Clinical trial results:
Randomised, multicentre, unblinded, phase III trial evaluating HBsAg loss at W96 following 48 weeks of treatment with pegulated interferon alpha-2a in patients with chronic hepatitis B (HBeAg-negative), on treatment and responders (undetectable viral load) to nucleoside analogue(s) and/or nucleotide analogue(s) therapy for at least 12 months.

Summary

EudraCT number	2010-019367-11
Trial protocol	FR
Global end of trial date	23 September 2015

Results information

Result version number	v1 (current)
This version publication date	08 December 2023
First version publication date	08 December 2023

Trial information

Trial identification

Sponsor protocol code	ANRS HB 06 PEGAN

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01170392
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Inserm-ANRS
Sponsor organisation address	101 rue de Tolbiac, Paris, France, 75013
Public contact	Dr. Yves BENHAMOU, Service d'hépato-gastroentérologie, +33 1 42 16 10 21, ybenhamou@teaser.fr
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 December 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of patients with HBsAg negative at W96 following 48 weeks of treatment with pegulated interferon alpha-2a.

Protection of trial subjects:

This study is conducted in accordance with the updated Declaration of Helsinki, in compliance with the approved protocol and its amendments, the International Council for Harmonisation guideline for Good Clinical Practice (ICH GPC), and French regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 January 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 183
Worldwide total number of subjects	183
EEA total number of subjects	183

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	179
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From January 2011 to September 2012, 401 participants were screened from 34 centres in France.

Pre-assignment

Screening details:

Main criteria:

Inclusion: age between 18 - 75 years old, HBsAg positive, HBeAg negative.
Non inclusion: polynuclear neutrophils < 1500 mm3, platelets < 70 000/mm3, HIV, HCV and/or HDV co-infections.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	PegIFN + analogue(s)

Arm description:

92 patients were first randomised in this arm. 2 patients were excluded from the analysis (1 withdrawal of consent and 1 breach of inclusion criteria).

Arm type	Experimental
Investigational medicinal product name	Pegylated-interferon alpha-2a
Investigational medicinal product code	
Other name	Pegasys
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Dose: 180 µg/week.
Storage: between +2°C and +8°C, protected from light.

Investigational medicinal product name	Analogues
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dosage and administrations details depends on the patient's ongoing treatment (Entecavir, Tenofovir, Adefovir and/or Lamivudine)

Arm title	Analogue(s) alone

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Analogues
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dosage and administrations details depends on the patient's ongoing treatment (Entecavir, Tenofovir, Adefovir and/or Lamivudine)

Number of subjects in period 1	PegIFN + analogue(s)	Analogue(s) alone
Started	90	93
Completed	65	93
Not completed	25	0
Discontinuation	4	-
Adverse event, non-fatal	16	-
Had PegIFN dose reduction	3	-
Lack of compliance	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	PegIFN + analogue(s)
Reporting group description:	
92 patients were first randomised in this arm. 2 patients were excluded from the analysis (1 withdrawal of consent and 1 breach of inclusion criteria).	
Reporting group title	Analogue(s) alone
Reporting group description: -	

Reporting group values	PegIFN + analogue(s)	Analogue(s) alone	Total
Number of subjects	90	93	183
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	47	48	
inter-quartile range (Q1-Q3)	41 to 57	39 to 54	-
Gender categorical			
Units: Subjects			
Female	15	10	25
Male	75	83	158

End points

End points reporting groups

Reporting group title	PegIFN + analogue(s)
Reporting group description:	
92 patients were first randomised in this arm. 2 patients were excluded from the analysis (1 withdrawal of consent and 1 breach of inclusion criteria).	
Reporting group title	Analogue(s) alone
Reporting group description: -	

Primary: HBsAg loss

End point title	HBsAg loss
End point description:	
End point type	Primary
End point timeframe:	
This endpoint was assessed at week 96.	

End point values	PegIFN + analogue(s)	Analogue(s) alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	93		
Units: Patients	7	3		

Attachments (see zip file)	HBsAg-W96-loss/PEGAN_HBsAg-loss.png

Statistical analyses

Statistical analysis title	Loss of HBsAg at week 96
Comparison groups	Analogue(s) alone v PegIFN + analogue(s)
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.15
Method	Cochran-Mantel-Haenszel

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During the entire period of follow-up.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	PegIFN + analogue(s)
Reporting group description: -	
Reporting group title	Analogue(s) alone
Reporting group description: -	

Serious adverse events	PegIFN + analogue(s)	Analogue(s) alone	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 90 (21.11%)	6 / 93 (6.45%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic neoplasm malignant			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 90 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic adenoma			
subjects affected / exposed	0 / 90 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			

subjects affected / exposed	2 / 90 (2.22%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant peritoneal neoplasm			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Renal artery stenosis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Shoulder operation			
subjects affected / exposed	0 / 90 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Caesarean section			
subjects affected / exposed	0 / 90 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrectomy			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip arthroplasty			
subjects affected / exposed	0 / 90 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 90 (1.11%)	2 / 93 (2.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Normal newborn			
subjects affected / exposed	2 / 90 (2.22%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	2 / 90 (2.22%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 90 (4.44%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase			

increased			
subjects affected / exposed	3 / 90 (3.33%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 90 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column injury			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cervical myelopathy			
subjects affected / exposed	0 / 90 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	4 / 90 (4.44%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abnormal faeces			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varices oesophageal			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic artery aneurysm			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			

subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 90 (1.11%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	2 / 90 (2.22%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Calculus urinary			
subjects affected / exposed	0 / 90 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
subjects affected / exposed	1 / 90 (1.11%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 90 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			

subjects affected / exposed	1 / 90 (1.11%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute HIV infection			
subjects affected / exposed	0 / 90 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	PegIFN + analogue(s)	Analogue(s) alone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 90 (94.44%)	89 / 93 (95.70%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic neoplasm			
subjects affected / exposed	7 / 90 (7.78%)	0 / 93 (0.00%)	
occurrences (all)	7	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 90 (2.22%)	8 / 93 (8.60%)	
occurrences (all)	3	8	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	67 / 90 (74.44%)	17 / 93 (18.28%)	
occurrences (all)	84	17	
Influenza like illness			
subjects affected / exposed	36 / 90 (40.00%)	3 / 93 (3.23%)	
occurrences (all)	38	3	
Injection site erythema			
subjects affected / exposed	6 / 90 (6.67%)	0 / 93 (0.00%)	
occurrences (all)	7	0	
Pyrexia			
subjects affected / exposed	12 / 90 (13.33%)	0 / 93 (0.00%)	
occurrences (all)	13	0	
Immune system disorders			

Bronchitis			
subjects affected / exposed	7 / 90 (7.78%)	4 / 93 (4.30%)	
occurrences (all)	8	4	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	6 / 90 (6.67%)	1 / 93 (1.08%)	
occurrences (all)	6	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 90 (16.67%)	5 / 93 (5.38%)	
occurrences (all)	16	5	
Dyspnoea			
subjects affected / exposed	5 / 90 (5.56%)	1 / 93 (1.08%)	
occurrences (all)	5	1	
Epistaxis			
subjects affected / exposed	6 / 90 (6.67%)	2 / 93 (2.15%)	
occurrences (all)	6	2	
Productive cough			
subjects affected / exposed	6 / 90 (6.67%)	2 / 93 (2.15%)	
occurrences (all)	6	2	
Psychiatric disorders			
Attention deficit hyperactivity disorder			
subjects affected / exposed	6 / 90 (6.67%)	0 / 93 (0.00%)	
occurrences (all)	6	0	
Depression			
subjects affected / exposed	5 / 90 (5.56%)	3 / 93 (3.23%)	
occurrences (all)	7	3	
Insomnia			
subjects affected / exposed	10 / 90 (11.11%)	2 / 93 (2.15%)	
occurrences (all)	11	3	
Irritability			
subjects affected / exposed	13 / 90 (14.44%)	1 / 93 (1.08%)	
occurrences (all)	14	1	
Sleep disorder			

subjects affected / exposed	7 / 90 (7.78%)	1 / 93 (1.08%)	
occurrences (all)	9	1	
Investigations			
Blood creatinine increased			
subjects affected / exposed	11 / 90 (12.22%)	8 / 93 (8.60%)	
occurrences (all)	15	8	
Blood phosphorus decreased			
subjects affected / exposed	37 / 90 (41.11%)	31 / 93 (33.33%)	
occurrences (all)	44	41	
Gamma-glutamyltransferase increased			
subjects affected / exposed	44 / 90 (48.89%)	9 / 93 (9.68%)	
occurrences (all)	46	11	
Weight decreased			
subjects affected / exposed	8 / 90 (8.89%)	0 / 93 (0.00%)	
occurrences (all)	8	0	
Blood bilirubin increased			
subjects affected / exposed	3 / 90 (3.33%)	5 / 93 (5.38%)	
occurrences (all)	3	7	
Creatinine renal clearance decreased			
subjects affected / exposed	4 / 90 (4.44%)	5 / 93 (5.38%)	
occurrences (all)	5	5	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 90 (17.78%)	10 / 93 (10.75%)	
occurrences (all)	18	10	
Vertigo			
subjects affected / exposed	12 / 90 (13.33%)	4 / 93 (4.30%)	
occurrences (all)	12	4	
Memory impairment			
subjects affected / exposed	5 / 90 (5.56%)	0 / 93 (0.00%)	
occurrences (all)	5	0	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	66 / 90 (73.33%)	24 / 93 (25.81%)	
occurrences (all)	90	30	
Lymphopenia			

subjects affected / exposed	26 / 90 (28.89%)	12 / 93 (12.90%)	
occurrences (all)	29	13	
Neutropenia			
subjects affected / exposed	56 / 90 (62.22%)	14 / 93 (15.05%)	
occurrences (all)	71	14	
Thrombocytopenia			
subjects affected / exposed	31 / 90 (34.44%)	3 / 93 (3.23%)	
occurrences (all)	37	6	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 90 (7.78%)	5 / 93 (5.38%)	
occurrences (all)	8	5	
Abdominal pain upper			
subjects affected / exposed	13 / 90 (14.44%)	8 / 93 (8.60%)	
occurrences (all)	13	9	
Diarrhoea			
subjects affected / exposed	14 / 90 (15.56%)	4 / 93 (4.30%)	
occurrences (all)	16	4	
Dry mouth			
subjects affected / exposed	6 / 90 (6.67%)	0 / 93 (0.00%)	
occurrences (all)	6	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 90 (0.00%)	5 / 93 (5.38%)	
occurrences (all)	0	5	
Nausea			
subjects affected / exposed	10 / 90 (11.11%)	1 / 93 (1.08%)	
occurrences (all)	11	1	
Constipation			
subjects affected / exposed	6 / 90 (6.67%)	2 / 93 (2.15%)	
occurrences (all)	6	2	
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	55 / 90 (61.11%)	15 / 93 (16.13%)	
occurrences (all)	104	26	
Hyperbilirubinaemia			

subjects affected / exposed	8 / 90 (8.89%)	3 / 93 (3.23%)	
occurrences (all)	8	3	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 90 (6.67%)	1 / 93 (1.08%)	
occurrences (all)	6	1	
Dry skin			
subjects affected / exposed	10 / 90 (11.11%)	1 / 93 (1.08%)	
occurrences (all)	10	1	
Pruritus			
subjects affected / exposed	11 / 90 (12.22%)	2 / 93 (2.15%)	
occurrences (all)	13	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 90 (8.89%)	3 / 93 (3.23%)	
occurrences (all)	9	3	
Back pain			
subjects affected / exposed	12 / 90 (13.33%)	5 / 93 (5.38%)	
occurrences (all)	13	8	
Musculoskeletal pain			
subjects affected / exposed	9 / 90 (10.00%)	2 / 93 (2.15%)	
occurrences (all)	9	2	
Myalgia			
subjects affected / exposed	20 / 90 (22.22%)	3 / 93 (3.23%)	
occurrences (all)	27	3	
Muscle spasms			
subjects affected / exposed	6 / 90 (6.67%)	3 / 93 (3.23%)	
occurrences (all)	6	3	
Infections and infestations			
Influenza			
subjects affected / exposed	7 / 90 (7.78%)	6 / 93 (6.45%)	
occurrences (all)	8	6	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 90 (17.78%)	0 / 93 (0.00%)	
occurrences (all)	16	0	

Vitamin D deficiency subjects affected / exposed occurrences (all)	8 / 90 (8.89%) 9	10 / 93 (10.75%) 10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 August 2010	The substantial modifications included in the amendment 1 of the protocol are: - Non-inclusion criterion; - Change of the centre's principal investigator
14 December 2011	The substantial modifications included in amendment 2 of the protocol are: - Precision on the inclusion criterion; - Extension of the inclusion period without change in follow-up in the main study; - Addition of new investigator centres - Change of the principal investigator of ANRS centre n°307 - La Pitié Salpêtrière - Change of ANRS correspondent - Change of pharmacovigilance correspondent - Change in the distribution of the number of patients participating in the immunological sub-study - Other minor changes (spelling, etc.)
09 May 2012	The substantial modifications included in amendment 3 of the protocol are: - Change of promoter - Correction of the duration of the research
14 November 2012	The substantial modification included in amendment 4 of the protocol is the addition of a secondary objective.
31 January 2013	The substantial modification for information : modification of the number of patients randomised in the trial

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28404133