log at week 4, PR/boceprevir will be administered for an additional 44 weeks. All cirrhotic patients will receive PR for 4 weeks, followed by RP/boceprevir for another 44 weeks

4.4 Compliance Statement

The study will be carried out in accordance with the principles emanating from the Declaration of Helsinki, and according to the legal regulations in force (Royal Decree 223/2004), and will not begin until the approval of the reference CEIC and the approval of the AEMPS have been obtained.

Patients will be informed orally and in writing and all relevant information tailored to their level of understanding will be communicated to participants.

(See Attachment III: Patient Information Sheet and Attachment III: Written Consent Sheet.)
The patient will be informed that their participation in the study will be treated with the same confidentiality as their clinical documentation and that only the people involved in the study will have access to their data. The patient's name will not appear in any publication or communication of the results of the study.

4.5 Study population

Adults with controlled HIV-1 infection and chronic HCV hepatitis genotype 1 (subtype a or b) who did not achieve SVR with prior treatment with any peginterferon alfa plus ribavirin.

4.6 Relevant bibliography

- Laguno M, Murillas J, Blanco JL, Martínez E, Miquel R, Sánchez-Tapias JM, Bargallo X, GarcíaCriado A, de Lazzari E, Larrousse M, León A, Loncá M, Milinkovic A, Gatell JM, Mallolas J. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. AIDS. 2004 Sep 3; 18(13):27-36.

- Laguno M, Mallolas J. Treatment of chronic hepatitis C in patients with HIV coinfection. Gastroenterol Hepatol. 2006 Oct; 29 Suppl 2:154-7.

-Laguno M, Cifuentes C, Murillas J, Veloso S, Larrousse M, Payeras et al. Randomized trial comparing pegylated interferon alpha-2b versus pegylated interferon alpha-2a, both plus ribavirin, to treat chronic hepatitis C in human immunodeficiency virus patients. Hepatology. 2009 Jan; 49(1):2231.

-Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, Reddy KR, Goodman ZD, Boparai N, DiNubile MJ, Sniukiene V, Brass CA, Albrecht JK, Bronowicki JP; SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31; 364(13):1195-206.

-Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, Poordad F, Goodman ZD, Sings HL, Boparai N, Burroughs M, Brass CA, Albrecht JK, Esteban R; HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31; 364(13):1207-17.

-Sulkowski M, Pol S, Cooper C, Fainboim H, Slim J, Rivero A, Laguno M, Thompson S, Wahl J, and Greaves W. Boceprevir + Pegylated Interferon + Ribavirin for the Treatment of HCV/HIV-co-infected Patients: End of Treatment (Week-48) Interim Results. 19th Conference on Retroviruses and Opportunistic Infections. March 5-8, 2012. Seattle. Abstract 47.

-Naggie S, Sulkowski MS. Management of patients coinfected with HCV and HIV: a close look at the role for direct-acting antivirals. Gastroenterology. 2012 May; 142(6):1324-1334.

-Thomas DL, Bartlett JG, Peters MG, Sherman KE, Sulkowski MS, Pham PA. Provisional guidance on the use of hepatitis C virus protease inhibitors for treatment of hepatitis C in HIV-infected persons. Clin Infect Dis. 2012 Apr; 54(7):979-83. Epub 2012 Feb 4.

-Wilby KJ, Greanya ED, Ford JA, Yoshida EM, Partovi N. A review of drug interactions with boceprevir and telaprevir: implications for HIV and transplant patients. Ann Hepatol. 2012 MarApr; 11(2):179-85.

-Seden K, Back D. Directly acting antivirals for hepatitis C and antiretrovirals: potential for drug-drug interactions. Curr Opin HIV AIDS. 2011 Nov; 6(6):514-26.

-Susser S, Welsch C, Wang Y, Zettler M, Domingues FS, Karey U, Hughes E, Ralston R, Tong X, Herrmann E, Zeuzem S, Sarrazin C. Characterization of resistance to the protease inhibitor boceprevir in hepatitis C virus-infected patients. Hepatology. 2009 Dec; 50(6):1709-18.

-Susser S, Vermehren J, Forestier N, Welker MW, Grigorian N, Füller C, Perner D, Zeuzem S, Sarrazin C. Analysis of long-term persistence of resistance mutations within the hepatitis C virus NS3 protease after treatment with telaprevir or boceprevir. J Clin Virol. 2011 Dec; 52(4):321-7. Epub 2011 Sep 15.

5. Objective and Purpose of the Trial

Main:

The primary objective of this study is to evaluate the safety and efficacy of response-guided therapy with boceprevir 800 mg three times daily orally (o.v.) in combination with peginterferon (alpha-2b or alpha-2a) and ribavirin in genotype 1 HIV- and HCV-infected patients in whom prior HCV treatment with ribavirin-associated pegylated interferon had failed.

Side:

- To define predictors of sustained virologic response (SVR), such as epidemiological factors, disease characteristics, clinical status of HIV infection, and response during treatment, especially at weeks 4, 8, 12, and at the end of treatment.
- To determine the percentage of patients with undetectable HCV RNA at treatment weeks (ST) 4, 8, and 12 and at the end of treatment.
- To evaluate the virological response according to baseline characteristics.
- To investigate HCV resistance after virological failure with a boceprevir-containing regimen (BOC). Blood samples should be obtained at baseline, at the time of virological failure (VF) (VF: two consecutive samples with signs of HCV replication after HCV was undetectable – below the lower limit of detection – or HCV RNA rebound equal to or greater than one logarithmic unit with respect to the RNA nadir) and six months after virological failure. The evaluation of resistance will be carried out in a single center (coordinating center: Hospital Clínic, Barcelona) by means of population sequencing of the genome that encodes the HCV protease.

6. Trial Design

Open-label, Phase III, prospective, multicenter study.

6.1 Main and secondary variables:

Primary endpoint:

The primary efficacy endpoint is the achievement of SVR, defined as an undetectable plasma HCV RNA at follow-up week (SS) 24.

If SS24 data are not available in a patient and the HCV RNA in SS12 is undetectable, SVR will be considered to be present.

Rules of futility:
HCV treatment failure is defined as follows:

- HCV RNA in serum >100 IU/mL at week 12

Or

- Confirmed increase in serum HCV RNA to >1,000 IU/mL at any time after week 12

Or

- detectable HCV RNA (above the lower limit of detection of HCV assay COBAS® Taqman® v2.0. de Roche) in week 24

Secondary endpoints:

- Percentage of patients with virologic response (HCV RNA undetectable at weeks 4, 8, or 12) in those who achieve SVR.
- Percentage of patients with HCV RNA undetectable in SS12.
- Percentage of patients with undetectable HCV RNA 72 weeks after randomization.
- HCV resistance after treatment with BOC-containing therapy. Blood samples will be obtained at baseline and after HCV virological failure, and at the end of the study a resistance analysis will be performed in a single center (Hospital Clínic, Barcelona).
- Safety.

6.2 Design

Phase III studies are usually randomized, often with one group receiving the current standard treatment. These studies may or may not be placebo-controlled. However, the population with co-infection with HCV and HIV is difficult to treat and has very few treatment options. In this population, the use of a standard care group is difficult to justify ethically because response rates with such a regimen are low and because the toxicity of the current standard of care (i.e., PEGIFN + RBV) is considerable.

In this regard, we could establish that SVR in the historical control group is between the 10% (95% confidence interval [CI]: 5%-18%) in previously treated patients and 26% described in the placebo control group in the phase II study of HCV-infected patients not previously treated with boceprevir

STUDY PROCEDURES

Selection Evaluations	
Clinical Evaluations	Selection
Informed consent	X
Inclusion and exclusion criteria	X
Assignment of the selection number	X
Vital signs	X
Weight Determination	X
Height determination	X
Demographics	X
Medical history	X
Physical examination	X
Adverse events	X
Concomitant medications	X
Liver biopsy or Fibroscan (not necessary if performed prior to 18 months)	X
Ultrasound (in patients with bridge fibrosis or cirrhosis) (6 months prior)	X
Confirmation of the use of contraceptive methods by the patient and his or her partner	X

Treatment Visit Schedule														
Clinical Evaluations	Day 1	ST 2	ST 4	ST 6	ST 8	ST 10	ST 12	ST 16	ST 20	ST 24	ST 30	ST 36	ST 42	ST 48/ dFT
Inclusion and exclusion criteria	X													
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X									X				X
Physical examination	X		X				X			X		X		X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Confirmation of the use of contraceptive methods by the patient and his or her partner	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Simplified Compliance Questionnaire	X	X	X		X		X		X	X		X	X	X
Haematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X

TP/TTP	X						X			X				X
Blood biochemistry (simplified, fasting)		X	X		X		X		X		X		X	
Blood biochemistry	X			X				X		X		X		X
(complete, without fasting)														
Thyrotropin (TSH)	X						X			X		X		X
Serum pregnancy test (women only)	X													X
Test of pregnancy in urine (in women only)		X	X	X	X	X	X	X	X	X	X	X	X	X
Samples for pharmacogenetics	X													
HCV RNA CPR*	X		X		X		X			X				X

All laboratory specimens should be obtained prior to administration of the first dose of study medication.

* Samples will be obtained for genotypic resistance testing if the patient has >100 IU/mL at week 12 or later.

Complete blood biochemistry: ALT, AST, creatinine, alkaline phosphatase, gammaglutamyltransferase (GGT), total bilirubin (direct and indirect), total proteins, albumin, uric acid, urea nitrogen, glucose, HbA1C (in patients diagnosed with diabetes, whether they are receiving pharmacological treatment or controlled with diet), amylase, lipase, sodium, potassium, chloride, phosphorus, calcium, triglycerides, and cholesterol.

Simplified blood biochemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, alkaline phosphatase, total bilirubin (direct and indirect), urea nitrogen, total proteins, albumin, uric acid and glucose.

Fibrosis evaluation: This will be done by liver biopsy or Fibroscan. In patients without cirrhosis on histology or Fibroscan, evaluation must have been performed no more than 18 months prior. A result of 12 kilopascals or more on the Fibroscan test would allow the patient to be considered cirrhotic.

Ultrasound: Patients with bridge fibrosis or cirrhosis must have an ultrasound performed within 6 months prior to inclusion in the study.

6.3 Guidelines for BOC Dose Modification

The dose of BOC cannot be reduced in the study.
Grade 1 and 2 AEs require close follow-up but no change in treatment.

All grade 3 toxicities will be treated by the facility investigator as appropriate. Any grade 4 toxicity that, in the opinion of the centre's investigator, is directly related to BOC, will be treated with the permanent suspension of the latter.

In case of intolerance to the BOC, its administration will be suspended; The dose cannot be reduced. If BOC is temporarily or permanently stopped, patients may continue to receive PEG-IFN and RVB.

6.4 Trial treatments

DRUG SUPPLY AND LABELLING

In this study, 2 drugs already on the market and authorized for use in HIV-HCV co-infected patients will be used; peginterferon and ribavirin; The study drug, boceprevir, will be provided by MSD throughout the study and distributed by the Coordinating Center. For clinical trials carried out in Spain, relabelling in Spanish is mandatory.

See section 4.3

6.5 Duration of the trial

The approximate expected duration for the inclusion of patients is 2 months, and the duration of treatment and follow-up of the included patients will be extended by a maximum of 72 weeks

6.6 Termination and/or Discontinuation Criteria

The treatment will be **compulsorily** terminated during the study for any of the following reasons:

- Patient with HCV RNA >100 IU/mL in ST12 or detectable HCV RNA in ST24.
- Suicide or homicide thoughts or attempts.
- Severe depression or major depressive episode.
- Positive test result for non-prescription opioids, methamphetamines, or cocaine.
- Pregnancy during the study.
- Virological rebound, defined as:

  Any patient who obtains an undetectable HCV RNA and subsequently presents an HCV RNA > 1,000 IU/ml.

Once virologic rebound has been identified, genotypic resistance will be characterized by HCV RNA sequencing in suitable samples, such as those collected at the time of rebound and during the follow-up period.

Treatment **may** be terminated during the study for any of the following reasons:

- The medical investigator determines that a SAE is possibly or likely related to the study drug.
- Failure to administer, evaluate, or other study requirements.

6.7 End of test

The end of the trial will be considered the time of the last visit of the last subject recruited.

7. Subject Selection

7.1 Criteria for inclusion of subjects

A patient must meet ALL of the criteria listed below in order to participate:

1. To participate in the study, patients must have been treated with peginterferon alfa-2a plus ribavirin or peginterferon alfa-2b plus ribavirin for a minimum of 12 weeks. If a patient has received more than one of these guidelines, the most recent one will be considered.

2. The patient must have a previously documented HCC caused by genotype 1 virus (subtype a or b). Patients with other genotypes or with mixed genotypes will not be able to participate. The HCV RNA result at the screening visit should confirm genotype 1 virus infection and be >10,000 IU/mL.

3. The patient must have a liver biopsy with HCC-compatible histology and no other etiology or evaluation with Fibroscan. In the event of:

    a. Absence of cirrhosis. Biopsies or Fibroscan must have been done within 18 months prior to the screening visit.

    b. Cirrhosis No specific time frame is required.

4. All patients with cirrhosis should have an ultrasound scan performed within 6 months prior to the screening visit.

5. Patients must be receiving stable antiretroviral therapy with a CD4 lymphocyte count greater than 100/mm3 and an undetectable HIV plasma viral load (< 50 copies/mL) for more than 6 months. Antiretroviral therapy should contain raltegravir (at least for the past 6 weeks).

6. The patient must be 18 years of age or older.

7. HIV treatment should not contain EFV, NVP, ddI, d4T, AZT, or HIV protease inhibitors.

8. The patient should weigh between 40 and 125 kg.

9. The patient and partner must commit to acceptable contraception from at least 2 weeks prior to Day 1 and until at least 6 months after the last dose of study drug. (negative pregnancy test in women of childbearing potential) (Postmenopause is defined as the absence of menstruation during the year prior to study entry.)

10. Patients must be willing to give written informed consent and, in the opinion of the investigator, be able to follow the protocol visit design.

7.2 Criteria for exclusion of subjects

Patients who meet ANY of the following criteria will be excluded from the study:

1. Patients with confirmed hepatitis B virus co-infection (HBsAg positivity).

2. Patients with chronic HCV infection of genotypes other than 1

3. CD4 lymphocyte count <100 cells/mm3.

4. HIV RNA in plasma greater than 50 copies/mL

5. Platelet count less than 80,000/mm3

6. Patients who had to discontinue prior interferon or ribavirin therapy due to a serious adverse event that the investigator considered possible or probably related to ribavirin or interferon.

7. Treatment with ribavirin in the previous 90 days and with any interferon alfa in the month prior to the screening visit.

8. Hepatitis C treatment with any investigational product. Previous treatments with phytotherapy products with known hepatotoxicity are grounds for exclusion.

9. Participation in another clinical trial within 30 days prior to randomization or intention to participate in another clinical trial during participation in the present study.

10. History of hemoglobinopathy (e.g., thalassemia) or other cause of hemolysis, or hemolytic tendency.

11. Signs of decompensated liver disease, such as a history or presence of clinical ascites, hemorrhagic varicose veins, or hepatic encephalopathy.

12. Diabetic or hypertensive patients with signs of clinical importance on ophthalmological examination.

13. Pre-existing, unstable, or untreated psychiatric illness.

14. Any known pre-existing medical conditions that could interfere with the patient's participation in the trial and its completion.

15. Any current signs of alcoholism or other drug use.

16. Patients receiving opioid agonist substitution therapy but not participating in any opioid substitution maintenance program.

7.3 Withdrawal criteria

Treatment with the study drug will be terminated **immediately** during the study for any of the following reasons:

- Patient with HCV RNA >100 IU/mL in ST12 or detectable HCV RNA in ST24.
- Suicide or homicide thoughts or attempts.
- Major depression, major depressive episode.
- Positive test result for non-prescription opioids, methamphetamines, or cocaine.
- Pregnancy during the study.
- Express wish of the patient
- Virological rebound, defined as:

  Any patient who obtains an undetectable HCV RNA and subsequently presents an HCV RNA > 1,000 IU/ml.
  Once virologic failure has been identified, genotypic resistance will be characterized by HCV RNA sequencing in suitable samples, such as those collected at the time of failure and during the follow-up period.

Treatment with the study drug **may** be terminated during the study for any of the following reasons:

- The medical investigator determines that a SAE is possibly or likely related to the study drug.
- Failure to administer, evaluate, or other study requirements.

8. Treatment of Subjects

8.1 Treatment branches

An open-label, single-arm, multicenter study to evaluate the safety and efficacy of a regimen with boceprevir in polytherapy with peginterferon alfa-2b 1.5 µg/kg or peginterferon alfa-2a 180 µg/kg once weekly subcutaneously (s.c.) and oral ribavirin in adult patients with controlled HIV coinfection in whom prior treatment of chronic hepatitis C with peginterferon and ribavirin has failed.

Since early response to peginterferon (PEG-IFN) and ribavirin (RVB) at week 4 is predictive of response to treatment, either SVR or null response (high negative predictive value: 96%), the duration of response-guided treatment with BOC will depend on the response in ST4, ST8, and ST12.

Patients who achieve a reduction in HCV RNA viral load greater than or equal to one logarithmic unit at week 4 (after the bitherapy phase) will then undergo triple therapy for 32 weeks. If HCV RNA is undetectable at week 8, they will end the tto after 32 weeks of triple therapy and will be followed for another 24 weeks. If HCV RNA is detectable at week 8, at the end of the 32 weeks of triple therapy, patients will receive dual therapy with pegylated interferon and ribavirin for an additional 12 weeks and then follow up for 24 weeks.

Patients who do not achieve a decrease in HCV RNA viral load greater than one logarithmic unit at week 4 after the initial phase of bitherapy (or those who have grade 4 fibrosis - cirrhosis) will receive triple therapy for 44 weeks and will be followed for an additional 24 weeks.

8.2 Concomitant and rescue medication

Any concomitant medication must be reflected in the CRF in an appropriate way (detailing the product, dosage, route, days of administration, reason for treatment, etc.).

Treatments not allowed:
The administration of treatments that are contraindicated with the study drugs will not be allowed. (see annex technical sheets) and section 10 of the protocol

8.3 Compliance Monitoring

Adherence: to ensure the control and registration of medication, an adherence questionnaire will be added to the data collection notebook. At each visit, the investigator will ask the patient about treatment adherence.

Tablet count: The patient will be asked to bring any leftover medication or empty bottles with them to check whether or not they have taken all the capsules or tablets of the medication since the previous visit.

9. Effectiveness Assessment

9.1 Efficiency parameters

***Virological tests* to.**

Viral RNA

Plasma will be obtained for viral RNA analysis prior to the start of the study and according to the study schedule.
Virological failure shall be defined as described in paragraph 6.1

b. Methods of Analysis and Sensitivity

A routine analysis of HIV RNA approved for clinical use will be performed with a lower limit of quantification of 50 copies/mL. The test used on each patient should be the same throughout the trial.
A routine analysis of HCV RNA approved for clinical use will be performed with a lower limit of quantification of 15IU/mL.

10. Safety Rating

10.1 Detection and Recording of Adverse Events

It is the investigator's responsibility to detect and document any event that meets the criteria and definitions of adverse event (AE) or serious adverse event (SAE) as set forth in this protocol. During the study, the existence of adverse events, whether serious or not, will be checked in accordance with the definition given in this section of the protocol.

a) Minimum information to be specified:

Description/definition:

Adverse event (AE) is any adverse health event in a patient or clinical trial subject treated with a medicine, even if it is not necessarily causally related to that treatment. Therefore, it can be any unfavorable and unintended signs (including an abnormal laboratory finding), symptom, or illness temporarily associated with the use of an investigational drug, whether or not related to the investigational drug.

Laboratory abnormalities of clinical importance that meet one or more of the following criteria are also considered AEs:

- It requires additional intervention or treatment.
- Requires a modification of the dose.
- It is accompanied by a clinical manifestation.

Any analytical anomaly that the investigating physician considers to be of clinical importance must be recorded as such in the printed copy of the laboratory report, indicating the physician's initials and the date of revision. An AA is also considered to be any event associated or observed in conjunction with an accidental or intentional overdose of the product, or with abuse or withdrawal of the product.
All AEs will be recorded in the subject's medical record and in the eCRDe. The start and end dates of each AA, the intensity and the relationship with the study drug will be recorded.

The criteria for subject treatment, dose discontinuation, dosage adjustment, withdrawal, or treatment changes will only apply to toxicities attributable to the study drugs (i.e., BOC, PEG-IFN, and RBV).

The classification system for drug toxicity is set out in the DAIDS Table for Grading the Intensity of Adverse Events in Adults and Children, which can be found on the DAIDS RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/.

In addition, for each AA, the measures taken or the outcome (e.g. hospitalization, discontinuation of treatment) will be recorded.

Adverse reaction (AR) is any harmful, unintended reaction to an investigational drug, regardless of the dose administered. In this case, there is a suspicion of a causal relationship between the investigational drug and the adverse event.

Serious adverse event (SAE) is any adverse event that, at any dose, results in death, threatens the life of the subject, makes hospitalization necessary or prolonged hospitalization, results in permanent or significant disability or disability, or results in a congenital anomaly or malformation. For the purposes of notification, suspected adverse events that are considered medically significant, even if they do not meet the above criteria, will also be treated as serious, including major medical events that require intervention to prevent one of the consequences described above from occurring. Likewise, all suspected transmission of an infectious agent through a drug will be reported as serious. Examples of these events include allergic bronchospasm requiring intensive treatment in an emergency department or at the individual's home, blood dyscrasia or seizures that do not require hospitalization, or the development of drug dependence or abuse.

Medical and scientific judgement should be used to decide whether other situations that have not resulted in the outcomes listed in the above definitions should be reported as SAGs.

A life-threatening term is defined as a situation where, in the opinion of the physician, the patient at the time of the adverse event or adverse reaction is at real risk of death.

Hospitalization or prolongation of a hospitalization is a criterion for considering an AA to be serious. Only admission in which the patient spends the night in the hospital should be considered as hospitalization. The following situations will not meet the AAG criteria:

- if hospitalization or prolongation of hospitalization is necessary to perform a procedure required by the protocol (for example, if day or night visits will be made for biopsies or surgeries required by the protocol).

- if hospitalization or prolongation of hospitalization is part of the facility's routine procedure (e.g., removal of a stent after surgery)

- in case of scheduled hospitalization for a pre-existing process that has not worsened (e.g. scheduled hospitalization for the implantation of a knee prosthesis for a previous osteoarthritis process)

Grade IV laboratory alterations will be considered AAG.
DO NOT confuse the concept of "serious" with "severe" which refers to the intensity of the adverse event or adverse reaction.

Unexpected serious adverse reaction (RAGI) is a serious adverse reaction whose nature or severity does not correspond to the information regarding the product (for example, the investigator's manual in the case of an investigational medicinal product not authorised for marketing or the product label in the case of an authorised medicinal product).

b) Imputability criteria.

The causal relationship between the investigational product and the occurrence of AA/AAG shall be established on the basis of clinical judgment. To this end, other causes will be considered and studied, such as the natural history of the underlying diseases, concomitant treatment, other risk factors and the temporal relationship of the event with the investigational product. In addition, the technical data sheet of the products will be consulted.

In order to analyse the possible cause-effect relationship, the temporal relationship between the administration of the drug and the AA, possible alternative causes, the evolution (complete remission,

partial recovery, death, sequelae, persistence), persistence or not after the suspension of administration, reappearance with the readministration of the product or the prior knowledge of said event coinciding with the known or expected response pattern of the drug under study will be considered.

The causal relationship of an AA with the medication under study will be established according to the following definitions:

Unlikely relationship: The adverse event does not occur after a plausible chronological sequence related to the administration of the product under study and/or is reasonably explainable by other factors, such as the patient's clinical status or other concomitant therapeutic, toxic, or environmental interventions. In addition, it does not match the known or expected response pattern of the drug.

Possible relationship: the adverse event occurs after a plausible chronological sequence related to the administration of the product under study, but can also be explained by the patient's clinical status or other concomitant therapeutic, toxic, or environmental interventions. It also matches the known or expected response pattern of the drug.

Probable relationship: The adverse event occurs after a plausible chronological sequence related to the administration of the product under study, cannot be reasonably explained by the patient's clinical status or other concomitant therapeutic, toxic, or environmental interventions, and after withdrawal or reduction of the dose of the suspect drug the event follows a logical clinical sequence. It also matches the known or expected response pattern of the drug.

Very likely relationship: the adverse event occurs after a plausible chronological sequence related to the administration of the product under study, cannot be reasonably explained by the clinical status of the patient or other concomitant therapeutic, toxic or environmental interventions, after withdrawal or reduction of the dose of the suspect drug the event follows a logical clinical sequence and it is necessary that after the readministration of the suspicious drug the adverse event reappears. It also matches the known or expected response pattern of the drug.

Unrelated: Adverse event clearly due to causes unrelated to the medication under study and the criteria for another causal relationship are not met.

Non-assessable relationship: any notification that suggests an adverse effect, which cannot be judged because the information is insufficient or contradictory and which cannot be supplemented or verified.

10.2. Notification

The investigator or designee **must notify all AAGs, regardless of whether or not they are considered drug-related or planned,** to the CTU manager. Dr. Anna Cruceta (acruceta@clinic.ub.es) tel 2275400 ext 4380 and fax 932279877 in order to notify local and national health authorities **within one working day of becoming aware of the event**., so that the contact of the designated promoter can prepare the corresponding written report. AAGs occurring will be reported at any time from the subject's inclusion in the study and up to 30 days after the study has been completed or discontinued. In the specific case of selection failure, the AAGs will be recorded from the moment the consent is signed until the subject is considered a selection failure.

Regardless of the classification of adverse effects, the Investigator must collect all the AEs in the corresponding section of the study data collection notebook (CRD) and fill in all the information pertaining to them.

The sponsor must notify in an EXPEDITIOUS manner all relevant SAFETY INFORMATION, i.e. that could modify the risk/benefit ratio of the investigational medicinal product, or determine changes in its administration schedule or in the conduct of the trial, for example:

- a qualitative change or an increase in the percentage of occurrence of expected RAGs, which is considered clinically important.
- RAGIs that occur after the completion of a clinical trial and that are notified by the investigator to the sponsor.
-New developments related to the conduct of the trial or the development of the investigational medicinal product and likely to affect the safety of the subjects, such as:
    - Serious adverse events that may be associated with the trial procedures and may modify the conduct of the trial
    - A significant risk to subjects such as the lack of efficacy of an investigational drug used for the treatment of a life-threatening disease.
    - Important new safety findings from new animal studies (such as cardiogenicity).
    - Any premature termination or temporary halt of a clinical trial with the same investigational medicinal product for safety reasons, carried out in another country and by the same sponsor.
    - GRAs related only to an MNI that are considered relevant as they are not subject to RAGI's general rules of expedited reporting of individual cases.
- Any recommendations from the data monitoring committee, which are relevant to the safety of the subjects.

This information must be notified as soon as possible and no later than 15 days after the promoter has become aware of it. In addition, if additional information that is relevant is obtained, it must be notified as quickly as possible.

10.3 Evaluation of toxicity parameters

The classification system for drug toxicity is set out in the DAIDS Table for Grading the Intensity of Adverse Events in Adults and Children, which can be found on the DAIDS RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/.

Treatment of PEG-IFN Side Effects

Side effects of PEG-IFN usually include flu-like symptoms such as myalgia, arthralgias, headache, chills, low-grade fever, nausea, vomiting, and tiredness, as well as erythema, pain, and edema at the injection site. Less common are side effects of the central nervous system (CNS), such as depression, insomnia, anxiety, and irritability. Abnormalities of thyroid function have been described, as well as neutropenia, thrombocytopenia, and alopecia. The decrease in neutrophil and platelet count is usually dose-dependent and usually reaches nadir by week 4. Reductions in the total number of white blood cells may also occur, although usually not below normal levels. In week 2, dose-related decreases have been observed for other analytical parameters, such as albumin, globulin, total proteins, potassium and calcium; however, most parameters normalize by week 4 of treatment. Inflammation at the injection site occurs intermittently throughout treatment, but usually does not limit it. In general, all these effects are reversed by decreasing or interrupting the dose; patients cannot continue to take RBV and BOC if PEG-IFN is permanently discontinued.

<u>Treatment of IFN-associated neutropenia</u>
Patients who develop neutropenia during treatment may receive G-CSF (not provided by the study) at the discretion of the center investigator.

Table 1. Treatment of toxicity: neutropenia

Parameter	Downward dose adjustment of PEG-IFN
RAN (cells/^{mm3})	
Grade 1 (1,000-1.300)	None

Grade 2 (750999)	No dose adjustment is necessary; G-CSF at the discretion of the centre's researcher
Grade 3 (500749)	Immediately reduce the dose by UN* one level and administer G-CSF at the discretion of the center investigator. If neutropenia disappears, the dose may be increased at the discretion of the center investigator.
Grade 4 (<500)	Study weeks 1 and 2: defer or discontinue administration until grade 2 is reached, then resume administration with dose reduction of DOS* levels. Study weeks 3 to 48: defer or discontinue administration until grade 2 is reached, then resume administration with a dose reduction of ONE level. Administer G-CSF at the discretion of the centre's investigator. If neutropenia disappears, the dose may be increased at the discretion of the center investigator.

* *The dose reduction levels of PEG-IFN are indicated in the label.*

Treatment of IFN-associated thrombocytopenia

Table 2. Treatment of toxicity: decreased platelet count

Platelet count (cells/mm3)	MEASURE
Grade 2 (50,000-99,999)	No
Grade 3 (25,000-49,999)	Halving the dose of interferon
Grade 4 (<25,000)	Suspend the PEG-IFN definitively.

* *The dose reduction levels of PEG-IFN are indicated in the label.*

Dose reduction of PEG-IFN

Dose reductions should be uniform between participating centers and patients. For this purpose, the following reductions shall be used:
Table 3. Guidelines for Recommended Dose Reduction of PEG-IFN 1.5 µg/kg

		Reduction of one level (decrease to 1.0 µg/kg)			Two-level reduction (decrease to 0.5 µg/kg)		
		Volume			Volume		
Weight at Sit Up*		Pen Size	Injection (ml)	Dosage (µg)	Pen Size	Injection (ml)	Dosage (µg)
40 to 50 kg	88 to 110 lbs	Redipen 50	0,45	45	Redipen 50	0,30	30
>50 to 60 kg	>110 to 132 lbs	Redipen 80	0,35	56	Redipen 50	0,30	30
>60 to 65 kg	>132 to 143 lbs	Redipen 80	0,40	64	Redipen 50	0,35	35
>65 to 75 kg	>143 to 165 lbs	Redipen 80	0,45	72	Redipen 50	0,35	35
>75 to 80 kg	>165 to 176 lbs	Redipen 80	0,5	80	Redipen 50	0,40	40
>80 to 85 kg	>176 to 187 lbs	Redipen 120	0,35	84	Redipen 50	0,40	40

>85 to 95 kg	>187 to 209 lbs	Redipen 120	0,40	96	Redipen 50	0,50	50
>95 to 105 kg	>209 to 231 lbs	Redipen 150	0,35	105	Redipen 50	0,50	50
>105 to 125 kg	>231 to 275 lbs	Redipen 150	0,35	105	Redipen 50	0,50	50

* *Use the usual rounding methods: values between 0.1 and 0.4 kg should be rounded down and those between 0.5 and 0.9 kg should be rounded up.*

Missed or deferred doses of PEG-IFN

If a dose of PEG-IFN is delayed but is finally administered, the following guidelines are recommended for the following scheduled doses:

- Dose delay of 1 or 2 days: administer on the usual day of administration of the week (for example, if Monday is the usual day of administration and the dose is delayed to Wednesday, the next dose will be administered as usual, on Monday).

- Dose delay of 3 to 5 days: Giving subsequent doses every 5 to 6 days until the patient gets back to their original schedule (for example, if Monday is the usual day of administration and the dose is delayed until Saturday, the next dose will be given on Thursday, the next dose on Tuesday, and the next dose on Monday).

- 6-day dose delay: discontinue that week's dose and continue with the usual schedule the following week (e.g. if Monday is the usual day of administration but the dose is delayed until the following Sunday, the dose is considered to have been interrupted and the next injection will coincide with the following week's dose, on Monday).

- Dose delay of 7 or more days: The investigator may resume administration of the study drug at any time up to 28 days after the last dose and, if necessary, administer the dose every 5 or 6 days until the weekly dose is received on the patient's usual scheduled day.

Treating the Side Effects of RBV

The most common AA in RBV treatment is anemia, which may be due to hemolysis or decreased release of red blood cells from the bone marrow. Anemia usually appears 1 to 2 weeks after you start receiving RBV and usually goes away within 4 to 8 weeks of withdrawal or reduction of the drug's dose. In patients with anemia secondary to RBV-induced hemolysis, an elevation of indirect bilirubin is common. BOC may increase the incidence or severity of anemia. In case of anaemia during treatment with BOC and RBV, the dose adjustment of RBV, as described below, takes precedence over BOC.

NOTE: A serious side effect of RBV is its teratogenicity; therefore, it is recommended not to administer RVB to pregnant or breastfeeding women and to men whose partner is pregnant. Women who become pregnant during the study will be required to discontinue study treatment and undergo withdrawal assessments.

The dose of RBV in this study will depend on weight at study entry (see section 5). The following table shows the recommendations for dose reduction in case of anemia. The administration of epoetin (EPO) will be at the discretion of the centre's researcher. If the administration of RBV is temporarily or permanently stopped, patients may continue to receive PEG-IFN and BOC.

Board. Recommended RBV dose reduction in anaemia

	Starting dose	Measure

Hemoglobin <10 g/dL, ≥8.0 g/dL.	1,400 mg/day 1,200 mg/day	Decrease RBV to 1,000 mg/day
	1,000 mg/day	Decrease RBV to 800 mg/day
	800 mg/day	Decrease RBV to 600 mg/day
	600 mg/day	Decrease RBV to 400 mg/day (Initiate treatment with EPO at the discretion of the center's investigator)
Hemoglobin <8.0 g/dl	All doses	Temporarily discontinue the RBV
Symptomatic decrease in haemoglobin will be treated at the discretion of the centre's investigator.		

Reintroduction of RBV

In the event that RBV is temporarily stopped due to anaemia, haemoglobin values should be checked again after two weeks and then at two-week intervals until stabilised. If hemoglobin returns to an acceptable level, RBV should be reintroduced at doses of 600 mg/day (with a regimen of 200 mg in the morning and 400 mg in the evening). The dose may be increased by 200 mg/day every two weeks until the initial dose is reached.

Treatment of anemia with EPO is recommended, but this is not provided in the study. On the other hand, it is not advisable to administer EPO with hemoglobin values ≥10 g/dl. If necessary, at the discretion of the centre investigator, the dose of RBV may be reduced by a haemoglobin value ≥10 g/dl.

Increasing the dose of RBV

Once haemoglobin has returned to an acceptable level, patients who have had their RBV dose reduced without discontinuing their administration may, at the discretion of the centre investigator, increase the dose by 200 mg/day every two weeks until the initial dose is reached.

Missed doses: If a patient misses a dose of RBV, they should take it as soon as possible, along with food, during the same day. If a full day has passed, you should skip the missed dose and continue with the normal schedule of administration. In no case should the dose be doubled to "compensate" for the missed dose.

Treatment of Adverse Events Related to PEG-IFN alfa-2a and Ribavirin (PEGASYS™ PCR)

Dose adjustment in case of adverse reaction

	Reduce ribavirin to 600 mg	Suspend ribavirin	Reduce Pegasys to 135/90/45 micrograms	Suspend Pegasys	Suspended r la combination
Absolute neutrophil count			<750/mm3	<500/mm3	
Platelet count			<50,000/mm3 >25.0 00/mm3		<25,000/mm3

Hemoglobin - absence of heart disease	<10 g/dl , and ≥8.5 g/dl	<8.5 g/dl			
Hemoglobin - stable heart disease	Decrease ≥2 g/dL for any 4 weeks	< 12 g/dL despite 4 weeks at a reduced dose			

Treating BOC Side Effects

The safety profile represented by nearly 1,500 patients treated with the combination of boceprevir with peginterferon alfa-2b and ribavirin is derived from pooled safety data from two clinical trials in treatment-naïve patients and one clinical trial in treatment-failed patients.

The most frequently reported adverse events in the BOC/PEG/RVB groups were largely the reflection of events that are associated with the treatment spine (PEG/RBV).

The most frequent adverse reactions were fatigue, anemia, nausea, headache and dysgeusia. Only two adverse events, anaemia and dysgeusia, are 20% more common in boceprevir-containing treatments and will be discussed as events of particular interest.

Boceprevir monotherapy did not cause a decrease in hemoglobin in either the animal studies or a phase I monotherapy study. In healthy adult males who received boceprevir for up to 57 days, no effects on red blood cell formation, survival, and destruction or on markers of anaemia were detected. However, boceprevir added to PEG and RVB therapy results in a gradual decrease in hemoglobin of approximately 1 g/dL.

Treatment of anemia in patients receiving boceprevir polytherapy is identical to that of anemia in patients treated with peginterferon plus ribavirin. The incidence of discontinuation of treatment due to anemia is just as low, close to 1%, both in the control group with PEGIFN plus RBV and in the experimental groups treated with boceprevir.

Anemia in patients treated with boceprevir is transient, as baseline hemoglobin values recover after treatment.

Based on the above data, BOC is usually well tolerated and has an AA profile similar to that of the standard of care (PEG-IFN + RBV) with the exception of dysgeusia, which is more common in patients treated with BOC. The anemia appears to be mainly due to exposure to RBV.

<u>Rules for processing</u>

The dose of BOC cannot be reduced in the study.

Anaemia should be treated initially by reducing the dose of ribavirin and an erythropoiesis stimulant whenever available and appropriate. For dysgeusia, attempts will be made to reduce symptoms (e.g., pills, plastic cutlery, etc.). Treatment of headache and nausea should also be symptomatic. **Grade 1 and 2 AEs require close follow-up but no change in treatment.**

All grade 3 toxicities will be treated by the facility investigator as appropriate. Any grade 4 toxicity that, in the opinion of the centre's investigator, is directly related to BOC, will be treated with the permanent suspension of the latter.

In case of intolerance to the BOC, its administration will be suspended; The dose cannot be reduced. If BOC is temporarily or permanently stopped, patients may continue to receive PEG-IFN and RVB.

NOTE: EPO with hemoglobin values greater than or equal to 10 g/dl is not recommended.

10.4 COMMUNICATION TO RESEARCHERS

The sponsor shall communicate to investigators any information that may affect the safety of the trial subjects as soon as possible.

It is advisable when deemed appropriate that information on serious and unexpected adverse reactions (RAGI) be presented in a list together with a brief analysis of the data provided.

Researchers must also be informed of the safety aspects that impact the conduct of the clinical trial or the development of the product. Including disruption of the development program or security-related protocol modifications.

Follow-up of subjects after adverse events will be performed by clinical and complementary examinations necessary for the duration of treatment and then on a monthly basis during follow-up and up to 30 days after the end of treatment. In the event of a possible pregnancy, the health status of both the mother and the newborn will be monitored during the trial, whether the person who has become pregnant is the one who is taking the investigational drug or if it has been taken by her partner.

No interim analyses are planned for the present study.

11. Statistics

11.1 Sample

Phase III studies are usually randomized, often with one group receiving the current standard treatment. These studies may or may not be placebo-controlled. However, the population with co-infection with HCV and HIV is difficult to treat and has very few treatment options. In this population, the use of a standard care group is difficult to justify ethically because response rates with such a regimen are low and because the toxicity of the current standard of care (i.e., PEGIFN + RBV) is considerable.

In this regard, we could establish that SVR in the historical control group is between 10% (95% confidence interval [CI]: 5%-18%) in previously treated patients and 26% described in the placebo control group in the phase II study of patients infected with HCV and not previously treated with boceprevir.

11.2 Sample size

The primary objective of this study is to estimate SVR with response-guided therapy with boceprevir in patients with controlled HIV infection and chronic hepatitis C with genotype 1 virus in whom prior treatment with peginterferon/ribavirin has failed.

Since no comparative analysis is to be performed, the sample size depends on the accuracy of the SVR calculation. SVR from double treatment with peginterferon and ribavirin ranges from 27% to 39%.

The expected SVR with boceprevir triple therapy is 60%. If we define a margin of error (60% ± 8.5%) that encompasses the maximum SVR observed with dual therapy (39%), the required sample size based on a bilateral 95% confidence interval is 128 patients.

The sample size calculation for the different RVM values was based on a bilateral 95% confidence interval for different levels of accuracy.

Stratification

Since this is a non-randomized study, no stratification is planned; however, for the purposes of data analysis, patients will be classified according to the type of failure of previous HCV treatment (no response, virologic rebound, and relapse).

No response: HCV RNA positivity at week 12.

1. Partial response. Patients who achieved at least a reduction in HCV RNA of two logarithmic units from baseline at week 12 but still had viremia at the end of treatment.

2. Null response. Patients who did not achieve a reduction of two logarithmic units of HCV RNA at week 12.

Rebound: negativity for HCV RNA at week 12, but positivity before week 48.

Relapse: HCV RNA undetectable at the end of treatment and subsequently detectable during 24 weeks of follow-up.

As this is an exploratory study, the inclusion of difficult-to-treat patients, such as those with no response (reduction in HCV RNA of less than two log units with prior HCV treatment) or with cirrhosis, will be limited to 30% of the study population.

11.3 Analysis

In this open study, all variables will be tabulated. Quantitative variables will be described by the number of available and omitted observations, the mean, the median, the standard deviation, the interval (minimum and maximum) and the first and third quartiles. Of the qualitative variables, the frequency and percentage will be presented. Omitted values will be tabulated with their frequency, but will not be included in the calculation of the percentages.

The primary endpoint will be assessed with a bilateral CI of 95% around the observed proportion of SVR. The analysis of the primary endpoint in SVR will be carried out in two ways. Patients who withdrew from the study within the first four weeks will be included in the main analysis, which will be counted as SVR failures. As a secondary analysis, an SVR analysis will also be performed, but restricted to patients who have not withdrawn from the study in the bitherapy period in the first four weeks. In both analyses, patients in whom SVR data are lacking due to premature withdrawal from the study at any time after the initial biterpia period of the first four weeks will be included and counted as SVR failures.

Inferential analysis of boceprevir efficacy will be assessed by SVR at week 24 and the 95% confidence interval. A similar analysis will be applied to evaluate the secondary variables. For continuous quantitative variables, the mean or median and the 95% confidence interval or the interquartile interval shall be calculated.

Descriptive analyses of treatment-occurring adverse events and treatment-occurring adverse events that are possibly or likely related to the study drug will be performed. With regard to the safety assessment in the AEs, the 95% CI of the percentage of grade 3 or higher adverse events and other serious adverse events reported by the centres shall be provided. The highest grade episode per person over time will be used. Descriptive tables will be provided summarizing the events and the number of people who have presented the events by grade.

Variations in HIV-1 viral load or RNA and CD4+ T cell count at each post-enrollment visit will be summarized. The rates and reasons for premature discontinuation of treatment, including HCV treatment failures, will be summarized.

In addition, a logistic regression analysis will be carried out taking SVR as a dependent variable. The importance of the previously identified prognostic factors will be confirmed by univariate logistic regression. The independence of these factors will then be evaluated using a stepwise method in which the factors that were significant in the univariate analyses will be used.

All analyses will be bilateral and will have a significance level of 5%. The following variables will be analyzed:

Efficacy: sustained virologic response, virologic response at weeks 4, 8, 12, and 24.

Safety: All adverse events, whether or not related to the study medication.

HCV resistance following BOC-containing treatment in patients with virologic failure.

* Predictive factors of SVR: SVR will be analyzed by subgroups according to sex, age, degree of fibrosis at baseline, previous null response, CD4 lymphocyte count at baseline, greater or lesser decrease of one logarithmic unit of HCV RNA at week 4), undetectable HCV RNA at week 8, and pharmacogenetic markers

11.4 Completion Criteria

The study will be considered to have been completed on the date of the last visit of the last subject recruited into the study.

11.5 Processing of lost data

Missing data imputation techniques will not be used. Only the available data will be analyzed.

11.6 Deviations from the statistical plan

Any deviation from the planned statistical analyses will be justified and detailed in the reports derived from the processing of the data.

11.7 Population under analysis

The population analyzed in the study will consist of all patients included in the study as detailed in the protocol and without major deviations from the protocol.

12. Direct Access to Source Data/Documents

The sponsor shall ensure that it is specified in the protocol or other written agreement that the investigator or institution shall allow direct access to the source data or documents for monitoring, auditing and review by the IRB as well as inspection of the trial by the competent health authorities.

13. Ethics

General considerations: The trial will be carried out in accordance with the principles emanating from the Declaration of Helsinki *(See Annex VIII)* and according to the legal regulations in force (Royal Decree 223/2004) and will not begin until the approval of the reference CEIC, the approval of the Management of all the participating centres, and the authorisation of the Spanish Agency for Medicines and Health Products have been obtained.

Information to the subjects: Patients will be informed orally and in writing and all relevant information adapted to their level of understanding will be communicated to the participants. *(See Attachment III: Patient Information Sheet/Written Consent Sheet)*

14. Data Management and Archiving of Records

The patient will be informed that their participation in the trial will be treated with the same confidentiality as their clinical documentation.

In the data collection notebook, the patient will be identified only by their inclusion code in the study.

The patient's name will not appear in any publication or communication of the results of the study.

The patient's participation in the trial will be reflected in their medical history.

The investigator will complete a list that will include the names of the patients participating in the trial, their inclusion number in the trial and their medical history.

Only researchers and data quality assurance and data analysis personnel will have access to the participant's clinical documentation. Eventually, persons duly authorised by the Sponsor and the Health Authorities and the Clinical Research Ethics Committee may audit or inspect the trial. Personal information will not be available to the public, in compliance with the provisions of Organic Law 15/1999, of 13 December, on the Protection of Personal Data.

Prior to the start of treatment, a clinical examination, electrocardiogram and blood and urine sample will be taken *(SEE TABLE OF DAILY DETERMINATIONS).*

The data will be collected through an online electronic CRD.

15. Financing and Insurance

The promoter has taken out civil liability insurance in accordance with current regulations.

16. Publication Policy

The Promoter undertakes to publish the results, both positive and negative, of this study as stated in art. 39 of RD 223/2004.

17. Table of examinations and treatment during follow-up

Treatment Visit Schedule														
Clinical Evaluations	Day 1	ST 2a	ST 4	ST 6	ST 8	ST 10	ST 12	ST 16	ST 20	ST 24	ST 30	ST 36	ST 42	ST 48/dFT
Inclusion and exclusion criteria	X													
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X									X				X
Physical examination	X		X				X			X		X		X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Confirmation of the use of contraceptive methods by the patient and his or her partner	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Simplified Compliance Questionnaire	X	X	X		X		X		X	X		X	X	X
Haematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TP/TTP	X						X			X				X
Blood biochemistry (simplified, fasting)		X	X		X		X		X		X		X	
Blood biochemistry (complete, not fasting)	X			X				X		X		X		X
Thyrotropin (TSH)	X						X			X		X		X
Serum pregnancy test (women only)	X													X
Urine pregnancy test (women only)		X	X	X	X	X	X	X	X	X	X	X	X	X
Samples for pharmacogenetics	X													
HCV RNA CPR*	X		X		X		X			X				X

All laboratory specimens should be obtained prior to administration of the first dose of study medication.

- Samples will be obtained for a genotypic resistance test if the patient has >100 IU/mL at week 12 or later. A single blood sample will be obtained for genetic studies.

Complete blood biochemistry: ALT, AST, creatinine, alkaline phosphatase, gammaglutamyl transferase (GGT), total bilirubin (direct and indirect), total proteins, albumin, uric acid, urea nitrogen, glucose, HbA1C (patients diagnosed with diabetes, either receiving pharmacological treatment or controlled with diet), amylase, lipase, sodium, potassium, chloride, phosphorus, calcium, triglycerides, and cholesterol.

Simplified blood biochemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, alkaline phosphatase, total bilirubin (direct and indirect), urea nitrogen, total proteins, albumin, uric acid and glucose.

Fibrosis evaluation: This will be done by liver biopsy or Fibroscan. In patients without cirrhosis on histology or Fibroscan, evaluation must have been performed no more than 18 months prior. A result of 12 kilopascals or more on the Fibroscan test would allow the patient to be considered cirrhotic.

Ultrasound: Patients with bridge fibrosis or cirrhosis must have an ultrasound performed within 6 months prior to inclusion in the study.