Sponsor

Novartis
Human Genome Sciences

Generic Drug Name

Albinterferon alfa-2b

Therapeutic Area of Trial

Hepatitis C

Approved Indication

Investigational for the treatment of hepatitis C in combination with ribavirin in patients with genotype 2 or 3 Hepatitis C Virus.

Study Number

CABF656B2202

Title

An open-label, randomized, multicenter, active-controlled, dose-ranging study to evaluate the safety and efficacy of albinterferon alfa-2b administered every 4 weeks plus ribavirin in interferon alfa-naïve patients with genotype 2/3 chronic hepatitis C.

Phase of Development

Phase IIb

Study Start/End Dates

12 Nov 2008 to 02 Dec 2010

Study Design/Methodology

This was a Phase 2b, open-label, randomized, multicenter, active-controlled, dose ranging study designed to evaluate the safety and efficacy of albinterferon alfa-2b (900 µg, 1200 µg,1500 µg, and possibly 1800 µg) administered every 4 weeks plus ribavirin in interferon alfa naïve patients with genotype 2/3 chronic hepatitis C. In Stage 1 of the study, approximately 390 eligible patients were randomized to one of 4 treatment groups in a 3:4:4:4 ratio [180 µg PEG-IFN alfa-2a every week; 900 µg albIFN every 4 weeks; 1200 µg albIFN every 4 weeks or 1500 µg albIFN every 4 weeks]. Stage 2 (1800 µg albIFN) was to be initiated based on confirmation of a satisfactory DMC review of Stage 1 and the sponsor's benefit/risk assessment of treating this particular patient population with higher doses of albIFN. Based on the DMC and sponsor review of all safety and efficacy data through 24 weeks of treatment of 100% of albIFN patients in Stage 1, the study did not enter stage 2.

Centres

53 sites in ten countries (Australia 6 sites, Canada 6 sites, Germany 6 sites, India 7 sites, Italy 5 sites, Poland 2 sites, Spain 8 sites, Taiwan 4 sites, Thailand 5 sites, UK 4 sites).

Publication

None at this time.

Objectives

Primary objective(s)

To evaluate the safety and tolerability of up to four doses of albIFN Q4w (900 µg, 1200 µg, 1500 µg and 1800 µg) plus daily RBV in IFNα naïve patients with genotype 2/3 CHC. Only three doses were studied (900 µg, 1200 µg, 1500 µg).

Secondary objective(s)

To characterize the efficacy of up to four 4 doses of albIFN Q4w (900 µg, 1200 µg, 1500 µg and 1800 µg; only stage 1 comprising of the first three does were completed in this study) plus daily RBV as measured by:

- Sustained Virologic Response (SVR), defined as undetectable HCV RNA (i.e., HCV RNA < limit of detection [LOD]; 20 IU/mL) at 24 weeks post-treatment.
- Virologic Response below historical limit of quantification (hLOQ [43 IU/mL]) at Treatment Week 12 (TW12).
- Rapid Virologic Response at Treatment Week 4 (RVR4), defined as HCV RNA < limit of quantification (hLOQ [43 IU/mL])
- Early Virologic Response at Treatment Week 12 (EVR12), defined as a ≥ 2 log10 reduction or HCV RNA < hLOQ (43 IU/mL)
- End of Treatment Response (ETR), defined as undetectable HCV RNA (< LOD [20 IU/mL]) at Week 24 or the visit closest to the date of last dose of either interferon or RBV within ±27 days of window
- Change from baseline in log10 HCV RNA at Weeks 4 and 12
- Time to HCV RNA < LOD (20 IU/mL)

Test Product (s), Dose(s), and Mode(s) of Administration

AlbIFN was supplied as a sterile, lyophilized product in single-use vials delivering a maximum of 2.4 mg/vial for subcutaneous injection.

Reference Product(s), Dose(s), and Mode(s) of Administration

PEG-IFNα2a (Pegasys®, Roche) was supplied as a sterile solution in pre-filled syringes, each containing 180µg PEG-IFNα2a in 0.5 mL for subcutaneous injection.

Criteria for Evaluation

Primary variables

- Frequency of AEs/SAEs

- AEs leading to discontinuation

- AEs leading to dose reduction or omission

- Laboratory abnormalities

Secondary variables

- HCV RNA samples at Screening, Baseline (Day1), and Weeks 2, 4, 12, 24, as well as 4, 12, and 24 weeks post-treatment

Safety and tolerability

- Patients were monitored for AEs, SAEs, laboratory abnormalities and immunogenicity status throughout the study.

- Spirometry (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], and FEV1/FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) testing were conducted at baseline, treatment weeks 12 and 24 (or end of treatment), and 24 weeks post-treatment.

Pharmacology

Sparse PK samplings were conducted at the following time points: Day 1, 15 (Week 2), 29 (Week 4), 43 (Week 6), 57 (Week 8), 85 (Week 12), 113 (Week 16) and 169 (Week 24). Intensive PK and HCV sampling was also conducted in a small group of patients during 5 additional timepoints.

Other

The exploratory pharmacogenetic assessment was optional and was performed on patients who agreed to participate in the pharmacogenetic component by signing a separate pharmacogenetic informed consent form.

Blood samples for the interleukin 28B (IL28B) single nucleotide polymorphism rs12979860 Gt were collected to investigate the association between the IL28B genotype and response to IFN therapy. Patients had to provide additional written informed consent for this test, and samples were obtained in one third of the study population (n = 117).

Statistical Methods

The safety population consisted of all patients who received at least one dose of study drug, analyzed according to treatment received. Statistical comparisons of each albIFN Q4w group with the PEG-IFNá2a control group was conducted for SAEs of particular interest and AEs leading to discontinuation, dose reduction or omission, and laboratory abnormalities. No formal statistical inference was intended a priori for the analysis of other safety parameters.
The intent-to-treat (ITT) population consisted of all patients randomized that received at least one dose of study drug. Following the ITT principle, patients were analyzed according to the treatment they were assigned to at randomization. Response rates for categorical efficacy endpoints were reported with their corresponding 95% CIs. Time to HCV RNA detection was assessed using the Kaplan-Meier method.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:
1. Age ≥ 18 years
2. Clinical diagnosis of CHC, including detectable HCV RNA at the time of screening
3. Infection with HCV genotype 2 or 3. Patients infected with mixed HCV genotypes (eg. genotype 1/2, 1/3, 2/3 etc.) at screening were not enrolled into the study. Patients with mixed genotype 2a/2b or 3a/3b were enrolled.
4. No previous IFNα-based therapy

Exclusion criteria:
1. Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, unless
• they met the definition of post-menopausal or
• Had passed 6 weeks from surgical bilateral oophorectomy with or without hysterectomy
• Agreed to use at least two reliable forms of effective contraception during treatment and during the 7-month post-treatment follow-up period.
2. Fertile males, defined as all males physiologically capable of conceiving offspring could be enrolled in this study if the patient agreed to use a condom with spermicide and his female partner agreed to use one or more of the acceptable methods of contraception listed in the protocol from the date of screening until 7 months after their last dose of RBV
3. Pregnant or nursing (lactating) women. Men whose female partners were pregnant or contemplating pregnancy
4. History or current evidence of decompensated liver
5. Other forms of liver disease.
6. Co-infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV)
7. History of moderate, severe or uncontrolled psychiatric disease
8. History of seizure disorder
9. History or clinical evidence of chronic cardiac disease; ECG (Electrocardiogram) with clinically significant abnormality. The Long QT syndrome or QTc >450 msec for males and > 470 msec for females at screening or baseline
10. Clinical evidence of preexisting interstitial lung disease
11. Clinical evidence of severe lung disease
12. Clinically significant findings on fundoscopic or retinal examination at screening
13. History of immunologically mediated disease
14. Organ transplantation other than cornea or hair transplant
15. History of clinically significant hemoglobinopathy
16. Diagnosis of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there was evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin
17. History of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption

18. History of hypersensitivity to any of the study drugs or to drugs with similar chemical structures
19. Drug or alcohol addiction within the last 6 months and/or positive drug screening tests
20. History of any other medical condition that, in the opinion of the investigator, would make the patient unsuitable for the study
21. Received systemic corticosteroids (prednisone equivalent of > 10mg/day) within 14 days prior to Baseline visit
22. Received concomitant systemic antibiotics, antifungals or antivirals for the treatment of active infection within 14 days prior to Baseline visit.
23. Received herbal therapies (including milk thistle or glycyrrhizin) or an investigational drug within 35 days prior to Baseline visit
24. Had a clinically significant laboratory abnormality at screening:
• Absolute neutrophil count (ANC) < 1,500/ mm^3 (1.5 x 10^9/L)
• Platelets < 90,000/ mm^3 (90 x 10^9/L)
• Hemoglobin < 13 g/dL for males; < 12 g/dL for females
• Serum creatinine > 1.5 x ULN or creatinine clearance < 50 mL/min
• Serum alanine transaminase (ALT) > 8 x ULN
• Fasting serum glucose > 140mg/dL and HbA1c > 7.5%
• Abnormal thyroid stimulating hormone (TSH) unless accompanied by a normal free thyroxine index and no clinical evidence of hyperthyroidism or hypothyroidism
• Alpha fetoprotein (AFP) > 20 ng/mL unless the patient had a liver imaging study (CT or MRI), within 6 months prior to Screening visit, which showed no evidence of focal lesion(s) suggestive of hepatocellular carcinoma
• High titre autoantibodies at screening, range greater than 1:80

Number of Subjects

	PEG-IFN n (%)	albIFN 900Q4w n (%)	albIFN 1200Q4w n (%)	albIFN 1500Q4w n (%)	Total n (%)
Screened					623
Randomized	79	103	104	105	391
Treated [1]	78 (98.7)	102 (99.0)	103 (99.0)	105 (100.0)	388 (99.2)
Number of patients completed [2,3]					
Treated for 24 weeks	76 (97.4)	97 (95.1)	96 (93.2)	98 (93.3)	367 (94.6)
Treated until discontinued due to EVR12 failure	1 (1.3)	2 (2.0)	2 (1.9)	2 (1.9)	7 (1.8)
Treated until discontinued due to Unsatisfactory therapeutic effect [3]					
Lack of EVR12	1 (1.3)	2 (2.0)	2 (1.9)	2 (1.9)	7 (1.8)
HCV RNA ≥100 IU/mL at week 24 or beyond	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued study medication [3]	2 (2.6)	5 (4.9)	7 (6.8)	7 (6.7)	21 (5.4)
Adverse Event (s)	1 (1.3)	1 (1.0)	3 (2.9)	4 (3.8)	9 (2.3)
Unsatisfactory therapeutic effect	1 (1.3)	2 (2.0)	2 (1.9)	2 (1.9)	7 (1.8)
Subject withdrew consent	0 (0.0)	2 (2.0)	1 (1.0)	1 (1.0)	4 (1.0)
Lost to follow-up	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Administrative problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal laboratory value (s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of patients completed study [4]					
Yes	76 (96.2)	97 (94.2)	98 (94.2)	98 (93.3)	369 (94.4)
No	3 (3.8)	6 (5.8)	6 (5.8)	7 (6.7)	22 (5.6)
Discontinued study [4]					
Lost to follow-up	2 (2.5)	3 (2.9)	1 (1.0)	3 (2.9)	9 (2.3)
Subject withdrew consent	0 (0.0)	3 (2.9)	3 (2.9)	2 (1.9)	8 (2.0)
Adverse Event (s)	0 (0.0)	0 (0.0)	2 (1.9)	2 (1.9)	4 (1.0)
Administrative problems	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

[1] Patients received at least one dose of study drug. Denominator used in percentage calculation is the number of randomized patients.
[2] Completed defined by treatment for 24 weeks or treated until discontinuation to EVR12 failure
[3] Denominator used in percentage calculation is the number of treated patients.
[4] Denominator used in percentage calculation is the number of randomized patients.

Demographic and Background Characteristics

	PEG-IFN N=78	albIFN 900Q4w N=102	albIFN 1200Q4w N=103	albIFN 1500Q4w N=105	Total N=388
Age (years)					
N	78	102	103	105	388
Mean (SD)	43.3 (11.38)	42.2 (12.42)	43.2 (12.00)	41.3 (11.28)	42.4 (11.78)
Min- Max	18.0-72.0	18.0-72.0	19.0-68.0	18.0-65.0	18.0- 72.0
Median	45.5	43.0	42.0	42.0	43.0
Race n (%) [+]					
Asian	39 (50.0)	53 (52.0)	60 (58.3)	50 (47.6)	202 (52.1)
Caucasian	36 (46.2)	46 (45.1)	41 (39.8)	51 (48.6)	174 (44.8)
Other	1 (1.3)	3 (2.9)	1 (1.0)	2 (1.9)	7 (1.8)
Black	1 (1.3)	0 (0.0)	1 (1.0)	2 (1.9)	4 (1.0)
Native American	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Sex n (%)					
Male	50 (64.1)	66 (64.7)	65 (63.1)	57 (54.3)	238 (61.3)
Female	28 (35.9)	36 (35.3)	38 (36.9)	48 (45.7)	150 (38.7)
BMI (kg/m²)					
N	78	102	101	105	386
Mean (SD)	26.0 (4.41)	25.4 (4.42)	24.9 (4.19)	25.1 (4.11)	25.3 (4.28)
Min-Max	19.4-47.1	17.0-41.4	18.0-37.6	17.5-39.0	17.0-47.1
Median	25.8	25.2	24.3	24.1	24.6

[+] Due to sparse data and too many categories, p-values could not be provided.
BMI = body mass index

Primary Objective Result(s)

The primary objective was to evaluate the safety and tolerability of albIFN Q4w regimens plus daily RBV in IFNα-naïve patients with genotype 2/3 CHC. The safety and tolerability of albIFN was evaluated by examining the overall safety profile for each treatment group, including AEs/SAEs, AEs of special interest, AEs leading to discontinuation, AEs leading to dose reduction or omission, and laboratory abnormalities. The results are listed in the Safety section below.

Efficacy (Secondary Objective Result)

	PEG-IFN N=78	albIFN 900Q4w N=102	albIFN 1200Q4w N=103	albIFN 1500Q4w N=105
SVR [1]				
n at 24 weeks post-treatment	78	102	103	105
n (%)	66 (84.6)	77 (75.5)	78 (75.7)	82 (78.1)
95% CI	(74.7, 91.8)	(66.0, 83.5)	(66.3, 83.6)	(69.0, 85.6)
P-value [2]		0.1333	0.1420	0.2674
VR below hLOQ (43 IU/ml) at week 12 [3]				
n at Week 12	78	102	103	105
n (%)	74 (94.9)	95 (93.1)	97 (94.2)	98 (93.3)
95% CI	(87.4, 98.6)	(86.4, 97.2)	(87.8, 97.8)	(86.7, 97.3)
P-value [2]		0.7589	>0.9999	0.7610
RVR4 [4]				
n at Week 4	78	102	103	105
n (%)	61 (78.2)	50 (49.0)	62 (60.2)	74 (70.5)
95% CI	(67.4, 86.8)	(39.0, 59.1)	(50.1, 69.7)	(60.8, 79.0)
P-value [2]		<0.0001	0.0101	0.2398
EVR12 [5]				
n at Week 12	78	102	103	105
n (%)	77 (98.7)	99 (97.1)	98 (95.1)	102 (97.1)
95% CI	(93.1, 100.0)	(91.6, 99.4)	(89.0, 98.4)	(91.9, 99.4)
P-value [2]		0.6343	0.2380	0.6374
ETR [6]				
n at Week 24	78	102	103	105
n (%)	75 (96.2)	94 (92.2)	92 (89.3)	96 (91.4)
95% CI	(89.2, 99.2)	(85.1, 96.6)	(81.7, 94.5)	(84.4, 96.0)
P-value [2]		0.3540	0.0883	0.2016
n with HCV RNA > LOD (20 IU/ml) at baseline	77	100	102	105
Median time (days) to HCV RNA < LOD (20 IU/ml) [7]	29	84	81	83
n [8]	76	92	97	97
95% CI	(29.0, 81.0)	(82.0, 85.0)	(29.0, 82.0)	(35.0, 85.0)
P-value [9]		0.0003	0.1861	0.0116
n with elevated ALT (>ULN) at baseline	66	79	76	86
Median time (days) to ALT normalization <= ULN [7]	29	29	29	27.5
n [8]	58	72	68	80
95% CI	(28.0, 43.0)	(27.0, 43.0)	(25.0, 29.0)	(17.0, 29.0)
P-value [9]		0.5179	0.3661	0.0502
SVR12 [10]				
n at 12 weeks post-treatment	78	102	103	105
n (%)	65 (83.3)	77 (75.5)	79 (76.7)	86 (81.9)
95% CI	(73.2, 90.8)	(66.0, 83.5)	(67.3, 84.5)	(73.2, 88.7)

P-value [2]		0.2013	0.2731	0.8014
Undetectable HCV RNA < LOD (20 IU/mL) at Week 2				
n at Week 2	78	102	103	105
n (%)	8 (10.3)	16 (15.7)	24 (23.3)	16 (15.2)
95% CI	(4.5, 19.2)	(9.2, 24.2)	(15.5, 32.7)	(9.0, 23.6)
P-value [2]		0.2883	0.0227	0.3235

-[1] SVR (Sustained Virologic Response) defined as HCV RNA < LOD (20 IU/mL) at 24 weeks post-treatment. Patients without a Week 48 assessment due to not achieving EVR12 or having HCV RNA ≥ 100 IU/mL at Week 24 or beyond were analyzed as non-responders. Remaining patients with no Week 48 assessment or 24-weeks post-treatment assessment were analyzed as non-responders.
- [2] Two-sided p-value for comparison of albIFN groups to PEG-IFN group obtained from Pearson chi-square test or Fisher's exact test.
- [3] VR below hLOQ (43 IU/ml) at week 12 defined as virologic response below hLOQ (43 IU/ml) at Week 12.
- [4] RVR4 (Rapid Virologic Response) defined as HCV RNA < hLOQ (43 IU/mL) at Week 4.
- [5] EVR12 (Early Virologic Response) defined as ≥2-log reduction in HCV RNA or HCV RNA < hLOQ (43 IU/mL) at Week 12.
- [6] ETR (End of Treatment Response) defined as HCV RNA < LOD (20 IU/mL) at Week 24 or the visit closest to date of last dose of either interferon or RBV within -28 /+ 27 days window.
- [7] Median time in days using Kaplan-Meier method.
- [8] Number of patients who reached this endpoint. Patients who did not achieve HCV RNA < LOD (20 IU/ml)/ALT < ULN were censored at last visit.
- [9] Two-sided p-value for comparison of albIFN groups to PEG-IFN group obtained from logrank testing.
- [10] SVR12 (Sustained Virologic Response at week 12 follow up) defined as HCV RNA < LOD (20 IU/mL) at 12 weeks post-treatment.

Interleukin 28B genetic variation and treatment response

	Peg-IFNα-2a 180 µg qwk (n = 21)	albIFN 900 µg q4wk (n = 33)	albIFN 1200 µg q4wk (n = 32)	albIFN 1500 µg q4wk (n = 31)	Total (n = 117)
RVR, n (%)					
CC	9/9 (100)	8/17 (47.1)	10/18 (55.6)	14/17 (82.4)	41/61 (67.2)
No -CC	9/12 (75.0)	7/16 (43.8)	10/14 (71.4)	6/14 (42.9)	32/56 (57.1)
CT	8/11 (72.7)	7/16 (43.8)	9/13 (69.2)	5/12 (41.7)	29/52 (55.8)
TT	1/1 (100.0)	0/0 (0)	1/1 (100.0)	1/2 (50,0)	3/4 (75.0)
SVR, n (%)					
CC	8/9 (88.9)	13/17 (76.5)	14/18 (77.8)	15/17 (88.2)	50/61 (82.0)
Non-CC	10/12 (83.3)	14/16 (87.5)	9/14 (64.3)	11/14 (78.6)	44/56 (78.6)
CT	9/11 (81.8)	14/16 (87.5)	9/13 (69.2)	9/12 (75)	41/52 (78.8)
TT	1/1 (100)	0/0	0/1 (0.0)	2/2 (100)	3/4 (75.0)

albIFN, albinterferon alfa-2b; Peg-IFNα-2a, pegylated interferon-α-2a; RVR, rapid virologic

Safety Results

Adverse Events by System Organ Class

Primary System Organ Class	PEG-IFN N=78 n (%)	albIFN 900Q4w N=102 n (%)	albIFN 1200Q4w N=103 n (%)	albIFN 1500Q4w N=105 n (%)
Any Primary System Organ Class	**76 (97.4)**	**95 (93.1)**	**97 (94.2)**	**102 (97.1)**
Blood and lymphatic system disorders	28 (35.9)	24 (23.5)	30 (29.1)	38 (36.2)
Cardiac disorders	2 (2.6)	5 (4.9)	4 (3.9)	6 (5.7)
Congenital, familial and genetic disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Ear and labyrinth disorders	5 (6.4)	5 (4.9)	6 (5.8)	8 (7.6)
Endocrine disorders	7 (9.0)	9 (8.8)	5 (4.9)	11 (10.5)
Eye disorders	25 (32.1)	28 (27.5)	24 (23.3)	34 (32.4)
Gastrointestinal disorders	38 (48.7)	50 (49.0)	55 (53.4)	60 (57.1)
General disorders and administration site conditions	64 (82.1)	88 (86.3)	89 (86.4)	91 (86.7)
Hepatobiliary disorders	1 (1.3)	3 (2.9)	1 (1.0)	1 (1.0)
Immune system disorders	1 (1.3)	2 (2.0)	0 (0.0)	0 (0.0)
Infections and infestations	21 (26.9)	28 (27.5)	15 (14.6)	25 (23.8)
Injury, poisoning and procedural complications	6 (7.7)	8 (7.8)	4 (3.9)	8 (7.6)
Investigations	17 (21.8)	22 (21.6)	29 (28.2)	28 (26.7)
Metabolism and nutrition disorders	22 (28.2)	31 (30.4)	32 (31.1)	30 (28.6)
Musculoskeletal and connective tissue disorders	36 (46.2)	42 (41.2)	51 (49.5)	40 (38.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.3)	4 (3.9)	0 (0.0)	1 (1.0)
Nervous system disorders	37 (47.4)	48 (47.1)	59 (57.3)	44 (41.9)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	28 (35.9)	38 (37.3)	37 (35.9)	40 (38.1)
Renal and urinary disorders	2 (2.6)	3 (2.9)	3 (2.9)	2 (1.9)
Reproductive system and breast disorders	4 (5.1)	3 (2.9)	1 (1.0)	3 (2.9)
Respiratory, thoracic and mediastinal disorders	33 (42.3)	47 (46.1)	38 (36.9)	46 (43.8)
Skin and subcutaneous tissue disorders	48 (61.5)	67 (65.7)	60 (58.3)	71 (67.6)
Social circumstances	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Vascular disorders	1 (1.3)	2 (2.0)	5 (4.9)	2 (1.9)

Primary system organ classes are presented in alphabetic order.
A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A subject with multiple AEs within a primary system organ class system is counted only once in the total row.

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

Preferred Term	PEG-IFN N=78 n (%)	albIFN 900Q4w N=102 n (%)	AlbIFN 1200Q4w N=103 n (%)	AlbIFN 1500Q4w N=105 n (%)	Total N=388 n (%)
Any Preferred Term	**76 (97.4)**	**95 (93.1)**	**97 (94.2)**	**102 (97.1)**	**370 (95.4)**
Alopecia	24 (30.8)	44 (43.1)	46 (44.7)	59 (56.2)	173 (44.6)
Pyrexia	26 (33.3)	49 (48.0)	46 (44.7)	49 (46.7)	170 (43.8)
Headache	29 (37.2)	34 (33.3)	44 (42.7)	37 (35.2)	144 (37.1)
Fatigue	29 (37.2)	33 (32.4)	35 (34.0)	30 (28.6)	127 (32.7)
Decreased appetite	21 (26.9)	28 (27.5)	29 (28.2)	26 (24.8)	104 (26.8)
Insomnia	21 (26.9)	26 (25.5)	27 (26.2)	26 (24.8)	100 (25.8)
Myalgia	20 (25.6)	24 (23.5)	27 (26.2)	23 (21.9)	94 (24.2)
Cough	16 (20.5)	24 (23.5)	22 (21.4)	31 (29.5)	93 (24.0)
Pruritus	19 (24.4)	25 (24.5)	17 (16.5)	23 (21.9)	84 (21.6)
Asthenia	15 (19.2)	13 (12.7)	24 (23.3)	21 (20.0)	73 (18.8)

Preferred terms are sorted in descending frequency of the adverse event for all patients in the study.
A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Serious Adverse Events and Deaths

	PEG-IFN N=78 n (%)	*albIFN 900Q4w N=102 n (%)*	*albIFN 1200Q4w N=103 n (%)*	*albIFN 1500Q4w N=105 n (%)*
Deaths	*0 (0.0)*	*0 (0.0)*	*1 (1.0)*	*0 (0.0)*
SAE	*3 (3.8)*	*11 (10.8)*	*3 (2.9)*	*3 (2.9)*
albIFN/PEG-IFN related SAEs	*1 (1.3)*	*7 (6.9)*	*1 (1.0)*	*1 (1.0)*
Ribavirin related SAEs	*0 (0.0)*	*4 (3.9)*	*0 (0.0)*	*1 (1.0)*
Discontinued due to AEs	*2 (2.6)*	*3 (2.9)*	*3 (2.9)*	*6 (5.7)*
AEs leading to discontinuation of albIFN/PEG-IFN	*1 (1.3)*	*1 (1.0)*	*3 (2.9)*	*4 (3.8)*
AEs leading to discontinuation of Ribavirin	*2 (2.6)*	*3 (2.9)*	*3 (2.9)*	*5 (4.8)*

Serious Adverse Events by System Organ Class

Primary System Organ Class Preferred Term	PEG-IFN N=78 n (%)	albIFN 900Q4w N=102 n (%)	albIFN 1200Q4w N=103 n (%)	albIFN 1500Q4w N=105 n (%)
Any Primary System Organ Class	**3 (3.8)**	**11 (10.8)**	**3 (2.9)**	**3 (2.9)**
Blood and lymphatic system disorders	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)
Anemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Neutropenia	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Endocrine disorders	1 (1.3)	1 (1.0)	0 (0.0)	0 (0.0)
Goitre	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperthyroidism	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Hypothyroidism	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	1 (1.3)	0 (0.0)	1 (1.0)	0 (0.0)
Diarrhea	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Gastric ulcer	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Gastric ulcer hemorrhage	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Rectal hemorrhage	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Hepatobiliary disorders	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Cholestasis	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	2 (2.6)	3 (2.9)	1 (1.0)	0 (0.0)
Bacterial sepsis	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Lobar pneumonia	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Malaria	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	0 (0.0)	2 (2.0)	1 (1.0)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	2 (2.0)	1 (1.0)	1 (1.0)
Drug exposure during pregnancy	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Intentional overdose	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Lower limb fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Narcotic intoxication	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Ketoacidosis	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Type 1 diabetes mellitus	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.3)	1 (1.0)	0 (0.0)	0 (0.0)
Colon cancer	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Thyroid cancer	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Paraplegia	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Spinal cord infarction	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)

Pregnancy, puerperium and peri-natal conditions	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Abortion	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Suicidal ideation	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Azotaemia	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Renal failure acute	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)
Lung consolidation	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Restrictive pulmonary disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Psoriasis	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class alphabetically.
A subject with multiple AEs within a primary system organ class system is counted only once in the total row.

Other Relevant Findings

Pulmonary Evaluations - Spirometry and DL_{CO}

	PEG-IFN N=78	albIFN 900Q4w N=102	albIFN 1200Q4w N=103	albIFN 1500Q4w N=105
FEV_1 Declines >10% from baseline				
Week 12	8.8	11.0	11.3	15.8
Week 24	14.8	10.3	15.6	12.3
Week 24 Post-Treatment	7.6	18.2	13.0	13.4
FVC Declines >10% from baseline				
Week 12	7.0	12.3	8.5	7.9
Week 24	6.6	11.5	13.0	13.7
Week 24 Post-Treatment	6.1	14.3	16.9	13.4
FEV_1 /FVC Ratio Declines >10% from baseline				
Week 12	3.5	1.4	1.4	0.0
Week 24	0.0	1.3	1.3	0.0
Week 24 Post-Treatment	0.0	1.3	1.3	1.2
DL_{CO} Declines >15% from baseline (Corrected for Hemoglobin)				
Week 12	42.4	25.9	24.7	41.3
Worst	53.4	38.3	46.7	56.1
Week 24 Post-Treatment	13.0	21.0	21.3	16.5

[FEV_1] forced expiratory volume in 1 second [FVC], forced vital capacity [DL_{CO}] diffusing capacity of the lung for carbon monoxide.

For spirometry and DL_{CO} assessments, patients were referred to a local pulmonary function laboratory that was certified by the central pulmonary function laboratory prior to study initiation. Spirometry and DL_{CO} tests were standardized according to American Thoracic Society/European Respiratory Society guidelines and DL_{CO} was corrected for haemoglobin. Data were transferred from the local pulmonary function laboratory to a central laboratory, where they were read for quality control purposes and processing prior to being transferred to the study sponsor.

Date of Clinical Trial Report

November 6, 2011

Date Inclusion on Novartis Clinical Trial Results Database

6 Dec 2011

Date of Latest Update

November 11, 2011