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ORIGINAL ARTICLE

Ropeginterferon alfa-2b in patients with genotype 1 chronic hepatitis C: Pharmacokinetics, safety, and preliminary efficacy

Hsien-Hong Lin,* Shih-Jer Hsu,[†,‡] Sheng-Nan Lu,[§] Wan-Long Chuang,[¶] Chao-Wei Hsu,[‖] Rong-Nan Chien,[‖] Sien-Sing Yang,** Wei-Wen Su,[††] Jaw-Ching Wu,[‡‡] Tzong-Hsi Lee,[§§] Cheng-Yuan Peng,[¶¶] Kuan-Chiao Tseng,[‖‖] Albert Qin,[‖‖] Yi-Wen Huang[***,*§,*¶] and Pei-Jer Chen*[‖,***]

*Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taipei Tzu Chi Hospital, **Liver Center, Department of Internal Medicine, Cathay General Hospital Medical Center, [‡‡]Medical Research Department, Taipei Veterans General Hospital, [‖‖]Department of Medical Research, PharmaEssentia Corp, [***]Division of Gastroenterology and Hepatology, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, *[§]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taipei Medical University Hospital, *[¶]Department of Internal Medicine, School of Medicine, *[‖]Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, ***Hepatitis Research Center, National Taiwan University Hospital, Taipei, [†]Department of Internal Medicine, National Taiwan University Hospital Yunlin Branch, Douliu and Huwei, [‡]Hepatology Medical Center, Department of Internal Medicine, National Taiwan University Hospital Yunlin Branch, Douliu, [§]Division of Hepatogastroenterology, Department of Internal Medicine, Chia-Yi Chang Gung Memorial Hospital, Puzi, [¶]Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, [‖]Division of Hepatology, Department of Gastroenterology and Hepatology, Linkou Medical Center, Chang Gung Memorial Hospital, Taoyuan, [††]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Changhua Christian Hospital, Changhua, [§§]Division Gastroenterology, Department of Internal Medicine, Far-Eastern Memorial Hospital, New Taipei City and [¶¶]Center for Digestive Medicine, Department of Internal Medicine, China Medical University Hospital, and School of Medicine, China Medical University, Taichung, Taiwan

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Correspondence
*Pei-Jer Chen, Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, No. 7, Chung-Shan South Rd., Taipei, Taiwan.
Email: peijerchen@ntu.edu.tw
Yi-Wen Huang, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taipei Medical University Hospital and School of Medicine, College of Medicine, Taipei Medical University, No. 252, Wuxing St, Xinyi District, Taipei, 110, Taiwan.
Email: yiwenhuang@tmu.edu.tw

Declaration of conflict of interest: Pei-Jer Chen has served as a speaker, a consultant, and an advisory board member for Pharmaessentia; Yi-Wen Huang was the Senior Director of Medical Research and Head of Pharmacovigilance at Pharmaessentia Corporation; all other authors declare no competing interests.

ABSTRACT

Background and Aim: Ropeginterferon alfa-2b (P1101) is a novel long-acting mono-PEGylated recombinant proline interferon (IFN) conjugated to a 40 kDa branched polyethylene glycol (PEG) chain at its N-terminus, allowing every-two-week injection. It received European Medicines Agency and Taiwan marketing authorization for the treatment of polycythemia vera in 2019 and 2020, respectively. This phase 2 study aimed to evaluate the pharmacokinetics, safety, and preliminary efficacy of ropeginterferon alfa-2b as compared with PEG-IFN-α2a in patients with chronic hepatitis C virus genotype 1 infection.

Methods: One hundred six treatment naive patients were enrolled in this phase 2 study and randomized to four treatment groups: subcutaneous weekly PEG-IFN-α2a 180 μg (group 1), weekly ropeginterferon alfa-2b 180 μg (group 2), weekly ropeginterferon alfa-2b 270 μg (group 3), or biweekly ropeginterferon alfa-2b 450 μg (group 4) plus ribavirin for 48 weeks.

Results: After multiple weekly administration, serum exposure ($AUC_{0-\tau}$) in ropeginterferon alfa-2b 180 μg was approximately 41% greater and the accumulation ratio of 2-fold greater than PEG-IFN-α2a 180 μg. The incidences of flu-like symptoms were 66.7% (18/27), 53.3% (16/30), 55.0% (11/20), and 48.3% (14/29), anxiety were 14.8% (4/27), 6.7% (2/30), 0%, and 0%, and depression were 25.9% (7/27), 13.3% (4/30), 0%, and 3.4% (1/29), for groups 1–4, respectively. Two grade 2 of 3 depression were noted in PEG-IFN-α2a arm, but none in ropeginterferon arms. The SVR24 rates were 77.8% (21/27), 66.7% (20/30), 80% (16/20), and 69% (20/29), respectively.

Conclusions: Ropeginterferon alfa-2b showed longer effective half-life and superior safety profile than PEG-IFN-α2a. Biweekly injection of ropeginterferon alfa-2b will be studied in larger viral hepatitis patient population.

Introduction

Ropeginterferon alfa-2b (P1101) is a novel mono-pegylated recombinant proline-interferon (pro-IFN) alfa-2b with a 40 kDa branched polyethylene glycol (PEG) chain conjugated predominantly at its N-terminus. Conjugation of PEG aldehyde with proline forms a tertiary amine linkage between PEG and pro-IFN

alfa-2b after reductive amination, which is expected to be chemically more stable than the linkage of pegylated interferon (PEG-IFN) alfa-2b (PegIntron) and PEG-IFN alfa-2a (Pegasys). Furthermore, ropeginterferon alfa-2b has unique structural characteristics of only one major form as opposed to the 8–14 isomers of the other PEG-IFNs (Pegasys, PegIntron). The unique characteristics have been filed in United States (Patent No. 8143214. 2012-03-27) with counterpart in Taiwan (Patent No. I381851. 2013-01-11), Japan (Patent No. 5613050. 2014-09-12), Korea (Patent No. 10/15888465. 2016-01-19), Australia (Patent No. 2008286742. 2014-09-11), and Canada (Patent No. 2696478. 2018-10-09). It received European Medicines Agency marketing authorization for the treatment of polycythemia vera (PV) in 2019. Approval for the same indication was obtained in Taiwan, Switzerland, and Liechtenstein in 2020 and Israel in 2021.

In phase 1 study, the geometric mean values of ropeginterferon alfa-2b for C_{max}, area under the curve (AUC), and $AUC_{0\text{-}t}$ showed an increase of 76%, 66%, and 82%, respectively compared with PEG-IFN alfa-2a at the 180 μg dose level (unpublished data). The superior pharmacokinetics (PK) profile and longer half-life of ropeginterferon alfa-2b allow less frequent injections of once every 2 weeks. Moreover, ropeginterferon alfa-2b dose up to 450 μg was safe and well-tolerated in patients with genotype 2 chronic hepatitis C (CHC), PV, and chronic hepatitis B (CHB).[1–3]

The World Health Organization (WHO) estimated that 71 million were infected by hepatitis C virus (HCV) and CHC are one of the common causes of liver cirrhosis, cancer, and viral hepatitis-related deaths. Globally, HCV infection remains a public health problem and WHO set a goal to eliminate viral hepatitis by 2030.[4,5] Based on the nucleotide variability of HCV sequences, seven genotypes (genotype 1–7) have been identified throughout the world.[6,7] In Taiwan, genotype 1 accounted for the largest proportion of HCV (45–70%), with genotype 1b being predominant, followed by 2a and 2b.[8–11] In addition to genotype 1 and 2, genotype 6 has also been reported in Taiwan.[12] HCV genotype is one of the predictors for response to treatment.[13–15] Before the launch of direct acting antiviral (DAA), IFN has been the standard treatment for CHC for decades. This study aims to study the PK, safety, and preliminary efficacy of ropeginterferon alfa-2b plus ribavirin in treatment-naïve patient with chronic genotype 1 HCV infection.

Methods

Ethics statement. The study was in accordance with the ethical standards of the Helsinki Declaration (1964, amended most recently in 2008) of the World Medical Association and approved by Institutional Review Board (IRB) of the participating study sites. This study was registered in ClinicalTrials.gov (https://clinicaltrials.gov/; No.: NCT01587586) and Taiwan CDE (http://www1.cde.org.tw/ct_taiwan/; No.: 1005016854) in 2011 before the launching of DAA therapy in Taiwan. The study conduct complied with the guidelines of the International Conference on Harmonization (ICH) and the Good Clinical Practice (GCP). Informed consent was obtained from each participant.

Patients. The patients were non-cirrhotic adults, 18–70 years, with chronic HCV genotype 1 infection and treatment-naïve. The eligible patients had compensated liver disease with baseline alanine aminotransferase (ALT) ≦5 times upper limit of normal (ULN) at screening.

Patients with any of the following condition at screening were not eligible: alcohol or substance abuse; pregnancy; co-infected with hepatitis B virus or human immunodeficiency virus; significant retinopathy; history or presence of major psychiatric, neurological, cardiovascular, pulmonary, hematological, immunological, endocrine disorders; cancers or any other clinical conditions that might interfere the study participation. Laboratory abnormality exclusion criteria included estimated glomerular filtration rate (eGFR) ≦60 mL/min, hemoglobin <13 g/dL in men or <12 g/dL in women, white blood cell (WBC) count <3500/mm^3, neutrophil count <1500/mm^3, platelet count <90 000/mm^3, bilirubin level ≥2 mg/dL or international normalized ratio (INR) ≥1.3.

Study design. This was a phase 2, multicenter, open label, randomized, active control study, conducted in 14 sites in Taiwan between 2011 and 2016. The study consisted of 2-stage patient enrollment (Fig. S1, Supporting information). At Stage I, eligible patients were stratified by HCV RNA (<800 000 IU/mL or ≥800 000 IU/mL) and IL-28B SNP rs12979860 (CC or non-CC [CT or TT] genotype), and randomized at 1:1 ratio to group 1 (PEG-IFN-α2a 180 μg QW) or group 2 (ropeginterferon alfa-2b 180 μg QW). Stage I was completed when at least 20 patients were enrolled in group 1 and 2. If no major safety concern (defined as >4 patients with dose reduction or >2 patients with discontinuation due to adverse event [AE] related to ropeginterferon alfa-2b) in group 2, then Stage II would be started. Ten patients were enrolled to group 3 (ropeginterferon alfa-2b 270 μg QW) without stratification and randomization. Safety data of these 10 patients at treatment week (TW) 5 were reviewed before further enrollment. When no major safety concern was noted in group 3, the enrollment was continued with stratification by HCV RNA and IL-28B and randomized into group 3 and group 4 (ropeginterferon alfa-2b 450 μg Q2W) at 1:2 ratio. The enrollment of Stage II was completed when at least 20 patients were enrolled in group 3 (including the first 10 patients who had undergone safety review) and group 4. However, if there was a major safety concern for group 3, enrollment to group 3-II (ropeginterferon alfa-2b 225 μg QW) would be performed instead of to group 4. Safety data review process was conducted for the first 10 subjects of group 3-II. If there was no major safety concern, additional 10 patients would be enrolled. All patients received PEG-IFN-α2a or ropeginterferon alfa-2b for 48 weeks plus daily oral ribavirin 1000 mg (≤75 kg) or 1200 mg (>75 kg) in two divided doses for 48 weeks. Patients who did not achieve ≥2 log reduction in serum HCV RNA levels at TW13 or undetectable serum HCV RNA levels at TW25 were discontinued from the treatment and entered a 24-week follow-up period.

Assessments and endpoints. The primary efficacy endpoints were undetectable HCV RNA at 24 weeks post-treatment (Sustained Virologic Response, SVR 24) and safety. The secondary endpoints were pharmacokinetic parameters of ropeginterferon alfa-2b, including drug concentration, C_{max}, T_{max}, C_{min}, C_t, λ_z, $t_{1/2}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}\tau}$, and $C_{avg\text{-}ss}$ across treatment groups and

immunogenicity (defined as percentage of patients with positive ADAs or neutralizing antibody of ropeginterferon alfa-2b). In addition to the pharmacokinetic evaluation (drug serum concentration), a total of 20 subjects from four groups had an additional sampling collection for multiple dose pharmacokinetic evaluation. Adverse events that occurred during treatment or 24 weeks follow-up were recorded and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Laboratory assessment was obtained at screening, TW1, 2, 3, 5, 7, 9, 13, 19, 25, 37, 48, and follow-up weeks 12 and 24. The Roche Linear Array HCV genotyping test and the COBAS TaqMan HCV Test were used for RNA quantification. Immunogenicity was analyzed by ELISA. The titer of neutralizing antibody was analyzed in positive samples by cytopathic effect (CPE) method.

Statistical analyses. The analysis was not hypothesis driven, but exploratory in nature. Safety and efficacy population included all randomized patients who received ≥1 dose of study drug. Significance test was performed, and confidence interval was provided where appropriate. All the statistical tests were two-sided. Continuous variables were summarized with number of subject (n), mean, SD, minimum, maximum, as well as 95% confidence interval, while number of subject and percentage were provided in categorical variables. If the normal distribution was violated, then the median, inter quartile range (IQR), minimum, maximum, and 95% confidence interval of the median were used.

Sample size. The sample size was not statistically powered. We expect to evaluate the safety and preliminary efficacy across treatment groups by approximately 100 patients in this study.

Results

Study enrollment and patient demographics. We screened 209 patients from 2012 to 2015, and the screening failure rate was 48.8% (102 patients, Fig. S2). Majority of the reasons of screening failure were non-genotype 1, not fulfilled HCV RNA or hemoglobin criteria, failure to pass eye examination, or withdraw consent (Table S1). One hundred seven patients were randomized into four groups. One subject in group 4 was found ineligible due to atrial fibrillation after randomization and was withdrawn from the study before treatment. Sixteen patients discontinued: five patients in group 1, six patients in group 2, and five patients in group 4. No major safety concern was detected in each stage of the enrollment. As shown in Table 1, a total of 106 patients were treated: 27 in group 1, 30 in group 2, 20 in group 3, and 29 in group 4. The age ranged from 20.2 to 71.4 years, with a median of 50.8 in group 1, 48.7 in group 2, 53.4 in group 3, and 55.3 in group 4. Overall, 44 patients (41.5%) were male. At baseline, patients with HCV RNA >800 000 IU/mL ranged from 72.4 to 85.0%, with 73.3–82.8% of IL28B CC type. Patients with ALT ≤1.5X ULN comprised of 56–76%.

Pharmacokinetics. Serum concentration of the study drug was evaluated in the safety population ($n = 106$). In Figure 1a, the serum concentration of ropeginterferon alfa-2b/Peg-IFN-α2a during the study by treatment group was shown. Group 3 had the highest mean serum concentration from TW3 to TW48, almost twice the mean serum concentration of the other three groups. After TW48, the drug concentration of all treatment groups declined to undetectable level. The mean concentration of ribavirin was similar in all treatment groups (Fig. 1b).

Twenty patients were included in additional multiple dose pharmacokinetic evaluation. In group 1, after administration of the first dose of 180 μg Peg-IFN-α2a ($n = 8$), the mean maximum serum drug concentration was 13.3 ± 7.43 ng/mL with a T_{max} ranging from 72 to 168 h after dose. The mean $AUC_{0\text{-}\tau}$ was 1559 ± 1061 h·ng/mL. After the last dose of 48 weeks ($n = 5$), the mean maximum serum drug concentration was 24.3 ± 9.23 ng/mL with a T_{max} ranging from zero to 168 h after dose. The mean $AUC_{0\text{-}\tau}$ and C_{av} were 3107 ± 1808 h·ng/mL and 18.5 ± 10.8 ng/mL, respectively. In group 2, after the first dose of 180 μg ropeginterferon alfa-2b ($n = 8$), the mean maximum serum drug concentration was 13.1 ± 5.13 ng/mL with a T_{max} ranging from 24 to 168 h after dose. The mean $AUC_{0\text{-}\tau}$ was 1548 ± 798 h·ng/mL. After the last dose of 48 weeks ($n = 6$), the mean maximum serum drug concentration was 29 ± 9.36 ng/mL with a T_{max} ranging from 0 to 144 h after dose. The mean $AUC_{0\text{-}\tau}$ and C_{av} were 4374 ± 1512 h·ng/mL and 26.0 ± 9.0 ng/mL, respectively. After multiple weekly administration, serum exposure ($AUC_{0\text{-}\tau}$) in ropeginterferon alfa-2b 180 μg was approximately 41% greater than PEG-IFN-α2a 180 μg (4374 *vs* 3107, Table 2). The accumulation ratio in ropeginterferon alfa-2b was 2-fold greater than PEG-IFN-α2a. A dose-dependent drug concentration was observed in ropeginterferon alfa-2b arms (Fig. 2a,b).

Immunogenicity. Assessment of immunogenicity was based on the presence of antidrug antibody (ADA) or neutralizing antibody at baseline (visit 1) and follow-up visits (FW12 & FW24). No ADA was detected in any patient at any planned visit, except for one patient in group 1. The patient who had positive ADA at FW24 was assessed as non-neutralizing ADA. This patient achieved undetectable HCV RNA starting from TW9 until the end of the study.

Safety. No AE was reported prior to the dosing of ropeginterferon alfa-2b/PEG-IFN-α2a and ribavirin. All AEs reported in this study were treatment-emergent adverse events (TEAEs). Overall, a total of 1105 TEAEs were reported and the incidence of AEs was similar among four treatment groups (Table 2). The TEAEs were grade 1 in 81.8% (904 events) and grade 2 in 14.7% (162 events). Thirty-four TEAEs (3.1%) were of grade 3 and 5 (0.5%) of grade 4. The serious adverse event (SAE), dose discontinuation, dose reduction, and grade 3 of 4 AEs were similar across the four groups. The incidence of overall AEs and IFN related AEs were comparable across the four groups. A total of seven SAEs were reported in seven patients (6.6%). Three in group 1, one in group 2, two in group 3, and one in group 4. All SAEs were resolved and no death was reported in this study.

TEAEs of 10% or higher are presented in Table 2. The most common TEAEs were anemia, headache, weight decreased, and pruritus (≥25% in all group), followed by insomnia, alopecia, cough, rash, and fatigue (≥20% in all group). The following TEAEs occurred more common in group 1: cough (44.4%), insomnia (40.7%), pruritus (40.7%), pyrexia (37.0%), weight

Table 1 Patient demographics and baseline characteristics

	PEG-IFN-α2a 180 μg QW ($n = 27$)	Ropeginterferon alfa-2b 180 μg QW ($n = 30$)	Ropeginterferon alfa-2b 270 μg QW ($n = 20$)	Ropeginterferon alfa-2b 450 μg Q2W ($n = 29$)
Age, years				
Mean ± SD	48.4 ± 11.3	48.9 ± 12.4	54.7 ± 7.6	55.5 ± 11.7
Median (min–max)	50.8 (23.7–69.2)	48.7 (20.2–66.8)	53.4 (36.2–69.9)	55.3 (27.7–71.4)
Gender				
Male, *n* (%)	14 (51.9)	10 (33.3)	9 (45.0)	11 (37.9)
Weight, kg				
Mean ± SD	65.9 ± 11.8	63.1 ± 8.6	62.5 ± 10.0	64.9 ± 12.3
HCV RNA, IU/mL				
Median (min–max)	2 610 000 (15–36 900 000)	1 675 000 (785–27 800 000)	2 060 000 (9490–12 500 000)	1 760 000 (12 300–7 910 000)
HCV RNA ≥800 000 IU/mL, *n* (%)	20 (74.1)	22 (73.3)	17 (85.0)	21 (72.4)
IL-28B SNP rs 12 979 860				
CC, *n* (%)	21 (77.8)	22 (73.3)	16 (80.0)	24 (82.8)
ALT, U/L				
Median (min–max)	54.0 (17.0–339.0)	32.0 (15.0–414.0)	48.0 (20.0–133.0)	40.0 (14.0–343.0)
Baseline ALT ≦1.5X ULN, *n* (%)	15 (55.6)	22 (75.9)	13 (65.0)	19 (65.5)
Albumin, g/dL				
Median (min–max)	4.2 (3.7–5.0)	4.4 (3.6–4.9)	4.4 (3.6–4.8)	4.3 (3.5–4.9)
Total bilirubin, mg/dL				
Median (min–max)	0.8 (0.3–1.4)	0.6 (0.4–1.4)	0.8 (0.3–1.3)	0.7 (0.4–1.5)
Prothrombin time (PT)†, s				
Median (min–max)	10.6 (9.8–12.0)	10.7 (9.9–12.1)	10.8 (9.8–12.2)	10.4 (9.5–13.3)
INR†				
Median (min–max)	1.0 (0.9–1.1)	1.0 (1.0–1.2)	1.0 (0.9–1.2)	1. 0 (0.9–1.2)
Hemoglobin, g/dL				
Median (min–max)	14.2 (12.1–16.8)	14.1 (12.6–17.6)	14.6 (12.4–17.1)	13.9 (12.3–17.0)
Platelet count, 10^3/μL				
Median (min–max)	212.0 (125.0–340.0)	221.0 (124.0–337.0)	181.5 (93.0–310.0)	195.0 (118.0–409.0)

†Results at screening visit (V1) was used as baseline for PT and INR.

ALT, alanine aminotransferase; HCV, hepatitis C virus; PEG-IFN, pegylated interferon; ULN, upper limit of normal.

decreased (33.3%), diarrhea (29.6%), fatigue (29.6%), malaise (29.6%), depression (25.9%), mouth ulceration (25.9%), neutropenia (22.2%), leukopenia (22.2%), nausea (22.2%), and myalgia (22.2%). At the same dose level of 180 μg ropeginterferon alfa-2b group (group 2), the incidence rates of insomnia (36.7%), pruritus (33.3%), weight decreased (30.0%), fatigue (26.7%), myalgia (20.0%), cough (20.0%), mouth ulceration (23.3%), leukopenia (16.7%), depression (13.3%), nausea (13.3%), neutropenia (10.0%), malaise (6.7%), pyrexia (3.3%), and diarrhea (3.3%) were all lower than that in group 1. However, incidence rates of anemia (53.3%), headache (36.7%), dizziness (36.7%), decreased appetite (23.3%), and dry mouth (20.0%) were higher in group 2 than group 1. Higher dose of ropeginterferon alfa-2b in group 3 and 4 had higher incidence of anemia, weight decreased, and rash. Cheilitis (10.0%) was only reported in group 3. Eczema (35.0%) had a higher incidence in group 3 as compared with the other groups. The cumulative incidence of flu-like symptoms, that is arthralgia, myalgia, pyrexia, chills, headache, and influenza like illness, was lower in ropeginterferon alfa-2b arms (Fig. 3).

Efficacy. Efficacy summary are presented in Table 3. Rapid virologic response (RVR) was achieved in 37.0% in group 1, 30.0% in group 2, 20.0% in group 3, and 24.1% in group 4. Early virologic response (EVR) was achieved in 81.9% in group 1, 86.7% in group 2, 90.0% in group 3, and 86.2% in group 4. SVR12 was 74.1% in group 1, 70.0% in group 2, 80.0% in group 3, and 69.0% in group 4. SVR24 for group 1–4 was 77.8%, 66.7%, 80.0%, and 69.0%, respectively. In patients who carried IL-28B CC genotype, the SVR12 rates were 81.0%, 81.8%, 87.5%, and 64.0% in group 1–4, respectively. The SVR24 rates were 85.7%, 77.3%, 87.5%, and 64.0% in group 1–4, respectively. The small sample size in some subgroups might affect the SVR rates (Table 4). The dynamic change of mean serum HCV RNA levels during the study by treatment group is illustrated in Figure S3. Group 3 has the lowest mean serum HCV RNA level at FW24, followed by group 4, group 2, and group 1.

Discussion

This study was the first prospective study describing PK, safety, tolerability, and efficacy of ropeginterferon alfa-2b (P1101) in treatment-naïve Taiwanese patients with HCV genotype 1 infection. The new formulation of ropeginterferon alfa-2b owns the unique structural characteristics of only one major form with

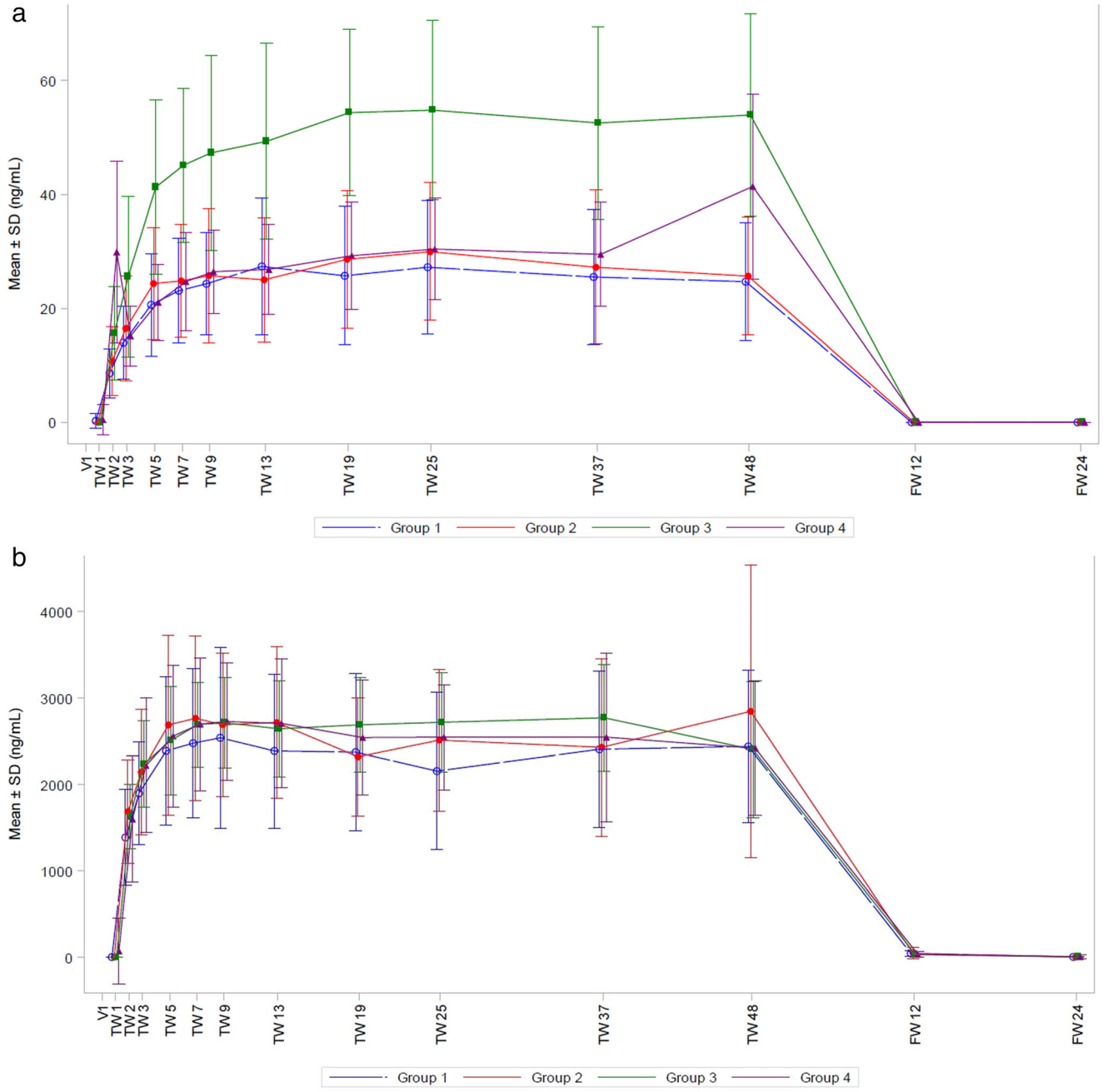

Figure 1 (a) Drug concentration of P1101/Pegasys across treatment week (safety population). Group 1: PEG-IFN-α2a 180 μg QW; group 2: ropeginterferon alfa-2b 180 μg QW; group 3: ropeginterferon alfa-2b 270 μg QW; group 4: ropeginterferon alfa-2b 450 μg Q2W. Group 3 had the highest mean serum concentrations from TW3 to TW48, almost twice the mean serum concentration of the other three groups. After TW48, the drug concentrations of all treatment groups declined to undetectable levels. (b) Drug concentration of ribavirin across treatment week (safety population). Group 1: PEG-IFN-α2a 180 μg QW; group 2: ropeginterferon alfa-2b 180 μg QW; group 3: ropeginterferon alfa-2b 270 μg QW; group 4: ropeginterferon alfa-2b 450 μg Q2W. The mean concentrations of ribavirin for all treatment groups showed similar trends at all study time points. PEG-IFN, pegylated interferon.

excellent PK and pharmacodynamics (PD) profiles in phase 1 study. The geometric mean values in C_{max}, AUC, and $AUC_{0\text{-}t}$ of ropeginterferon alfa-2b showed an increase of 76%, 66%, and 82%, respectively, as compared with PEG-IFN-α2a at the same 180 μg dose levels (unpublished data). At the same 180 μg dose level, longer half-life of the ropeginterferon alfa-2b (group 2: 478.04 h) was observed as compared with PEG-IFN-α2a (group 1:197.72 h). After multiple weekly administration, serum

Table 2 Single dose (first dose) and multiple dose (last dose) pharmacokinetic parameters

PK parameters (first dose)	PEG-IFN-α2a 180 μg QW, $n = 8$	Ropeginterferon alfa-2b 180 μg QW, $n = 8$	Ropeginterferon alfa-2b 270 μg QW, $n = 2$	Ropeginterferon alfa-2b 450 μg Q2W, $n = 2$
C_{max} (ng/mL)				
Mean	13.33	13.05	9.66	47.6
SD	7.43	5.13	2.77	39.03
T_{max} (h)				
Mean	114	138	144	120
SD	45.81	47.57	0	67.88
C_{last}, C_{min} (ng/mL)				
Mean	9.93	11.98	9.08	19.4
SD	4.47	4.59	2.39	3.82
τ (h)				
Mean	168	168	168	336
SD	0	0	0	0
$AUC_{0-\tau}$ (h ng/mL)				
Mean	1558.90	1547.89	1223.89	9960.84
SD	1060.86	797.72	482.38	6871.89
$AUC_{0-tlast}$ (h ng/mL)				
Mean	1558.90	1547.89	1233.89	9960.84
SD	1060.86	797.72	482.38	6871.89
PK parameters (last dose)	PEG-IFN-α2a 180 μg QW, $n = 5$	Ropeginterferon alfa-2b 180 μg QW, $n = 6$	Ropeginterferon alfa-2b 270 μg QW, $n = 2$	Ropeginterferon alfa-2b 450 μg Q2W, $n = 2$
C_{max} (ng/mL)				
Mean	24.30	28.99	43.20	50.85
SD	9.23	9.36	8.63	6.15
T_{max} (h)				
Mean	62.4	72.0	48.0	144
SD	69.14	45.54	33.94	0
C_{last} (ng/mL)				
Mean	3.05	3.04	10.64	14.15
SD	2.28	1.49	8.00	10.25
t_{last} (h)				
Mean	638.4	672.0	672.0	588
SD	75.13	0	0	118.79
$AUC_{0-\tau}$ (h ng/mL)				
Mean	3107.42	4374.35	6802.20	14 509.2
SD	1807.62	1512.24	1176.91	1579.96
C_{av} (ng/mL)				
Mean	18.50	26.04	40.49	43.19
SD	10.76	9.00	7.00	4.7
$AUC_{0-tlast}$ (h ng/mL)				
Mean	7856.62	10 160.14	16 213.56	20 108.22
SD	3219.88	3494.66	777.76	979.46

PEG-IFN, pegylated interferon; PK, pharmacokinetics.

exposure (AUC0-τ) in ropeginterferon alfa-2b 180 μg was approximately 41% greater than Peg-IFN-α2a 180 μg. The accumulation ratio in ropeginterferon alfa-2b was 2-fold greater than PEG-IFN-α2a. The longer effective half-life (Table S2) in the ropeginterferon alfa-2b, as compared with the PEG-IFN-α2a, suggests a slower accumulation of ropeginterferon alfa-2b. These characteristics allows once every 2 weeks injection that increase the compliance and reduce psychological stress of the patients.

The majority of TEAEs were comparable among all treatment groups and have previously been reported in marketed PEG-IFNs.[16–18] However, psychiatric disorders including anxiety, depression, and insomnia were numerically higher in PEG-IFN-α2a group (180 μg QW) than ropeginterferon alfa-2b groups (180 μg QW, 270 μg QW, and 450 μg Q2W) (Table 2; Figs. S4 and S5). Among the common side effects of PEG-IFNs, depression and suicidal ideation correlate with poorer treatment response independent of dose reduction and need more attention.[19] A SAE of grade 4 suicidal ideation and grade 4 major depression were reported in a patient in the PEG-IFN-α2a group. This patient was hospitalized and discontinued from the

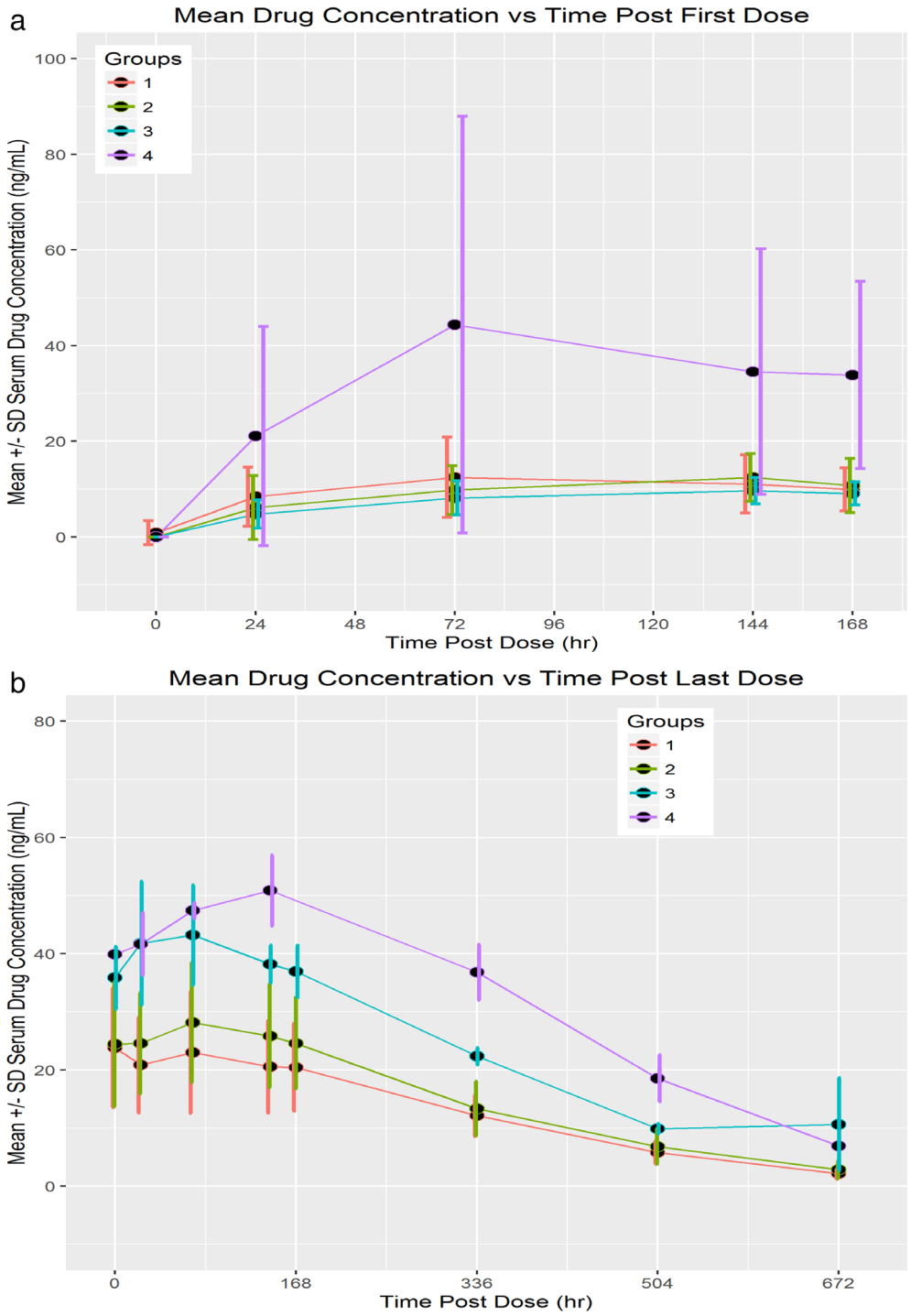

Figure 2 (a) Mean serum drug concentration–time profiles (after first dose). Group 1: PEG-IFN-α2a 180 μg QW; group 2: ropeginterferon alfa-2b 180 μg QW; group 3: ropeginterferon alfa-2b 270 μg QW; group 4: ropeginterferon alfa-2b 450 μg Q2W. Single (first dose) and multiple dose (last dose) serum concentration–time plots by group. (b) Mean serum drug concentration–time profiles (after last dose). Group 1: PEG-IFN-α2a 180 μg QW; group 2: ropeginterferon alfa-2b 180 μg QW; group 3: ropeginterferon alfa-2b 270 μg QW; group 4: ropeginterferon alfa-2b 450 μg Q2W. Single (first dose) and multiple dose (last dose) serum concentration–time plots by group. PEG-IFN, pegylated interferon.

treatment. The rate of depression in PEG-IFN-α2a group was 25.9% (7/27), which was numerically higher than the pooled (6.3%) or individual ropeginterferon alfa-2b group (3.4–13.3%, Table 2). In pooled 48-week monotherapy and 48-week combination therapy of PEG-IFN-α2a treated CHC patients, the rates of depression were 18–20% (PEGASYS package insert, South

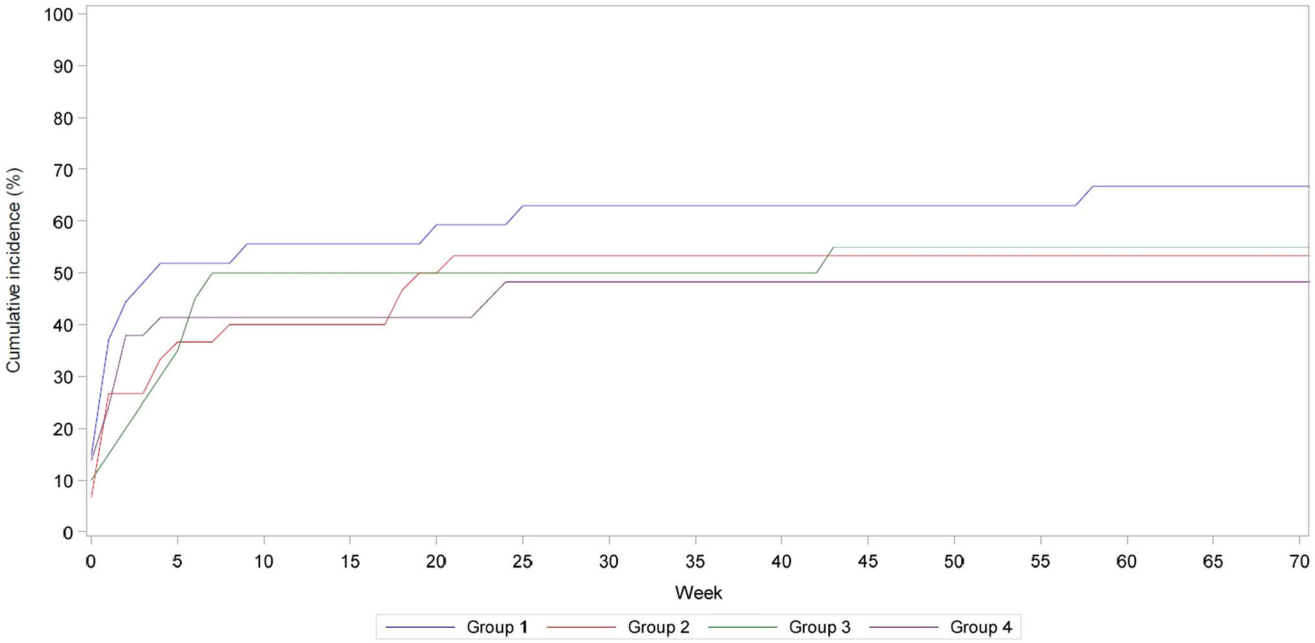

Figure 3 Cumulative incidence of flu-like symptoms (safety population). Group 1: PEG-IFN-α2a 180 μg QW; group 2: ropeginterferon alfa-2b 180 μg QW; group 3: ropeginterferon alfa-2b 270 μg QW; group 4: ropeginterferon alfa-2b 450 μg Q2W; In the analysis of the flu-like symptoms, the MedDRA preferred term arthralgia, myalgia, pyrexia, chills, headache, and influenza like illness were added for analysis. PEG-IFN, pegylated interferon.

San Francisco, CA, USA: Hoffman-La Roche, Inc. 2017). With references to PEG-IFN treatment for myeloproliferative neoplasms, ropeginterferon alfa-2b treated PV patients showed low rate of depression (1.6%; 3/127).[3] In contrast, higher rates of depression were observed in PV (8.0%; 4/50) and essential thrombocythemia (ET) (12.5%; 12/64) patients who were treated with PEG-IFN-α2a.[20]

Previously, Novartis has put efforts in development of a new recombinant human albumin-interferon α-2b (Albuinterferon), which was designed to dose every 2 weeks for treatment of chronic viral hepatitis.[21] However, increased pulmonary AEs were reported in the phase 3 trial and the project was discontinued in 2010.[22] In contrast, no lung toxicities was observed in ropeginterferon alfa-2b use, up to totally 629 patients, including 102 healthy subjects, 313 patients with CHB or C, and 214 PV patients.[1–3]

There are limitations in this study. Firstly, the rates of discontinuation rate were slightly higher than the average. In this study, rates of discontinuation were 18.5% (5/27), 20% (6/30), and 17.2% (5/29) for group 1, 2, and 4, respectively. Group 3 (ropeginterferon alfa-2b 270 μg QW) had no patient discontinued from the study. Fried et al. reported the discontinuation rates of 7–10% for PEG-IFN-α2a plus ribavirin and Manns et al. showed the discontinuation rates of 13–14% for PEG-IFN-α2b plus ribavirin.[23,24] Furthermore, the quality of life (QOL) was not evaluated. The QOL evaluation may provide information on the advantages of biweekly injection of ropeginterferon alfa-2b.

In this study, ropeginterferon alfa-2b demonstrated superior PK characteristics and safety profiles. In contrast, one patient in PEG-IFN-α2a group had to reduce the dose and subsequently discontinued the treatment due to severe depression.

Although PEG-IFN was removed from current HCV treatment guidelines, ropeginterferon alfa-2b is still the backbone of treatment for CHB or chronic hepatitis D (CHD), due to its antiviral mechanisms, which include direct inhibition of viral replication and the modulation of immune response. In our phase I/II study in CHB patients, ropeginterferon alfa-2b showed comparable safety profile and better HBeAg seroconversion rate than PEG-IFN alfa-2a.[2] There are several approved treatments including PEG-IFN, nucleoside analogues (lamivudine, entecavir, and telbivudine), and nucleotide analogues (adefovir dipivoxil, tenofovir disoproxil fumarate, and tenofovir alafenamide) in CHB. The goal of CHB therapies is to prevent the development of cirrhosis, liver failure, hepatocellular carcinoma, and CHB-related deaths, which can be achieved by clearance of hepatitis B surface antigen (HBsAg). Monotherapy, sequential or simultaneous combination therapy of PEG-IFN plus nucleos(*t*)ide analogues have been tested over the past decade, however, the rate of functional cure (defined as a sustained loss of HBsAg and undetectable HBV DNA in serum, with or without HBsAg seroconversion) is still lower than expectation and remains an unmet medical need.[25–27] Ropeginterferon alfa-2b with the potential efficacy and favorable safety may fill the gap of the need for CHB treatment.

The first line therapy in CHD is 12-month or longer PEG-IFN alpha. The response rates range from 17 to 47%, however, with high relapse rates.[28–32] Longer treatment duration with marketed PEG-IFN alpha or combination with nucleos(*t*)ide analogues such as adefovir, lamivudine, or entecavir did not increase the response rates.[33,34] Bulevirtide recently received conditional approval by European Medicines Agency for the treatment of

Table 3 Safety summary

	Pooled Ropeginterferon alfa-2b ($n = 79$)	PEG-IFN-α2a 180 μg QW ($n = 27$)	Ropeginterferon alfa-2b 180 μg QW ($n = 30$)	Ropeginterferon alfa-2b 270 μg QW ($n = 20$)	Ropeginterferon alfa-2b 450 μg Q2W ($n = 29$)
Overall AE	810	295	326	217	267
Overall AE incidence rate[†]	NA	0.239	0.240	0.209	0.207
IFN related AE incidence rate[†]	NA	0.147	0.136	0.148	0.158
Important safety event, *n* (%)[‡]					
Serious AE	4 (5.1)	3 (11.1)	1 (3.3)	2 (10.0)	1 (3.4)
Severe AE (grade 3)	16 (20.3)	7 (25.9)	5 (16.7)	3 (15.0)	8 (27.6)
Severe AE (grade 4)	2 (2.5)	2 (7.4)	0 (0)	1 (5.0)	1 (3.4)
TEAE ≥10% in any group, *n* (%)[‡]					
Anemia	**46 (58.22)**	**14 (51.9)**	**16 (53.3)**	**12 (60.0)**	**18 (62.1)**
Leukopenia	11 (13.9)	**6 (22.2)**	5 (16.7)	1 (5.0)	5 (17.2)
Neutropenia	11 (13.9)	**6 (22.2)**	3 (10.0)	**4 (20.0)**	4 (13.8)
Thrombocytopenia	5 (6.3)	0 (0)	1 (3.3)	1 (5.0)	3 (10.3)
Tinnitus	5 (6.3)	1 (3.7)	2 (6.7)	2 (10.0)	1 (3.4)
Hyperthyroidism	3 (3.8)	0 (0)	3 (10.0)	0 (0)	0 (0)
Hypothyroidism	8 (10.1)	2 (7.4)	5 (16.7)	1 (5.0)	2 (6.9)
Abdominal distension	7 (8.9)	5 (18.5)	2 (6.7)	3 (15.0)	2 (6.9)
Abdominal pain upper	7 (8.9)	3 (11.1)	5 (16.7)	0 (0)	2 (6.9)
Cheilitis	2 (2.5)	0 (0)	0 (0)	2 (10.0)	0 (0)
Constipation	7 (8.9)	3 (11.1)	2 (6.7)	1 (5.0)	4 (13.8)
Diarrhea	6 (7.6)	**8 (29.6)**	1 (3.3)	2 (10.0)	3 (10.3)
Dry mouth	9 (11.4)	3 (11.1)	**6 (20.0)**	1 (5.0)	2 (6.9)
Dyspepsia	3 (3.8)	2 (7.4)	1 (3.3)	2 (10.0)	0 (0)
Gastritis	5 (6.3)	0 (0)	3 (10.0)	1 (5.0)	1 (3.4)
Gastrooesophageal reflux disease	4 (5.1)	3 (11.1)	1 (3.3)	2 (10.0)	1 (3.4)
Mouth ulceration	13 (16.5)	**7 (25.9)**	**7 (23.3)**	2 (10.0)	4 (13.8)
Nausea	8 (10.1)	**6 (22.2)**	4 (13.3)	2 (10.0)	2 (6.9)
Vomiting	5 (6.3)	2 (7.4)	2 (6.7)	2 (10.0)	1 (3.4)
Fatigue	**17 (21.5)**	**8 (29.6)**	**8 (26.7)**	**5 (25.0)**	4 (13.8)
Injection site reaction	3 (3.8)	0 (0)	0 (0)	2 (10.0)	1 (3.4)
Malaise	4 (5.1)	**8 (29.6)**	2 (6.7)	1 (5.0)	1 (3.4)
Pyrexia	11 (13.9)	**10 (37.0)**	1 (3.3)	**5 (25.0)**	5 (17.2)
Bronchitis	4 (5.1)	3 (11.1)	1 (3.3)	1 (5.0)	2 (6.9)
Cellulitis	2 (2.5)	1 (3.7)	0 (0)	2 (10.0)	0 (0)
Upper respiratory tract infection	13 (16.5)	4 (14.8)	4 (13.3)	**6 (30.0)**	3 (10.3)
Urinary tract infection	9 (11.4)	1 (3.7)	4 (13.3)	3 (15.0)	2 (6.9)
Platelet count decreased	5 (6.3)	1 (3.7)	1 (3.3)	3 (15.0)	1 (3.4)
Weight decreased	**34 (43.0)**	**9 (33.3)**	**9 (30.0)**	**9 (45.0)**	**16 (55.2)**
White blood cell count decreased	9 (11.4)	0 (0)	2 (6.7)	3 (15.0)	4 (13.8)
Decreased appetite	10 (12.7)	**6 (22.2)**	**7 (23.3)**	2 (10.0)	1 (3.4)
Arthralgia	5 (6.3)	0 (0)	3 (10.0)	1 (5.0)	1 (3.4)
Back pain	6 (7.6)	1 (3.7)	2 (6.7)	2 (10.0)	2 (6.9)
Myalgia	15 (19.0)	**6 (22.2)**	**6 (20.0)**	**4 (20.0)**	5 (17.2)
Dizziness	**20 (25.3)**	4 (14.8)	**11 (36.7)**	**5 (25.0)**	4 (13.8)
Headache	**24 (30.4)**	**9 (33.3)**	**11 (36.7)**	**5 (25.0)**	**8 (27.6)**
Anxiety	2 (2.5)	4 (14.8)	2 (6.7)	0 (0)	0 (0)
Depression	5 (6.3)	**7 (25.9)**	4 (13.3)	0 (0)	1 (3.4)
Insomnia	**24 (30.4)**	**11 (40.7)**	**11 (36.7)**	**7 (35.0)**	**6 (20.7)**
Cough	**17 (21.5)**	**12 (44.4)**	**6 (20.0)**	**5 (25.0)**	**6 (20.7)**
Dyspnea	9 (11.4)	3 (11.1)	3 (10.0)	1 (5.0)	5 (17.2)
Oropharyngeal pain	6 (7.6)	2 (7.4)	4 (13.3)	2 (10.0)	0 (0)
Respiratory distress	3 (3.8)	3 (11.1)	3 (10.0)	0 (0)	0 (0)
Rhinitis allergic	7 (8.9)	2 (7.4)	3 (10.0)	1 (5.0)	3 (10.3)
Alopecia	**23 (29.1)**	**7 (25.9)**	**6 (20.0)**	**9 (45.0)**	**8 (27.6)**
Dermatitis	12 (15.2)	3 (11.1)	4 (13.3)	2 (10.0)	2 (6.9)
Eczema	10 (12.7)	0 (0)	2 (6.7)	7 (35.0)	1 (3.4)

(*Continues*)

Table 3 (Continued)

	Pooled Ropeginterferon alfa-2b ($n = 79$)	PEG-IFN-α2a 180 μg QW ($n = 27$)	Ropeginterferon alfa-2b 180 μg QW ($n = 30$)	Ropeginterferon alfa-2b 270 μg QW ($n = 20$)	Ropeginterferon alfa-2b 450 μg Q2W ($n = 29$)
Pruritus	**29 (36.7)**	**11 (40.7)**	**10 (33.3)**	**5 (25.0)**	**14 (48.3)**
Rash	**20 (25.3)**	**6 (22.2)**	**6 (20.0)**	**5 (25.0)**	**9 (31.0)**

Bold: TEAE frequency ≥20%.

AE, adverse event; NA, not available; TEAE, treatment-emergent adverse event.

[†]Number of TEAEs/patient's treatment week.

[‡]Data in number of events, number of subjects (% of subjects).

Table 4 Efficacy summary

	Pooled Ropeginterferon alfa-2b $n = 79$	PEG-IFN-α2a 180 μg QW, $n = 27$	Ropeginterferon alfa-2b 180 μg QW, $n = 30$	Ropeginterferon alfa-2b 270 μg QW, $n = 20$	Ropeginterferon alfa-2b 450 μg Q2W, $n = 29$
Undetectable HCV RNA					
TW2	9 (11.4)	4 (14.8)	4 (13.3)	1 (5.0)	4 (13.8)
TW3	13 (16.5)	6 (22.2)	8 (26.7)	1 (5.0)	4 (13.8)
TW5	20 (25.3)	10 (37.0)	9 (30.0)	4 (20.0)	7 (24.1)
TW9	52 (65.8)	20 (74.1)	20 (66.7)	15 (75.0)	17 (58.6)
TW13	69 (87.3)	22 (81.5)	26 (86.7)	18 (90.0)	25 (86.2)
TW25	73 (92.4)	24 (88.9)	27 (90.0)	20 (100.0)	26 (89.7)
TW48	69 (87.3)	23 (85.2)	24 (80.0)	20 (100.0)	25 (86.2)
FW12 (SVR12)	57 (72.2)	20 (74.1)	21 (70.0)	16 (80.0)	20 (69.0)
FW24 (SVR24)	56 (70.9)	21 (77.8)	20 (66.7)	16 (80.0)	20 (69.0)
≥2 log reductions from baseline at TW13	74 (93.7)	24 (88.9)	27 (90.0)	20 (100.0)	27 (93.1)
Relapse[†]	14 (17.7)	3 (11.1)	4 (13.3)	4 (20.0)	6 (20.7)
Non-response[‡]	9 (11.4)	3 (11.1)	6 (20.0)	0 (0)	3 (10.3)
SVR12 in IL-28B CC[§]	48 (76.2)	17 (81.0)	18 (81.8)	14 (87.5)	16 (64.0)
SVR12 in IL-28B Non-CC[§]	9 (56.3)	3 (50.0)	3 (37.5)	2 (50.0)	4 (100.0)
SVR24 in IL-28B CC[§]	47 (74.6)	18 (85.7)	17 (77.3)	14 (87.5)	16 (64.0)
SVR24 in IL-28B Non-CC[§]	9 (56.3)	3 (50.0)	3 (37.5)	2 (50.0)	4 (100.0)

HCV, hepatitis C virus; PEG-IFN, pegylated interferon; TW, treatment week.

[†]Undetectable serum HCV RNA at TW48 and detectable serum HCV RNA at follow-up.

[‡]Detectable serum HCV RNA throughout the treatment and follow-up, or early discontinuation before TW48 and lost to follow-up.

[§]Denominator was the number of patients in CC or Non-CC. Number of CC patient was 21, 22, 16, and 25 in group 1–4, respectively. Number of Non-CC patient was 6, 8, 4, and 4 in group 1–4, respectively.

CHD based on phase 2 data.[35] The preliminary result of ongoing trials by adding PEG-IFN showed better treatment efficacy.[35] Therefore, newly formulated PEG-IFN alpha is exceptionally needed for CHD patients. Taking together, ropeginterferon alfa-2b with longer effective half-life and superior safety profile will benefit larger viral hepatitis patient population.

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Supporting information

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

Table S1. Reason for screening failure.
Table S2. Accumulation and effective half life.

Figure S1. Enrolment process. Group 1: PEG-IFN-α2a 180 μg QW; Group 2: Ropeginterferon alfa-2b 180 μg QW; Group 3:

Ropeginterferon alfa-2b 270 μg QW; Group 4: Ropeginterferon alfa-2b 450 μg Q2W. After the enrolment completion of Stage I and there was no major safety concern, 10 subjects were enrolled into Group 3 at Stage IIa. If there was no major safety concern in first 10 subjects in group 3, the enrolment of Group 3 and Group 4 will be continued.

Figure S2. Patient disposition. Group 1: PEG-IFN-α2a 180 μg QW; Group 2: Ropeginterferon alfa-2b 180 μg QW; Group 3: Ropeginterferon alfa-2b 270 μg QW; Group 4: Ropeginterferon alfa-2b 450 μg Q2W; #: This patient received one dose of study drug and was found to be co-infected with HBV. *: Patient was found ineligible due to atrial fibrillation after randomization and did not receive any study medication. **: Three patients met the protocol-defined stopping rule. Two patients were discontinued at TW13 due to lack of efficacy. The other patient discontinued at TW25 due to lack of efficacy. ***: One patient was repatriate return to China because overstay.

Figure S3. Mean serum HCV RNA by treatment group (Efficacy Population) Group 1: PEG-IFN-α2a 180 μg QW; Group 2: Ropeginterferon alfa-2b 180 μg QW; Group 3: Ropeginterferon alfa-2b 270 μg QW; Group 4: Ropeginterferon alfa-2b 450 μg Q2W; Four groups showed rapid decline in serum HCV RNA levels by TW2 to almost undetectable levels until TW48. An increase in mean serum HCV RNA during follow-up was due to relapse and non-response. Group 3 had the lowest serum HCV RNA level at FW24, followed by Group 4, Group 2, and then Group 1.

Figure S4. Cumulative incidence of depression (Safety Population) Group 1: PEG-IFN-α2a 180 μg QW; Group 2: Ropeginterferon alfa-2b 180 μg QW; Group 3: Ropeginterferon alfa-2b 270 μg QW; Group 4: Ropeginterferon alfa-2b 450 μg Q2W. In the analysis of cumulative incidence, the MedDRA preferred term depression was used for analysis.

Figure S5. Cumulative incidence of anxiety (Safety Population). Group 1: PEG-IFN-α2a 180 μg QW; Group 2: Ropeginterferon alfa-2b 180 μg QW; Group 3: Ropeginterferon alfa-2b 270 μg QW; Group 4: Ropeginterferon alfa-2b 450 μg Q2W. In the analysis of cumulative incidence, the MedDRA preferred term anxiety was used for analysis.