Sponsor Novartis
Generic Drug Name Albinterferon alfa-2b
Therapeutic Area of Trial Chronic hepatitis C (CHC)
Approved Indication Investigational

Study Number

CABF656A1202

Title

A Phase I study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of escalating single dose of albinterferon alfa-2b (albIFN), recombinant human albumin-interferon alfa fusion protein in Japanese chronic hepatitis C patients.

Phase of Development

Phase I

Study Start/End Dates

22 Jul 2008 to 30 Jul 2009

Study Design/Methodology

Phase I, multi-center, open-label, dose evaluation study of up to 5 escalating single doses of albIFN (600 µg, 900 µg, 1200 µg, 1500 µg and 1800 µg). Thirty-one IFN treatment-naïve or treatments- experienced patients with CHC were enrolled in the study. Each subject received a single injection of albIFN after the screening period (up to 28 days). Inpatient hospitalization was required from Day 0 (or prior to Day 0) to Day 7. Within each dose level, six subjects were enrolled per cohort. After the safety and tolerability of each dose was established, subjects were enrolled in the next escalating dose cohort. After the administration of each dose of albIFN, blood samples were collected at specified times for the determination of albIFN serum concentrations, HCV RNA viral levels and clinical laboratory tests. All adverse events encountered after dosing were recorded and graded according to modified Division of Microbiology & Infectious Disease (DMID) adult toxicity tables.

Dose Escalation:
The recommendation for the sponsor to escalate from doses 600 µg to 900 µg and from 900 µg to 1200 µg was done by internal medical advisor(s) and an external medical expert who was Knowledgeable about the use of interferon and associated side effects following a review of all safety information, including adverse events and safety laboratory assessments from the preceding cohort. The recommendation for the sponsor to escalate to doses above 1200 µg was done by the internal medical advisor(s), the external medical expert and an external Data Monitoring Board. The final decision for dose escalation was made by the sponsor based on these recommendations.

Centres

8 centers in Japan

Publication

None

Objectives

Primary objective(s)

To evaluate safety and tolerability of albIFN administered subcutaneously in Japanese Patients with CHC.

Secondary objective(s)

- To evaluate pharmacokinetics (PK) of albIFN in Japanese CHC patients
- To evaluate pharmacodynamics (PD) of albIFN in Japanese CHC patients

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

AlbIFN is a recombinant protein of alpha interferon (rIFNα2b) genetically fused to human albumin (rHA) with a molecular mass of 85.7 kDa. AlbIFN was supplied as a sterile, single-use, lyophilized product. Each vial delivered 2.4 mg of albIFN at a concentration of 3.0 mg/mL by reconstitution with 0.9 mL sterile water for injection (WFI).
AlbIFN was administered by subcutaneous (SC) injection over 2 hours.

Duration of treatment: Subjects received a single injection and were observed for a total of 35 days after the dose.

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

Not applicable

Criteria for Evaluation

Primary variables

Not applicable

Secondary variables

Not applicable

Safety and tolerability

Safety and tolerability assessments consisted of collecting all adverse events, serious adverse events, with their severity and relationship to study drug, and pregnancies. They included the following measurements and assessments.

- Vital signs and body measurements: body weight, body temperature, systolic and diastolic blood pressure, and pulse rate.
- Standard clinical laboratory evaluations: Hematology, Blood chemistry, and Urinalysis
- Immunogenicity assessment: antibody titer
- Immunologic assessment: KL-6 test
- Other safety assessments: funduscopic test, chest X ray, oxygen saturation by pulse oximetry test

Pharmacology

For subjects receiving a single subcutaneous injection of albIFN, blood samples were collected at the following times for the determination of albIFN concentrations: pre-dose, 12 hours post dose (Day 0), Day 1, 3, 4, 7, 14, 28, and 35.

Other

Pharmacodynamic assessments:

• HCV RNA Analysis

• ALT activity

Statistical Methods

A total of 30 patients with 6 patients per dose level was planned to be included in this study, as this number of subjects was considered adequate. The rationale for the sample size was based on the frequency of severe adverse events of grade 3 or grade 4 (except flu like symptoms), the possibility to detect AEs, and the probability to observe any serious adverse event.
Frequencies were obtained from study ALFR-HC01 (Phase I study in IFN treatment experienced

patients) and calculated per dose group. The event rate for severe adverse events classified as grade 3 or grade 4 was found to be equal to 20% in 1200 µg arm. Thus the probabilities to see two or more adverse events of grade 3 or 4 would be 34.5% if the true event rate was 20% as observed in the ALFR-HC01 study. Furthermore the probability to detect at least one change in neutrophil counts from grade 0 (at baseline) to grade 3 was equal to 99.6%, given an event rate of 60.0%. The probability of seeing one or more serious adverse events, given an observed event rate of 16.7%, was equal to 66.6%.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Have a clinical diagnosis of CHC established on the basis of a detectable viral load as measured by a serum HCV RNA test at least 6 months before and during the screening period.
- Age 20 to 69 years (at getting informed consent).
- Have compensated liver disease results on screening laboratory assessment:
  - WBC : ≥ 3,000/mm^3
  - Neutrophil count : ≥ 2,000/mm^3
  - Platelets : ≥ 100,000/mm^3
  - Total bilirubin : < 2.0 mg/dL
  - Albumin : > 3.5 g/dL
  - Prothrombin time : within normal limits (WNL)
  - Serum creatinine : WNL
  - Fasting glucose should be 70-140 mg/dL. Results between 116-140 mg/dL require a HbA1c ≤ 7.5%.
  - WBC, neutrophil count and platelets at baseline should also meet the criteria.
- Any woman with an intact uterus, regardless of age (unless amenorrheic for the previous 24 months) must have a negative blood pregnancy test at screening and agree to practice a medically approved method of contraception over the course of the study and for 45 days after the injection of study agent.
- All males must agree to practice a medically approved method of contraception over the course of the study and for 45 days after the injection of study agent.
- Have the ability to understand the requirements of the study provide written informed consent (including consent for use and disclosure of research-related health information) and comply with the study protocol procedures.

Exclusion criteria

- Evidence of decompensate liver disease and/or liver cirrhosis.
- Pregnant or lactating.
- Body weight < 50 kg (at screening and baseline).
- Patients with history of hypersensitivity to IFN or any other component of the albIFN product.
- Patients with history of hypersensitivity to the yeast products (bread, miso, soy sauce, brewed beverage etc) or the yeast-based medicine or genetically-modified medicine based on the yeast as a host (genetically-modified precipitated vaccine for hepatitis B etc).
- Clinical diagnosis of other causes of chronic liver disease; hepatitis B, autoimmune hepatitis, primary biliary cirrhosis, alcohol or drug abuse, hemochromatosis, Wilson's Disease, or α1-antitrypsin deficiency.
- A history of severe or uncontrolled psychiatric disease.
- Patients with severe or uncontrolled hypertension.
- A history of convulsive seizure.
- A history of immunologically mediated disease (e.g., rheumatoid arthritis, inflammatory bowel disease, systemic lupus Erythematosus).
- A history of thyroid disease that is poorly controlled on medication.
- Coagulation disorders (e.g., history of pulmonary embolism or thrombophlebitis).

- A history or other clinical evidence of chronic cardiac or pulmonary disease associated with functional limitation including the oxygen saturation at screening is < 90%.
- A history or other clinical evidence of interstitial lung disease; radiographic findings including significant exaggerated interstitial opacity by chest X ray at screening or interstitial shadow at the sub pleural region on the basal part of the lung by the CT within 12 weeks prior to screening; or KL-6 ≥ 500 U/mL at screening.
- A current drug or alcohol addiction (patients who have documented addiction-free period of at least 2 years may be enrolled based on the clinical judgment of the Investigator).
- A history of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases.
- A history of any other medical disease or condition that would make the patients (in the opinion of the investigator) unsuitable for the study.
- Requirement for concomitant theophylline, antipyrine, warfarin.
- Requirement for chronic systemic corticosteroids (prednisone equivalent of > 10 mg/day).
- Requirement for the maintenance therapies for liver function (e.g., ursodeoxycholic acid, Glycyrrhizin). Glycyrrhizin should not be used 1 week prior to the baseline.
- Requirement of treatment by Sho-sai-ko-to. Sho-sai-ko-to should not be used 1 week prior to the baseline.
- Requirement for systemic antiviral, hematopoietic growth factors or immunomodulatory treatments.
- A positive test for serum antigen/antibodies to the human immunodeficiency virus (HIV-1) or serum hepatitis B virus surface antigen.
- Received an experimental drug within 4 months prior to screening.
- Received IFN treatment within 3 months prior to screening.
- Donation or loss of 400 ml or more of blood within 3 months prior to participation, donation or loss of 200 ml or more of blood within 1 month prior to participation, or donation of component blood within 2 weeks prior to participation.

Number of Subjects

Disposition	600 µg n (%)	900 µg n (%)	1200 µg n (%)	1500 µg n (%)	1800 µg n (%)	Total n (%)
Patients						
Screened						56
Failed inclusion criteria						25
Eligible						31
Exposed	7	6	6	6	6	31
Completed	7(100.0)	6(100.0)	6(100.0)	6(100.0)	6(100.0)	31(100.0)
Discontinued	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Analysis populations						
Safety	7(100.0)	6(100.0)	6(100.0)	6(100.0)	6(100.0)	31(100.0)
PK	7(100.0)	5(83.3)	6(100.0)	6(100.0)	6(100.0)	30(96.8)
PD	7(100.0)	5(83.3)	6(100.0)	6(100.0)	6(100.0)	30(96.8)

Demographic and Background Characteristics

Variable	Statistics /Category	600 µg n=7	900 µg n=6	1200 µg n=6	1500µg n=6	1800µg n=6	Total n=31
Age (years)	Mean	59.3	57.7	59.0	45.0	54.2	55.2
	SD	6.70	11.18	9.53	14.60	9.35	11.14
Sex - n(%)	Male	3(42.9)	1(16.7)	3(50.0)	4(66.7)	4(66.7)	15(48.4)
	Female	4(57.1)	5(83.3)	3(50.0)	2(33.3)	2(33.3)	16(51.6)
Weight (kg)	Mean	62.39	65.20	60.83	61.27	70.90	64.06
	SD	12.225	12.209	10.931	14.020	17.350	13.095
Height (cm)	Mean	160.4	158.8	161.2	165.8	164.0	162.0
	SD	11.10	5.91	8.61	10.93	10.53	9.36
BMI (kg/m^2)	Mean	24.124	25.670	23.300	22.102	25.983	24.232
	SD	3.2514	3.2947	2.7292	3.3199	3.4908	3.3382
Duration from diagnosis of Hepatitis C (years)	Mean	10.54	11.73	10.45	8.78	3.66	9.08
	SD	4.618	5.825	5.072	7.698	3.905	5.899
Interferon Treatment - n(%)	Naive	0(0.0)	0(0.0)	2(33.3)	3(50.0)	6(100.0)	11(35.5)
	Experienced	7(100.0)	6(100.0)	4(66.7)	3(50.0)	0(0.0)	20(64.5)
Relevant medical history - n(%)	Yes	3(42.9)	3(50.0)	2(33.3)	2(33.3)	2(33.3)	12(38.7)
	No	4(57.1)	3(50.0)	4(66.7)	4(66.7)	4(66.7)	19(61.3)
Current medical conditions - n(%)	Yes	7(100.0)	6(100.0)	6(100.0)	6(100.0	5(83.3)	30(96.8)
	No	0(0.0)	0(0.0)	0(0.0)	) 0(0.0)	1(16.7)	1(3.2)
HCV Genotype - n(%)	1b	5(71.4)	5(83.3)	5(83.3)	4(66.7)	1(16.7)	20(64.5)
	2a	1(14.3)	1(16.7)	1(16.7)	1(16.7)	4(66.7)	8(25.8)
	2b	0(0.0)	0(0.0)	0(0.0)	1(16.7)	0(0.0)	1(3.2)
	Missing	1(14.3)	0(0.0)	0(0.0)	0(0.0)	1(16.7)	2(6.5)
HCV RNA (log IU/mL)	Mean	6.60	6.45	6.50	6.15	6.92	6.53
	SD	0.688	1.716	0.613	0.680	0.194	0.890

Variable	Statistics /Category	600 µg n=7	900 µg n=6	1200 µg n=6	1500µg n=6	1800µg n=6	Total n=31
ALT (U/L)	Mean	76.1	68.0	67.5	70.0	52.0	67.0
	SD	51.20	60.29	72.90	62.20	36.59	54.32
ECG C.S.As. - n(%)	Yes	0(0.0)	0(0.0)	0(0.0)	1(16.7)	0(0.0)	1(3.2)
	No	7(100.0)	6(100.0)	6(100.0)	5(83.3)	6(100.0)	30(96.8)
Ultrasound or abdominal CT C.S.As. - n(%)	Yes	0(0.0)	0(0.0)	0(0.0)	1(16.7)	0(0.0)	1(3.2)
	No	7(100.0)	6(100.0)	6(100.0)	5(83.3)	6(100.0)	30(96.8)
Chest CT C.S.As. - n(%)	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	7(100.0)	6(100.0)	6(100.0)	6(100.0)	6(100.0)	31(100.0)

BMI [kg/m^2] = (weight [kg] / height[m]**^{2}).
. All the data used in this table are collected at Screening.

Primary Objective Result(s)

The primary objective of this study is to evaluate safety and tolerability of albIFN administered subcutaneously in Japanese patients with CHC. See the safety result section.

Secondary Objective Result(s)

Mean(SD) for PK parameters (PK population)

PK parameter	Statistics	600 µg n=7	900 µg n=5	1200 µg n=6	1500 µg n=6	1800 µg n=6
AUC 0-inf	Mean	14778.0	22390.1	33648.7	35137.5	37901.6
(hr*ng/mL)	SD	4676.03	6860.47	10295.43	12758.29	7502.59
	Geo-mean	14109.0	21434.7	32483.6	33404.7	37260.7
AUC 0-t	Mean	14328.4	21720.3	32030.1	40473.7	36539.6
(hr*ng/mL)	SD	4655.74	6259.10	9088.70	18974.53	6614.19
	Geo-mean	13625.1	20883.9	31074.3	37121.7	36025.7
Cmax	Mean	41.286	67.160	85.433	115.917	93.267
(ng/mL)	SD	13.1563	20.2269	26.6105	41.9573	12.9050
	Geo-mean	38.972	64.380	82.558	109.521	92.473
λz	Mean	0.00485	0.00514	0.00436	0.00407	0.00487
(1/hr)	SD	0.000755	0.000970	0.000986	0.001437	0.001045
tmax	Minimum	72	72	96	72	168
(hr)	Median	96.3	95.8	132.0	96.2	168.0
	Maximum	168	168	168	168	168
t1/2	Mean	146.6	139.1	165.7	203.9	147.4
(hr)	SD	27.52	29.03	36.05	119.49	28.12
CL/f	Mean	44.708	44.174	38.139	47.178	49.172
(mL/hr)	SD	15.8638	16.9099	10.0634	16.5566	10.3156
Vλz/F	Mean	9840.581	8517.883	8713.310	10321.445	10113.786
(mL)	SD	5574.3721	2373.0083	1098.1698	3279.6190	393.7414

Mean (SD) for change from baseline (including maximum reduction) of HCV RNA level (log 10 IU/mL) by time point (PD population)

Visit	Statistic	600 µg n=7	900 µg n=5	1200 µg n=6	1500 µg n=6	1800 µg n=6
Day 1	Mean	-0.74	-0.92	-0.73	-0.03	-2.23
	SD	0.637	0.402	0.561	2.148	0.572
Day 4	Mean	-1.30	-2.14	-1.53	-1.23	-3.30
	SD	1.049	0.805	0.728	1.454	0.654
Day 7	Mean	-1.84	-1.90	-1.85	-1.67	-3.75
	SD	1.594	0.970	0.948	1.642	0.675
Day 14	Mean	-2.10	-1.92	-2.12	-2.17	-4.62
	SD	1.609	1.126	1.266	1.973	1.139
Day 21	Mean	-2.06	-1.90	-2.22	-2.70	-4.70
	SD	2.106	0.992	1.751	2.534	1.230
Day 28	Mean	-2.04	-1.78	-2.28	-2.53	-4.73
	SD	2.109	1.062	1.707	2.556	1.069
Endpoint	Mean	-1.30	-1.40	-2.57	-2.15	-4.45
	SD	1.387	0.834	1.806	2.574	1.178

Visit	Statistic	600 µg n=7	900 µg n=5	1200 µg n=6	1500 µg n=6	1800 µg n=6
Maximum reduction	Mean	-2.59	-2.36	-2.70	-2.82	-4.83
	SD	1.926	1.043	1.695	2.363	1.178

Baseline is the Day 0 value, or Screening value in the case where the Day 0 value is missing. Endpoint is the Day 35 value for the patients who completed the study, or LOCF value for the patients who discontinued from the study prior to Day 35.Maximum reduction is the change from baseline when HCV RNA achieved its lowest level. At each time point, only patients with a value at both Baseline and this time point are included.

Mean (SD) for percent change from baseline in ALT(%) by time point (PD population)

Visit	Statistic	600 µg n=7	900 µg n=5	1200 µg n=6	1500 µg n=6	1800 µg n=6
Day 1	Mean	2.27	-2.04	4.69	13.96	-10.64
	SD	20.398	12.538	20.430	14.715	9.511
Day 3	Mean	-5.12	10.68	12.40	16.00	-6.57
	SD	19.628	21.252	34.463	18.036	15.514
Day 4	Mean	-4.18	-0.11	16.29	2.66	-8.07
	SD	28.946	15.894	40.130	21.905	9.735
Day 7	Mean	-5.42	-19.01	21.08	3.78	-5.46
	SD	49.831	16.642	69.877	51.296	19.660
Day 14	Mean	-8.78	-17.32	15.81	-6.18	1.54
	SD	53.105	18.353	80.081	75.946	31.142
Day 21	Mean	-27.73	1.09	0.40	-22.27	-18.74
	SD	36.696	58.383	83.847	76.254	24.032
Day 28	Mean	-27.00	6.24	-15.83	-24.43	-38.07
	SD	38.900	69.284	65.418	75.976	21.177
Endpoint	Mean	-23.42	-7.60	-18.05	-28.11	-46.43
	SD	47.404	48.885	63.802	67.843	20.986

Baseline is the Day -1 value, or Screening value in the case where the Day -1 value is missing.Endpoint is the Day 35 value for the patients who completed the study, or LOCF value for the patients who discontinued from the study prior to Day 35. At each time point, only patients with a value at both Baseline and this time point are included.

Safety Results

Number of patients with adverse events by system organ class (Safety population)

System organ class	600 µg n= 7 n(%)	900 µg n= 6 n(%)	1200 µg n= 6 n(%)	1500µg n= 6 n(%)	1800µg n= 6 n(%)	Total n= 31 n(%)
Any system organ class	7(100.0)	6(100.0)	6(100.0)	6(100.0)	6(100.0)	31(100.0)
Blood and lymphatic system disorders	1(14.3)	3(50.0)	5(83.3)	4(66.7)	3(50.0)	16(51.6)
Cardiac disorders	1(14.3)	1(16.7)	0(0.0)	2(33.3)	0(0.0)	4(12.9)
Ear and labyrinth disorders	0(0.0)	0(0.0)	1(16.7)	1(16.7)	0(0.0)	2(6.5)
Eye disorders	0(0.0)	1(16.7)	2(33.3)	1(16.7)	1(16.7)	5(16.1)
Gastrointestinal disorders	3(42.9)	4(66.7)	4(66.7)	2(33.3)	1(16.7)	14(45.2)
General disorders and administration site conditions	4(57.1)	4(66.7)	6(100.0)	6(100.0)	5(83.3)	25(80.6)
Infections and infestations	3(42.9)	0(0.0)	0(0.0)	1(16.7)	3(50.0)	7(22.6)
Investigations	4(57.1)	5(83.3)	2(33.3)	3(50.0)	3(50.0)	17(54.8)
Metabolism and nutrition disorders	1(14.3)	3(50.0)	2(33.3)	1(16.7)	1(16.7)	8(25.8)
Musculoskeletal and connective tissue disorders	6(85.7)	4(66.7)	4(66.7)	5(83.3)	4(66.7)	23(74.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(16.7)	1(3.2)
Nervous system disorders	5(71.4)	3(50.0)	0(0.0)	4(66.7)	5(83.3)	17(54.8)
Psychiatric disorders	0(0.0)	2(33.3)	1(16.7)	1(16.7)	0(0.0)	4(12.9)
Respiratory, thoracic and mediastinal disorders	1(14.3)	1(16.7)	1(16.7)	2(33.3)	1(16.7)	6(19.4)
Skin and subcutaneous tissue disorders	3(42.9)	2(33.3)	3(50.0)	2(33.3)	1(16.7)	11(35.5)
Vascular disorders	0(0.0)	0(0.0)	1(16.7)	0(0.0)	0(0.0)	1(3.2)

Number of patients with most frequent adverse events (>= 10% in all cohorts combined) by preferred term (Safety population)

Preferred Term	600 µg n= 7 n(%)	900 µg n= 6 n(%)	1200 µg n= 6 n(%)	1500 µg n= 6 n(%)	1800 µg n= 6 n(%)	Total n= 31 n(%)
Any preferred term	7(100.0)	6(100.0)	6(100.0)	6(100.0)	6(100.0)	31(100.0)
Pyrexia	4(57.1)	4(66.7)	4(66.7)	6(100.0)	5(83.3)	23(74.2)
Arthralgia	4(57.1)	2(33.3)	3(50.0)	3(50.0)	3(50.0)	15(48.4)
Headache	5(71.4)	3(50.0)	0(0.0)	4(66.7)	3(50.0)	15(48.4)
Neutropenia	0(0.0)	3(50.0)	5(83.3)	3(50.0)	3(50.0)	14(45.2)
Leukopenia	1(14.3)	3(50.0)	3(50.0)	4(66.7)	1(16.7)	12(38.7)
Malaise	2(28.6)	3(50.0)	2(33.3)	3(50.0)	2(33.3)	12(38.7)
Platelet count decreased	2(28.6)	4(66.7)	1(16.7)	0(0.0)	3(50.0)	10(32.3)
Myalgia	1(14.3)	2(33.3)	0(0.0)	3(50.0)	3(50.0)	9(29.0)
Neutrophil count decreased	2(28.6)	2(33.3)	1(16.7)	2(33.3)	2(33.3)	9(29.0)
White blood cell count decreased	2(28.6)	2(33.3)	1(16.7)	1(16.7)	2(33.3)	8(25.8)
Back pain	2(28.6)	2(33.3)	2(33.3)	1(16.7)	0(0.0)	7(22.6)
Fatigue	0(0.0)	0(0.0)	2(33.3)	3(50.0)	2(33.3)	7(22.6)
Stomatitis	2(28.6)	2(33.3)	1(16.7)	0(0.0)	1(16.7)	6(19.4)
Thrombocytopenia	0(0.0)	1(16.7)	2(33.3)	1(16.7)	1(16.7)	5(16.1)
Anorexia	1(14.3)	1(16.7)	1(16.7)	1(16.7)	0(0.0)	4(12.9)
Insomnia	0(0.0)	2(33.3)	1(16.7)	1(16.7)	0(0.0)	4(12.9)
Lymphopenia	0(0.0)	0(0.0)	1(16.7)	1(16.7)	2(33.3)	4(12.9)
Musculoskeletal pain	3(42.9)	0(0.0)	1(16.7)	0(0.0)	0(0.0)	4(12.9)

Serious Adverse Events and Deaths

No patients died during the study.
One SAE (bladder cancer) occurred in the cohort 1800 µg.
No patients discontinued from the study due to AEs.

Date of Clinical Trial Report

6 Jan 2010

Date Inclusion on Novartis Clinical Trial Results Database

August 10, 2010

Date of Latest Update

August 10, 2010