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ORIGINAL ARTICLE

A Phase 3 clinical trial validating the potency and safety of an innovative, extra-long-acting interferon in chronic hepatitis C

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Key words
chronic hepatitis B, chronic hepatitis C, chronic hepatitis C genotype 2, chronic viral hepatitis, clinical trial, ropeginterferon alfa-2b.

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Declaration of conflict of interest: Pei-Jer Chen and Wan-Long Chuang serve as consultants of PharmaEssentia. Albert Qin, Chan-Yen Tsai, Ting-Fang Wang, and Hsin-Hui Lai work for PharmaEssentia Corporation headquarter in Taipei, Taiwan. Kuan-Chiao Tseng worked for PharmaEssentia Corporation headquarter in Taipei,

Abstract

Background and Aim: Ropeginterferon alfa-2b is a novel mono-pegylated, extra-long-acting interferon. It is administered infrequently and showed good tolerability and clinical activity for the chronic hepatitis B or C treatment in our previous Phase 2 clinical trials. This study aims to validate the potency and safety of this novel agent in a Phase 3 chronic viral hepatitis setting.
Methods: Patients with chronic hepatitis C genotype 2 were randomized to receive subcutaneous injections of ropeginterferon alfa-2b biweekly or the conventional pegylated interferon alfa-2b weekly for 24 weeks, combined with ribavirin. The primary endpoint was to assess the safety and antiviral potency of ropeginterferon alfa-2b by the non-inferiority in sustained virologic response at 12 weeks after treatment.
Results: A total of 222 patients were enrolled. Ropeginterferon alfa-2b group showed a favorable safety profile. Side effects that were generally associated with prior interferon therapies, including neutropenia, asthenia, fatigue, alopecia, dizziness, decreased appetite, nausea, flu-like symptoms including myalgia, pyrexia, and headache, and administration site reactions, were notably less in the ropeginterferon alfa-2b group. The cumulative incidence of adverse events of special interest was also notably higher in the control group. The primary endpoint was met and ropeginterferon alfa-2b showed a better SVR12 rate of 79.8% than 71.9% of the control group.
Conclusion: Ropeginterferon alfa-2b is efficacious and has a favorable safety profile as compared with the conventional pegylated interferon alfa-2b. This study together with previous Phase 2 data validated ropeginterferon alfa-2b to be a new treatment option for chronic hepatitis C genotype 2.

Taiwan from 2013 to 2020. Yi-Wen Huang worked for PharmaEssentia Corporation headquarter in Taipei, Taiwan from 2018 to 2021. Yi-Wen Huang moved to Taipei Medical University Hospital, Taipei, Taiwan. Other authors do not declare any conflicts of interest.

Author contribution: The study was designed by Pei-Jer Chen, Wan-Long Chuang, and PharmaEssentia clinical team. Chi-Yi Chen, Wen-Hua Zhang, Li-Ying Zhu, Guo-Qiang Zhang, Jyh-Jou Chen, Ching-Chu Lo, Xinmin Zhou, Xiaorong Mao, Jia Shang, Hsing-Tao Kuo, Wen Xie, Chien-Hung Chen, Gin-Ho Lo, Dae Won Jun, Shuangsuo Dang, Wan-Long Chuang, and Pei-Jer Chen recruited patients and collected the data. Ting-Fang Wang, Hsin-Hui Lai, Yi-Wen Huang, Albert Qin, Kuan-Chiao Tseng, and Pei-Jer Chen analyzed the data. All authors interpreted the data and were involved in the development, review, and approval of the manuscript. Albert Qin, Yi-Wen Huang, Chan-Yen Tsai, and Pei-Jer Chen wrote the manuscript. The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

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Introduction

Ropeginterferon alfa-2b is a novel, site-selective mono-pegylated proline-interferon alfa-2b. It has improved pharmacokinetic (PK) properties, making it extra-long-acting as compared with the conventional pegylated interferons (IFNs) and allowing it to be dosed clinically once every 2–4 weeks.[1–6] It is a single chemically predominant homogenous isomer, as compared with the conventional pegylated IFNs, which contain multiple isomers that may affect their PK parameters and can contribute to the development of adverse effects.[7,8] Ropeginterferon alfa-2b was recently approved for the treatment of polycythemia vera (PV) in Europe, Taiwan, Switzerland, Israel, and the United States,[6,9] becoming the first-ever approved IFN-based therapy for the PV treatment for an indefinite period of time.

Chronic viral hepatitis has been a major application of interferon alfa. We previously evaluated ropeginterferon alfa-2b for the treatment of chronic hepatitis B (CHB) and chronic hepatitis C (CHC) in Phase 2 clinical trials, in which safety and preliminary efficacy against CHB and CHC genotypes 1 or 2 were observed.[1,3,10] To further comprehensively validate the potency and safety of ropeginterferon alfa-2b in a chronic viral hepatitis setting, we conducted a Phase 3 regional clinical study in Asian patients with CHC genotype 2 because its prevalence is high in Asia.

CHC affects an estimated 71 million people worldwide and the infection causes inflammation of the liver, leading to liver fibrosis and cirrhosis, and complications including hepatocellular carcinoma (HCC).[11] There are seven major genotypes of hepatitis C virus (HCV) including genotypes 1–7.[12] In Asia, the prevalence of genotype 2 can be as high as 60% in certain areas. Direct-acting antiviral (DAA) therapy is highly effective for HCV treatment, leading to impressive sustained virologic responses (SVRs) in all HCV genotypes.[12] For DAAs, viral drug resistance can be a factor in reducing their antiviral efficacy.[13] In addition, HCC could still recur in some patients who achieved the SVR.[14–16]

Pegylated IFN-alfa therapy has been shown to cause clinically appreciable SVR, for example, 70–90% SVR rate in patients with CHC genotype 2 infection,[17,18] and alleviate fibrosis and reduce the risk of HCC development.[19] Two pegylated interferon products, peginterferon alfa-2a and peginterferon alfa-2b, have been used for CHC treatment. However, their frequent weekly dosing schedule and notable side effects such as flu-like symptoms, injection site reactions, and depression limited their use.[17,18]

In this report, we show our Phase 3 results of the extra-long-acting ropeginterferon alfa-2b compared with the previously approved, conventional pegylated IFN alfa-2b in patients with CHC genotype 2. We validated ropeginterferon alfa-2b as a novel, safe, and effective IFN therapy in a Phase 3 clinical hepatitis C genotype 2 setting.

Methods

Study design. This was a Phase 3 multicenter, open-label, randomized study conducted at 39 study centers in Taiwan, Korea, and China mainland (Table S8, Supporting information). This study assessed the efficacy and safety of ropeginterferon

alfa-2b subcutaneously (SC) administered at a dose of 400 μg once every 2 weeks (biweekly) plus oral ribavirin daily for the treatment of CHC genotype 2. Eligible patients were stratified by IL28B single-nucleotide polymorphism (SNP)[20] and baseline serum HCV RNA[21] and were randomized (1.4:1) to receive either ropeginterferon alfa-2b SC biweekly plus ribavirin daily or the previously approved, conventional pegylated IFN alfa-2b control (PEG-Intron®, Merck) weekly at 1.5 μg/kg plus ribavirin daily for a duration of 24 weeks. The ribavirin daily dose was determined by weight.[17] All patients were followed up for 24 weeks after treatment. Details of the randomization, stratification, and the ribavirin daily dose are provided in the Supplemental Materials. The study was conducted in accordance with the Helsinki Declaration 2008. Study protocol and informed consent (ICF) were approved by the Institutional Review Board of participating hospitals. ICF was obtained from all patients before participation. This study was registered in ClinicalTrials.gov (NCT04382937).

Patients. Adult patients with CHC genotype 2 and compensated liver disease were enrolled. Patients with HBV or HIV positivity and severe neurological, cardiovascular, or pulmonary conditions were excluded. The main inclusion/exclusion criteria are provided in Supplemental Materials.

Outcomes. The primary endpoint was to compare the percentage of patients with SVR12 (undetectable serum HCV RNA at FW12) between the treatment groups and to assess the non-inferiority of the ropeginterferon alfa-2b group to the control with a predefined non-inferiority margin (NIM) of 15%.[17]

Main secondary endpoints included the measurement of HCV RNA levels, the percentage of patients with undetectable serum HCV RNA, and percentage of patients with relapse defined as HCV RNA detectable at the end of follow-up but undetectable when treatment is discontinued.

Safety assessment included treatment emergent adverse events (TEAEs) and TEAE of special interest, which were defined as the known side effects that may be caused by IFN-based therapy, for example, flu-like symptoms, depression, anxiety, thyroid gland disorder, and administration site reactions. See Supplemental Materials for the details of safety assessment.

Statistics. All statistical analyses were performed using SAS version 9.4.

Continuous variables were summarized using descriptive statistics and were presented as number of patients, mean, standard deviation (SD), median, minimum, maximum, and 95% confidence interval (CI). Multi-way analysis of variance with adjustment for stratification factors was used to compare groups.

Table 1 Demographic data and baseline characteristics (ITT population)

	Peginterferon alfa-2b + RBV (control group) $n = 90$	Ropeginterferon alfa-2b + RBV (study group) $n = 125$	Total $n = 215$
Age, years			
Median	54.8	55.6	55.3
Range (min–max)	21.8–79.7	20.9–78.1	20.9–79.7
Male, *n* (%)	33 (36.7)	47 (37.6)	80 (37.2)
Race, *n* (%)			
Asian	90 (100)	125 (100)	215 (100)
Country/area, *n* (%)			
Taiwan	53 (58.9)	50 (40.0)	103 (47.9)
China	30 (33.3)	61 (48.8)	91 (42.3)
Korea	7 (7.8)	14 (11.2)	21 (9.8)
HCV RNA (IU/mL), *n* (%)			
Median	1 093 514.5	1 711 415.0	1 532 353.0
Range (min–max)	1220–13 781 965	454–11 909 719	454–13 781 965
HCV RNA category			
<800 000 IU/mL	35 (38.9)	50 (40.0)	85 (39.5)
≥800 000 IU/mL	55 (61.1)	75 (60.0)	130 (60.5)
ALT level (U/L)			
Median	38.5	40.0	39.0
Range (min–max)	3.6–251.0	10.4–353.0	3.6–353.0
ALT × ULN, *n* (%)			
≤1.5 × ULN	63 (70.0)	89 (71.2)	152 (70.7)
>1.5 × ULN	27 (30.0)	36 (28.8)	63 (29.3)
IL-28B SNP, *n* (%)			
CC	77 (85.6)	105 (84.0)	182 (84.7)
Non-CC	13 (14.4)	20 (16.0)	33 (15.3)

% = percentage of patients with *n* as the denominator.

ALT, alanine aminotransferase; HCV, hepatitis C virus; IL28B, interleukin 28B; ITT, intention-to-treat; IU/mL, International unit/milliliter; Max, maximal; Min, minimal; RBV, ribavirin; RNA, ribonucleic acid; SNP, single-nucleotide polymorphism; U/L, unit/liter; ULN, upper limit of normal.

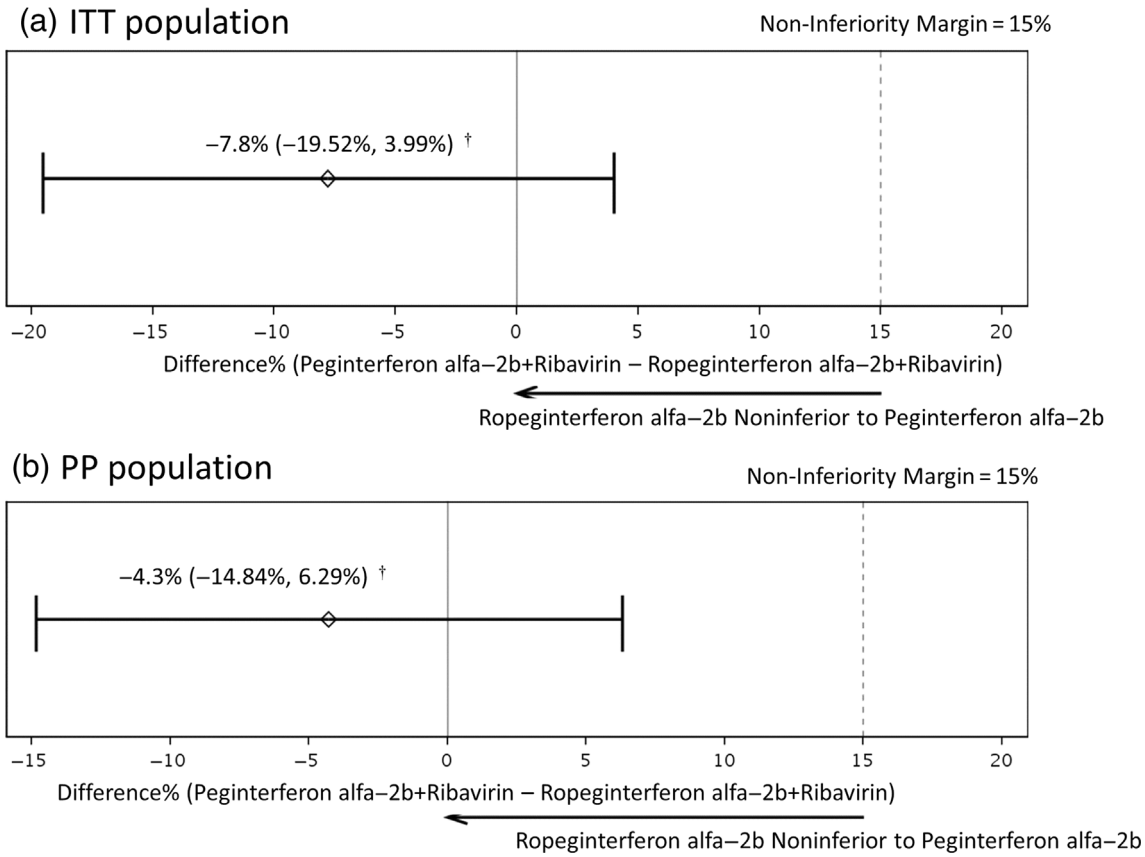

Figure 1 Non-inferiority plot comparing the SVR12 of the peginterferon alfa-2b control group *versus* the ropeginterferon alfa-2b study group. (a) ITT population; (b) PP population (*treatment difference, % [95% CI]). CI, confidence interval; ITT, intent-to-treat; PP, per protocol; SVR, sustained virologic response.

Table 2 Patients with undetectable serum HCV RNA overtime

	ITT population		PP population	
	Peginterferon alfa-2b + RBV (control group) $n = 90$	Ropeginterferon alfa-2b + RBV (study group) $n = 125$	Peginterferon alfa-2b + RBV (control group) $n = 78$	Ropeginterferon alfa-2b + RBV (Study group) $n = 113$
Undetectable serum HCV RNA, *n* (%)				
TW4	47 (52.2)	87 (69.6)	46 (59.0)	80 (70.8)
TW8	71 (78.9)	116 (92.8)	70 (89.7)	110 (97.3)
TW12	75 (83.3)	116 (92.8)	74 (94.9)	110 (97.3)
TW24	72 (80.0)	109 (87.2)	72 (92.3)	107 (94.7)
FW12	64 (71.1)	97 (77.6)	64 (82.1)	96 (85.0)
FW24	60 (66.7)	101 (80.8)	60 (76.9)	99 (87.6)

% = percentage of patients with N as the denominator. Missing data were not imputed.
FW, follow-up week; HCV, hepatitis C virus; ITT, intention-to-treat; PP, per protocol; RBV, ribavirin; RNA, ribonucleic acid; TW, treatment week.

Categorical data were summarized with descriptive statistics and were presented as number of patients, frequency, percentage, and 95% CI and analyzed with Chi-square, or Cochran–Mantel–Haenszel (CMH) test, adjusting for stratification factors, if appropriate.

P-values <0.05 were considered statistically significant. All statistical tests were two-sided where applicable.

In the primary efficacy analysis, SVR12 was compared with a predefined NIM of 15%. The non-inferiority was met if the upper bound of the one-sided 97.5% CI of the difference (i.e., percent of patients with SVR12 of the control group minus that of the ropeginterferon alfa-2b group) was less than the NIM.

For the impact of COVID-19, the SVR12 missing data were imputed (see Supplemental Materials).

Basic characteristics and the achievement of rapid virological response (RVR, undetectable HCV RNA at TW4) or early virological response (cEVR, undetectable HCV RNA at TW12) were analyzed for the effect on SVR12 using univariate and multivariate logistic regression analyses (see Supplemental Materials).

The efficacy analysis was conducted on the ITT and PP populations. ITT included all patients who were randomized and PP included those who received at least 80% compliance with study treatment, had no major protocol deviations, and had the primary endpoint assessment. The safety population included all patients who received at least one dose of the study drug.

Results

Baseline characteristics. This study was conducted from January 2016 to July 2020. Patients were randomized to receive ribavirin daily plus either ropeginterferon alfa-2b biweekly or the conventional pegylated IFN alfa-2b control weekly for a duration of 24 weeks (Figure S1). Overall, 215 patients were included in the ITT population, including 125 in the ropeginterferon alfa-2b group and 90 in the control group. The PP population included 113 patients in the ropeginterferon alfa-2b group and 78 in the control group.

Median age was 55.3 years old (Table 1). Sex distribution was 80 (37.2%) male and 135 (62.8%) female. For baseline characteristics, most patients had HCV RNA ≥800 000 IU/mL (60.5%), alanine aminotransferase (ALT) ≤1.5 × ULN (70.7%), and CC allele (84.7%). Generally, the two treatment groups had comparable baseline characteristics (Table 1).

Efficacy. In the ITT population, the ropeginterferon alfa-2b treatment group had a notably higher percentage of patients who achieved SVR12 compared with the control group: 79.8% *versus* 71.9% (Fig. 1a and Table S1). The strata-adjusted treatment difference was −7.8% (2-sided 95% CI: −19.52%, 3.99%). The primary endpoint of non-inferiority of ropeginterferon alfa-2b was met both in the ITT and PP populations, because the upper bound of the one-sided 97.5% CI of the treatment difference was less than the NIM of 15% (Fig. 1 and Table S1). Furthermore, the ropeginterferon alfa-2b group had a statistically significant higher percentage of patients who achieved SVR24 when compared with the control group: 81.5% *versus* 67.4% ($P = 0.021$, Table S2).

Missing data were imputed in the SVR12 analysis for the primary endpoint. When using non-imputed data, the ropeginterferon alfa-2b group consistently showed a better virological response than the control group at all the study visits (Table 2).

The mean HCV RNA levels decreased dramatically from baseline to Treatment Week (TW) 8 after study treatment and remained low until a slight increase at follow-up week (FW) 12 and FW24 for both treatment groups (Fig. 2). The mean HCV RNA levels were significantly lower in the ropeginterferon alfa-2b group at TW4 (0.58 $\log_{10}$ IU/mL *vs* 0.95 $\log_{10}$ IU/mL, $P = 0.009$) and TW8 (0.08 $\log_{10}$ IU/mL *vs* 0.27 $\log_{10}$ IU/mL, $P = 0.005$). There was no statistically significant difference between the mean HCV RNA levels between the treatment groups at other time points ($P \geq 0.05$), although the virus RNA levels were higher in the control group than the ropeginterferon alfa-2b group at FW12 (1.09 $\log_{10}$ IU/mL *vs* 0.69 $\log_{10}$ IU/mL) and FW24 (1.03 $\log_{10}$ IU/mL *vs* 0.61 $\log_{10}$ IU/mL). In addition, higher number of patients experienced relapse in the control group (18.9%) as compared with the ropeginterferon alfa-2b group (12.8%; Table S3). For the SVR-related factors, both the univariate and multiple logistic regression analyses showed that

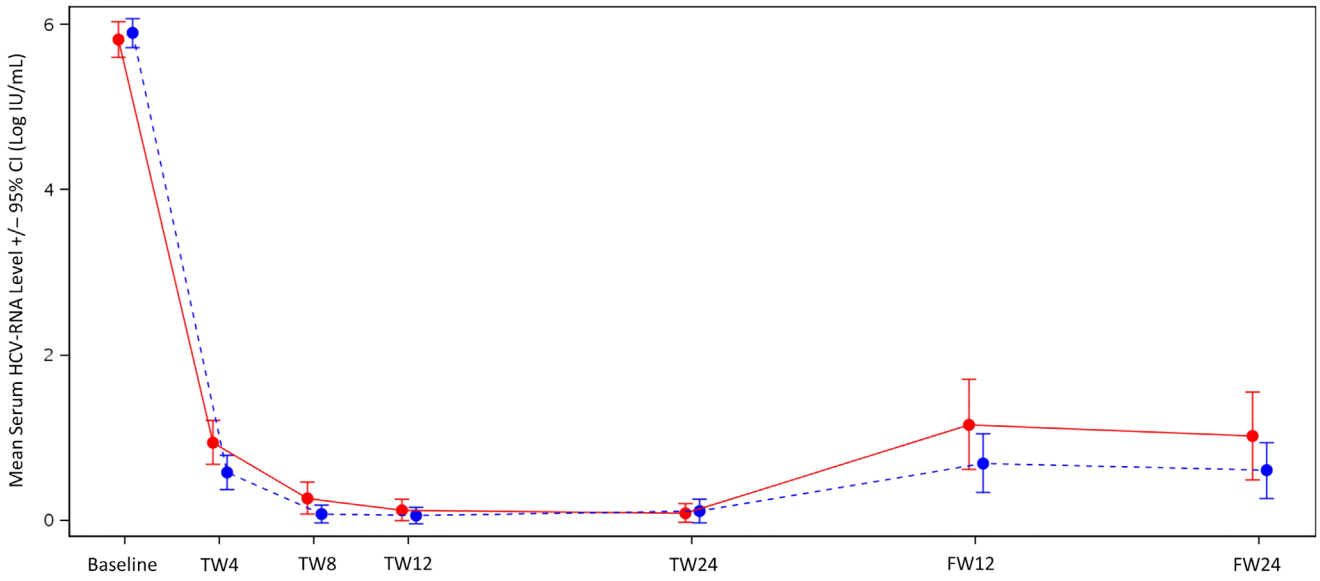

Figure 2 Mean serum log HCV RNA level over time (ITT population). CI, confidence interval; FW, follow-up visit; HCV, hepatitis C virus; ITT, intent-to-treat; TW, treatment-week visit. Treatment group: ——, peginterferon alfa-2b + ribavirin; ------, ropeginterferon alfa-2b + ribavirin

Table 3 Overall summary of treatment emergent adverse events (safety population)

	Peginterferon alfa-2b + RBV (control group) $n = 95$	Ropeginterferon alfa-2b + RBV (study group) $n = 127$	Total $n = 222$
Any TEAE	94 (98.9)	127 (100)	221 (99.5)
Any study treatment related TEAE[†]	94 (98.9)	124 (97.6)	218 (98.2)
Any ropeginterferon alfa-2b/peginterferon alfa-2b related TEAE	92 (96.8)	119 (93.7)	211 (95.0)
Any ribavirin-related TEAE	87 (91.6)	110 (86.6)	197 (88.7)
Any TEAE by severity, *n* (%)			
Grade 1	93 (97.9)	126 (99.2)	219 (98.6)
Grade 2	66 (69.5)	102 (80.3)	168 (75.7)
Grade 3	19 (20.0)	27 (21.3)	46 (20.7)
Grade 4	1 (1.1)	2 (1.6)	3 (1.4)
Grade 5	0	2 (1.6)	2 (0.9)
Any TEAE with severity grade ≥3	20 (21.1)	28 (22.0)	48 (21.6)
Any serious TEAE, n (%)	5 (5.3)	7 (5.5)	12 (5.4)
Any study treatment related serious TEAE, *n* (%)	3 (3.2)	1 (0.8)	4 (1.8)
Any ropeginterferon alfa-2b/peginterferon alfa-2b related serious TEAE	3 (3.2)	1 (0.8)	4 (1.8)
Any ribavirin-related serious TEAE	0 (0)	1 (0.8)	1 (0.5)
Any TEAE leading to ropeginterferon alfa-2b/ peginterferon alfa-2b dose discontinuations	4 (4.2)	8 (6.3)	12 (5.4)
Any TEAE ≥10%			
White blood cell count decreased	45 (47.4)	68 (53.5)	113 (50.9)
Anemia	44 (46.3)	64 (50.4)	108 (48.6)
Neutropenia	36 (37.9)	37 (29.1)	73 (32.9)
Leukopenia	24 (25.3)	34 (26.8)	58 (26.1)
Pyrexia	24 (25.3)	19 (15.0)	43 (19.4)
Pruritus	19 (20.0)	24 (18.9)	43 (19.4)
Headache	22 (23.2)	20 (15.7)	42 (18.9)
Platelet count decreased	15 (15.8)	24 (18.9)	39 (17.6)
Cough	16 (16.8)	18 (14.2)	34 (15.3)
Urinary tract infection	15 (15.8)	17 (13.4)	32 (14.4)
Weight decreased	13 (13.7)	19 (15.0)	32 (14.4)
Insomnia	14 (14.7)	16 (12.6)	30 (13.5)
Alopecia	18 (18.9)	12 (9.4)	30 (13.5)
Rash	13 (13.7)	13 (10.2)	26 (11.7)
Decreased appetite	20 (21.1)	6 (4.7)	26 (11.7)
Dizziness	16 (16.8)	9 (7.1)	25 (11.3)
Nausea	15 (15.8)	10 (7.9)	25 (11.3)
Thrombocytopenia	9 (9.5)	15 (11.8)	24 (10.8)
Asthenia	14 (14.7)	10 (7.9)	24 (10.8)

[†]Any ropeginterferon alfa-2b/peginterferon alfa-2b related or ribavirin-related TEAE was characterized as study treatment related TEAE.
% = percentage of patients with *n* as the denominator.
RBV, ribavirin; TEAE, treatment emergent adverse event.

age (continuous variable), RVR, and cEVR were associated with the SVR12 rate ($P < 0.05$, Table S4).

Safety. Most TEAEs were mild or moderate in severity (Table 3). Seven (5.5%) patients in the ropeginterferon alfa-2b group and five (5.3%) in the control group reported serious adverse events (SAEs). One (0.8%) patient in ropeginterferon alfa-2b group and three (3.2%) in control group experienced treatment-related serious TEAEs (Table S5). In addition, there were two treatment unrelated deaths in the study (Table S6). No suspected unexpected serious adverse reaction was reported in the study.

For study discontinuations, the ropeginterferon alfa-2b group had less discontinuations than the control (7.9% *vs* 14.7%, Figure S1). The common TEAEs included WBC count decrease and anemia. Overall, the ropeginterferon alfa-2b group showed notably less neutropenia, pyrexia, asthenia, fatigue, alopecia, headache, dizziness, decreased appetite, nausea, myalgia, flu-like symptoms, and administration site reactions (Table 3). Other common TEAEs were generally comparable between the two treatment groups.

Prior IFN-based therapies have known side effects including flu-like symptoms, depression, anxiety, and administration site reactions,[17,18] and they were evaluated as TEAEs of special interest in this study. Of these TEAEs, the incidences of administration

site reactions (1.6% in the study group *vs* 7.4% in the control group), depressions (3.1% in the study group *vs* 5.3% in the control group), and flu-like symptoms (37.8% in the study group *vs* 54.7% in the control group) were notably lower in the ropeginterferon alfa-2b group than the control group (Fig. 3a). During the study, the control group had 68.4% of the patients experiencing TEAEs of special interest while the ropeginterferon alfa-2b group had 47.2%. Throughout the study, the cumulative incidence of TEAEs of special interest was notably higher in the control group compared with the ropeginterferon alfa-2b group (Fig. 3b).

In both groups, most hematologic parameters declined during the treatment period and returned to the respective baseline level during the follow-up period. Most biochemistry values and urinalysis were normal or abnormal without clinical significance throughout the study. The levels of ALT and aspartate aminotransferase (AST) in most patients declined from higher levels at baseline to the normal range during the treatment and follow-up period in both groups. Most patients had normal or no clinically significant (NCS) abnormal antinuclear–antibodies test, vital signs, pulse oximetry, electrocardiogram, chest X-ray, and physical examinations throughout the study.

Immunogenicity. Overall, the antidrug antibody (ADA) was not detected in most patients (Table S7). Two (2.0%) and four (3.5%) patients in the ropeginterferon alfa-2b group had positive ropeginterferon alfa-2b ADA at FW12 and FW24, respectively. Six (8.5%) and three (4.1%) patients in the control group had positive peginterferon alfa-2b ADA at FW12 and FW24, respectively. Lower percentage of patients in the ropeginterferon alfa-2b group had positive PEG ADA compared with the control group at FW12 (7.0% *vs* 14.1%) and FW24 (6.2% *vs* 11.0%). Of the patients with the positive ADA, all were negative for the neutralizing antibody except one in the ropeginterferon alfa-2b group and two in the control group.

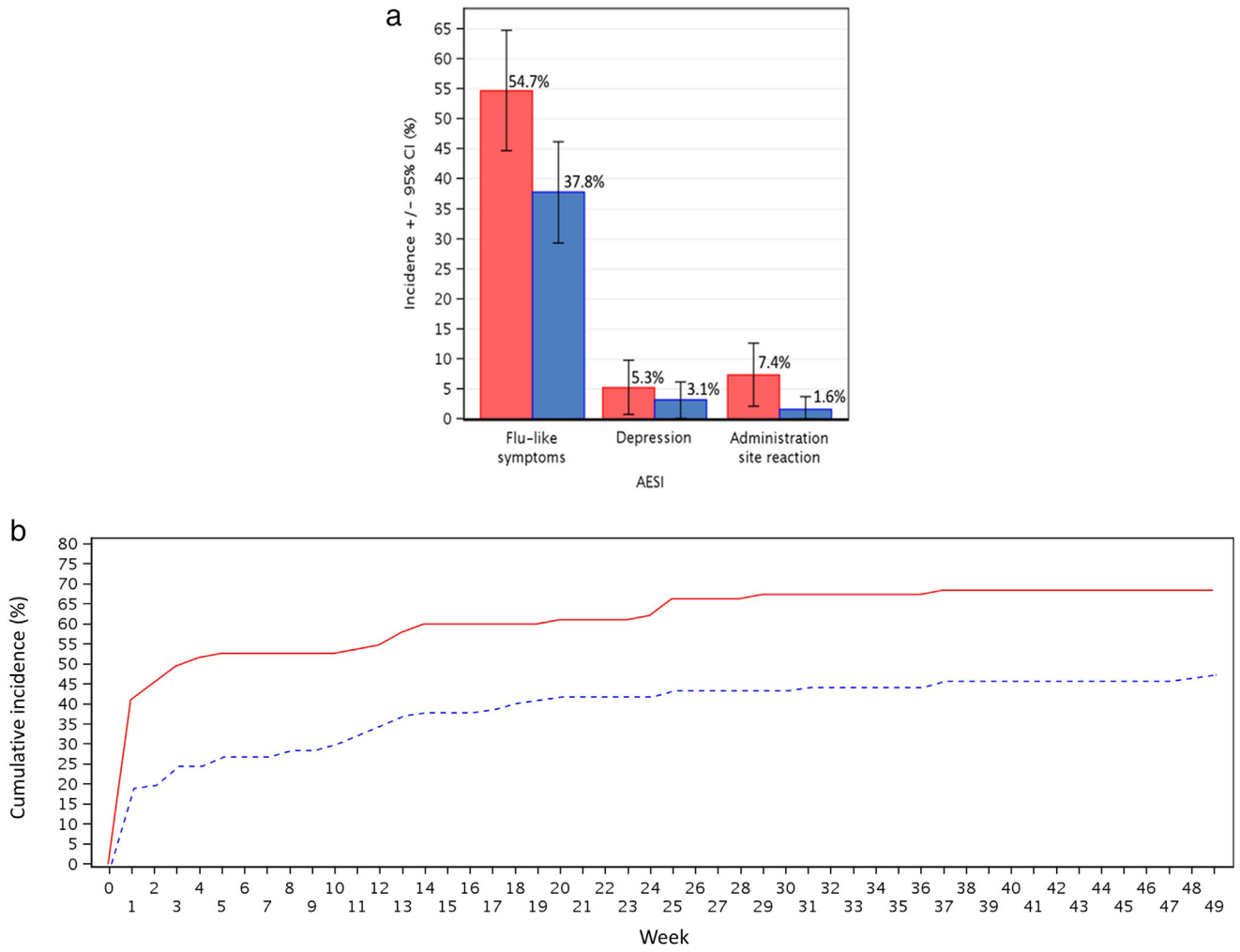

Figure 3 Incidence of TEAEs of special interest (safety population) (a) incidence of TEAEs of special interest by event and treatment group. ■, peginterferon alfa-2b + ribavirin; ■, ropeginterferon alfa-2b + ribavirin. (b) Cumulative incidence of TEAEs of special interest by treatment group. ——, peginterferon alfa-2b + ribavirin; -----, ropeginterferon alfa-2b + ribavirin. AESI, adverse event of special interest; CI, confidence interval; TEAEs, treatment emergent adverse events.

Discussion

Ropeginterferon alfa-2b is a novel, extra-long-acting, site-selective mono-pegylated interferon alfa-2b. It exists as a predominantly single, homogenous isoform, differing from the conventional pegylated IFNs, which contain multiple isomers that can affect their PK properties and may contribute to the occurrence of side effects. Ropeginterferon alfa-2b has improved PK properties, making it extra-long-acting and rendering it to be dosed at a much less frequent schedule.[1–6] Ropeginterferon alfa-2b was recently approved for the treatment of PV, a myeloproliferative neoplasm.[6,9] It is the first approved IFN-based therapy for an MPN by the US FDA. In addition, it was used as an off-label treatment for other indications.[22–24]

The data from this Phase 3 study showed that in the clinical viral hepatitis C genotype 2 setting, ropeginterferon alfa-2b was efficacious, meeting the primary endpoint of non-inferiority to the weekly given, conventional pegylated IFN alfa-2b, previously approved for the CHC treatment. The ropeginterferon alfa-2b group also had numerically better virologic responses consistently in every time point of the measurements during the study. This study demonstrated the efficacy and safety of ropeginterferon alfa-2b in patients with CHC genotypes 2. Previously, conventional pegylated IFN-alfa products were approved for the treatment of CHC infections including genotypes 1 and 2, and CHB. They were also recommended for the CHD treatment by both European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD). In our previous Phase 1 and 2 clinical studies, ropeginterferon alfa-2b showed solid clinical activities or efficacy against CHC genotype 1 or 2, or CHB.[1,3,10] This study further validates the efficacy and safety of the ropeginterferon alfa-2b as a new IFN therapy for CHC genotype 2 in the Phase 3 setting and suggests that it may be effective on other chronic viral hepatitis.

To date, most pegylated protein therapeutics approved by FDA are products with nonspecific pegylated sites.[7,8] This often leads to a heterogeneous mixture of pegylated molecules with each conjugate having its own bioactivity, stability, and immunogenicity properties. For example, the conventional pegylated IFN alfa-2a has eight different pegylated isomers with different bioactivity, approximately three-fold range between the most and the least active isomers.[7] Similarly, the conventional pegylated IFN alfa-2b has a major positional isomer comprising 47% among the mixtures and having a higher bioactivity five times than the least active isomer.[8] Multiple isoforms of pegylated IFN-alfas may thereby impact the PK properties and their efficacies. Their frequent weekly dosing scheme and mixture of isomers with various activities and immunogenicity can further affect the safety profile. The dosing schedule and clinical side effects, notably, flu-like symptoms, administration site reactions, and depression, limited the clinical use of the conventional pegylated IFN alfa products. In this Phase 3 study, ropeginterferon alfa-2b treatment showed a favorable safety profile, having less neutropenia, asthenia, fatigue, alopecia, dizziness, decreased appetite, and nausea, compared with the conventional pegylated IFN control. The TEAEs of special interest to IFN therapy, mainly flu-like symptoms, administration site reactions, and depressions, were also less in the ropeginterferon alfa-2b group compared with the control. It is also worthwhile to note that in the Phase 3 studies in PV patients, the rate of depression from the long-term consecutive treatment with ropeginterferon alfa-2b up to 5 years was minimal and did not appear to be significantly different from that of the control drug hydroxyurea.[6] By contrast, depression was observed at a much higher rate with the weekly given, conventional pegylated IFN alfa products.[17,18] Furthermore, our previous data in the Phase 2 setting also indicated that anxiety and depression were significantly less in the ropeginterferon alfa-2b group than the control pegylated IFN alfa group.[1] Grade 2 or 3 depression was only noted in the control group, but not in the ropeginterferon alfa-2b group. These safety findings are consistent with the fact that ropeginterferon alfa-2b is a single homogenous isoform and has an infrequent doing scheme with improved PK properties.

IFN alfa is an anticancer agent and its therapies can reduce the risk of CHC or HBV-associated HCC development.[19,25] In the Phase 3 studies in patients with myeloproliferative neoplasm PV, there was no occurrence of secondary cancers during the ropeginterferon alfa-2b treatment, while five cases of cancer progression, including two secondary acute leukemia, were observed in the control group.[6,26] This is consistent with a notion that ropeginterferon alfa-2b as an IFN alfa-based therapy is potentially an effective antineoplastic or anticancer agent. Type 1 IFNs alfa and beta bind the same receptor termed IFNAR to elicit their biological activities.[27] They selectively induce cell growth-inhibitory effects such as cell cycle inhibitions in transformed or cancer cells, but not in normal cells.[28] Low-copy gene delivery via a lentivirus vector or the extrachromosomal gene expression of IFN beta by an adenoviral vector led to very efficient suppression of tumor formation in vivo.[29,30] Therefore, ropeginterferon alfa-2b therapy may be helpful in inhibiting cancer development possibly by both inducing the SVR and exerting its direct anticancer activities during the chronic viral hepatitis treatment. In this respect, it would be interesting to examine whether ropeginterferon alfa-2b could have anticancer effect on HCC cells or in patients with HCC in the future.

DAAs are currently the first-line therapy for CHC patients. However, viral drug resistance and HCC development occur in a small population of patients after the treatment of DAA.[13–16] Their availability, especially in resource-limited areas, also limits their use for fighting against CHC. Ropeginterferon alfa-2b can potentially be a new option in HCV patients who have treatment failures to DAAs or for whom DAAs are not available. It can also potentially be used in combination therapies with DAAs, potentially generating a complementary effect in curing CHC and preventing HCC occurrence.

Ropeginterferon alfa-2b could also be useful in combination therapies for CHB or CHD. Pegylated IFN therapy can lead to high rates of HbeAg and HbsAg seroconversion, which may be due to its ability to enhance the covalently closed circular DNA (cccDNA) degradation and have epigenetic modifications of the cccDNA transcription.[31] Nucleoside analogue (NA) therapy, especially the long-term NA treatment, is also effective in depleting the cccDNA.[32] However, the antiviral efficacies need to significantly improve for clearing HbsAg and achieving the goal of functional or complete cure of CHB. There is a potential for a combination therapy approach with NAs and a novel and effective pegylated IFN alfa such as ropeginterferon alfa-2b in curing CHB. Indeed, our previous Phase 2 trial in patients with CHB showed that ropeginterferon alfa-2b administered biweekly achieved a notably higher HbeAg seroconversion rate than the weekly given, conventional pegylated IFN alfa

control and exhibited a favorable safety profile.[10] Therefore, we anticipate that ropeginterferon alfa-2b can potentially serve as a treatment option or component in the emerging anti-HBV or anti-HDV combination treatment regimens.

In summary, our study further validates the potency and safety of ropeginterferon alfa-2b as a novel and effective IFN alfa-based, anti-viral hepatitis therapy with a favorable safety profile in a Phase 3 hepatitis C genotype 2 setting. Ropeginterferon alfa-2b showed a favorable safety profile with lower accumulative rates of TEAEs of special interest and notably lesser side effects including neutropenia, asthenia, fatigue, alopecia, dizziness, decreased appetite, nausea, flu-like symptoms, administration site reaction, and depression compared with the weekly given, conventional pegylated IFN alfa-2b control. With its efficacy, favorable dosing scheme, and safety profile, and potential as an anti-neoplastic agent, ropeginterferon alfa-2b could potentially provide a new treatment option for patients with chronic viral hepatitis.

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Data availability statement. Data sharing for the study is being managed by PharmaEssentia Corporation. The clinical study report synopsis and deidentified patient-level data from clinical trial analysis datasets can be made available 6 months after approval of the study drug by the Taiwan Food and Drug Administration and China's National Medical Products Administration (NMPA) and for as long as the drug is on the market. Research proposals should be submitted to PharmaEssentia Corporation at info@pharmaessentia.com. Access to these data will be provided in a secured analysis environment to qualified external researchers who have been approved by PharmaEssentia Corporation, depending on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. To gain access, approved requestors will need to sign a data sharing agreement.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Appendix S1. Supporting Information.