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GENERIC DRUG NAME and COMPOUND NUMBER: Filibuvir / PF-00868554

PROTOCOL NO.: A8121014

PROTOCOL TITLE: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Filibuvir Plus Pegylated Interferon Alfa-2a and Ribavirin in Treatment Naïve, HCV Genotype 1 Infected Subjects

Study Centers: A total of 65 centers participated in the study and enrolled subjects, including 23 centers in the United States; 8 centers in Spain; 7 centers each in Canada, France, and Germany; 6 centers in Belgium; 4 centers in Hungary; and 3 centers in the Republic of Korea.

Study Initiation and Final Completion Dates: 10 November 2009 to 27 January 2012

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- To determine if the addition of filibuvir to a regimen of pegylated interferon-α (pegIFN)/ ribavirin (RBV) increased the proportion of subjects who achieved a sustained viral response (SVR) at the end of study compared to pegIFN/RBV alone

Secondary Objectives:

- To determine if filibuvir in combination with pegIFN/RBV increased the proportion of subjects who achieved undetectable hepatitis C virus (HCV) ribonucleic acid (RNA) concentrations at study Weeks 4, 12, 24, and 48 (Path 2 only) compared to pegIFN/RBV therapy alone
- To determine if the addition of filibuvir to a regimen of pegIFN/RBV increased the proportion of subjects who achieved a SVR at 12 weeks following the completion of therapy (SVR_{12}) compared to pegIFN/RBV therapy alone
- To determine the proportion of subjects in Path 1 who achieved a SVR at 24 weeks following the completion of therapy (SVR_{24})
- To determine the proportion of subjects with breakthrough or relapsed viremia in each treatment arm

- To identify the optimal safe and effective dose of filibuvir in combination with pegIFN and ribavirin

- To assess the safety and tolerability of filibuvir when administered in combination with pegIFN and RBV

- To determine the pharmacokinetics (PK) of filibuvir, pegIFN, and RBV

METHODS

Study Design: This was a 72-week, multicenter, multinational, double-blind, randomized, placebo-controlled Phase 2b study to assess the safety and efficacy of filibuvir (300 mg and 600 mg twice daily [BID]) in combination with pegIFN and RBV in treatment-naive HCV genotype 1-infected subjects. Subjects were randomized to 1 of 3 treatment arms in a 1:1:1 ratio of 96 subjects per group. A semen sub-study was conducted as part of this study at qualified sites in the United States only. The sub-study was to enroll 60 male subjects (20 subjects per arm). Randomization was stratified by screening plasma HCV RNA and participation in the semen sub-study into 4 strata (HCV RNA ≤400,000 IU/mL and participating in the semen sub-study; HCV RNA ≤400,000 IU/mL and not participating in the semen sub-study; HCV RNA >400,000 IU/mL and participating in the semen sub-study; and HCV RNA >400,000 IU/mL and not participating in the semen sub-study). Randomization of genotype 1A subjects was limited to 70% to ensure a minimum of 30% genotype 1B subjects in the study.

Subjects were randomly assigned to treatment in Arms A, B, or C (Table 1).

Table 1. Treatments Administered

Arm	Regimen
A	Filibuvir 600 mg BID + pegIFN/RBV x 24 weeks (Path 1); or Filibuvir 600 mg BID + pegIFN/RBV x 24 weeks followed by pegIFN/RBV x 24 weeks (Path 2)
B	Filibuvir 300 mg BID + pegIFN/RBV x 24 weeks (Path 1); or Filibuvir 300 mg BID + pegIFN/RBV x 24 weeks followed by pegIFN/RBV x 24 weeks (Path 2).
C	Placebo + pegIFN/RBV x 24 weeks followed by pegIFN/RBV x 24 weeks.

Path 1: A subject in a filibuvir arm was designated as in Path 1 if the subject completed 24 weeks of therapy with undetectable HCV RNA (HCV RNA <15 IU/mL) from Weeks 4 through 24.
Path 2: A subject in a filibuvir arm was designated as in Path 2 if the subject completed 24 weeks of therapy and had HCV RNA ≥15 IU/mL at any time from Weeks 4 through 20, but undetectable at Week 24.
BID = twice daily; HCV = hepatitis C virus; pegIFN = pegylated interferon-α; RBV = ribavirin; RNA = ribonucleic acid

The disposition of subjects following study Week 24 was as follows:

- Those subjects in Arms A and B who were in Path 1 discontinued all therapy at study Week 24 and entered into a 48-week follow-up period.

- Those subjects in Arms A and B who were in Path 2 and all subjects in Arm C whose HCV RNA was undetectable at study Week 24 continued on pegIFN/RBV therapy for an additional 24 weeks. Those subjects whose HCV RNA was undetectable at study Week 48 entered into a 24-week follow-up period.

The schedule of activities is presented in Table 2 (Path 1) and Table 3 (Path 2). Subjects participating in the semen sub-study had an additional blood sample taken for assessment of reproductive hormones at Week 1 and semen samples taken at each visit for assessment of semen parameters.

Table 2. Schedule of Activities for Path 1 for Arm A (Filibuvir 600 mg + pegIFN/RBV) and Arm B (Filibuvir 300 mg + pegIFN/RBV)

Protocol Activity	Screen	Day 1/ Week 0	Week 2	Weeks 4, 8, 12, 16, and 20	Week 24/ End of Treatment	Week 36	Week 48	Week 72/Final Follow-Up/ Early Termination/ 6-Month Follow-Up[a]
Informed consent	X							
Medical history	X	X						
Concomitant medications	X	X		X	X	X	X	X
Full physical examination	X				X		X	X
Targeted physical examination		X		X[b]		X		
Weight[c]	X	X		X	X	X	X	X
Height	X							
Electrocardiogram	X		X[d]		X		X	X
Vital signs	X	X		X	X	X	X	X
Child-Pugh score	X							
Liver biopsy[e]	X							
Ultrasound[f]	X							
Laboratory								
Hematology	X	X	X	X	X	X	X	X
Blood chemistry	X	X		X	X	X	X	X
Urinalysis	X							
Reproductive hormones[g]	X	X		X[h]	X	X		X
Coagulation	X	X		X	X	X	X	X
Follicle-stimulating hormone[i]	X							
Other[j]	X							
Urine drug screen	X							
Pregnancy test[k]	X	X		X	X	X	X	X
Viral serology	X							
HCV genotype	X							
HCV RNA	X	X	X	X	X	X	X	X
Filibuvir susceptibility		X	X	X	X		X	X
HCV NS5B sequence		X	X	X	X		X	X
Filibuvir PK sample[l]		X	X	X	X			X[m]
PegIFN PK sample		X		X	X			
RBV PK sample		X		X	X			
Biomarkers[n]								
IP-10		X		X	X			
OAS2		X		X	X			
Randomization		X						

Table 2. Schedule of Activities for Path 1 for Arm A (Filibuvir 600 mg + pegIFN/RBV) and Arm B (Filibuvir 300 mg + pegIFN/RBV)

Protocol Activity	Screen	Day 1/ Week 0	Week 2	Weeks 4, 8, 12, 16, and 20	Week 24/ End of Treatment	Week 36	Week 48	Week 72/Final Follow-Up/ Early Termination/ 6-Month Follow-Up[a]
Adverse events assessment		X	X	X	X	X	X	X
Dispense study treatment		X		X				
Study treatment[o]								
Filibuvir or placebo		X----------	----------	----------	----------X			
PegIFN		X----------	----------	----------	----------X			
RBV		X----------	----------	----------	----------X			

AFP = alpha-fetoprotein; ANA = antinuclear antibody; BID = twice daily; HbA1c = glycosylated hemoglobin A1c; HCV = hepatitis C virus; IP-10 = interferon-inducible protein 10; NS5B = nonstructural 5B protein; OAS2 = 2'5'–oligoadenylate synthase; pegIFN = pegylated interferon-α; PK = pharmacokinetics; RBV = ribavirin; RNA = ribonucleic acid.

a. Subjects who had terminated early were to return for a 6-month follow-up visit and repeat the early termination procedures.
b. Targeted physical examination was performed at Weeks 4 and 12 only.
c. Weight was measured at screening; monthly through the completion of therapy, and during the posttreatment follow-up visits occurring at Weeks 36, 48, and 72.
d. Electrocardiogram was to be conducted at the time of the second filibuvir PK sample collection (30 minutes to 3 hours postdose).
e. For those subjects with liver biopsy outside of the time window (2 years) or for those subjects with no history of a liver biopsy, a biopsy was performed prior to randomization, but after the Investigator had determined the subject met all other inclusion/exclusion criteria.
f. Ultrasound was performed within 6 months of screening for those subjects with bridging fibrosis or for those subjects with AFP >50 ng/mL and <100 ng/mL with no evidence of hepatocellular carcinoma. For those subjects with an ultrasound conducted outside the 6-month time window, an ultrasound was performed prior to randomization, but after the Investigator determined the subject met all other inclusion/exclusion criteria.
g. Reproductive hormones in males only (follicle-stimulating hormone, luteinizing hormone, total testosterone, and inhibin B). Samples were collected between 8:00 AM and 12:00 PM.
h. Samples were collected at Week 4 and Week 12 only.
i. Women aged >45 years and amenorrheic for >2 years only.
j. Included AFP, ANA, HbA1c, and creatinine clearance.
k. A serum pregnancy test was performed at screening; a urine pregnancy test was performed at all other visits for women of childbearing potential only.
l. During the Week 0 (Day 1) and Weeks 2, 12, and 24 visits, the morning dose of filibuvir/placebo was administered in the clinic, and 2 venous blood samples were drawn from each subject for filibuvir determination. The times of the draws for the 2 samples were as far apart as possible and were separated by at least 30 minutes. It was recommended that the first sample be obtained as soon as possible upon arrival and, if possible, before administering filibuvir/placebo, and that the second sample be obtained immediately prior to leaving the clinic but at least 30 minutes following the administration of filibuvir. During each of the Weeks 4, 8, 16, and 20 visits, 1 venous blood sample was taken from each subject for filibuvir determination.
m. Early termination only if visit occurred ≤24 weeks.
n. Samples for IP-10 and OAS2 biomarkers were collected at Weeks 0 (predose), 4, 8, 12, 16, 20, and 24.
o. Filibuvir or placebo was administered orally, BID through Week 24; pegIFN was administered subcutaneously weekly through Week 24; RBV was administered orally, BID through Week 24.

Table 3. Schedule of Activities for Path 2 for Arm A (Filibuvir 600 mg + pegIFN/RBV) and Arm B (Filibuvir 300 mg + pegIFN/RBV), and All Subjects of Arm C (Placebo + pegIFN/RBV)

Protocol Activity	Screen	Day 1/ Week 0	Week 2	Weeks 4, 8, 12, 16, 20, and 24	Weeks 28, 32, 36, 40, and 44	Week 48 End of Treatment	Week 60	Week 72 Final Follow Up/Early Term/ 6-Month Follow-Up[a]
Informed consent	X							
Medical history	X	X						
Concomitant medications	X	X		X	X	X	X	X
Full physical examination	X					X		X
Targeted physical examination[b]		X		X	X		X	
Weight[c]	X	X		X	X	X	X	X
Height	X							
Electrocardiogram	X		X[d]	X[d]		X		X
Vital signs	X	X		X	X	X	X	X
Child-Pugh score	X							
Liver biopsy[e]	X							
Ultrasound[f]	X							
Laboratory								
Hematology	X	X	X	X	X	X	X	X
Blood chemistry	X	X		X	X	X	X	X
Urinalysis	X							
Reproductive hormones[g]	X	X		X[h]	X[i]		X	X
Coagulation	X	X		X	X	X	X	X
FSH[j]	X							
Other[k]	X							
Urine drug screen	X							
Pregnancy test[l]	X	X		X	X	X	X	X
Viral serology	X							
HCV genotype	X							
Filibuvir susceptibility		X	X	X		X		X
NS5B sequence		X	X	X		X		X
Filibuvir PK sample[m]		X	X	X				X[n]
PegIFN PK sample		X		X		X		
Ribavirin PK sample		X		X		X		
Biomarkers[o]								
IP-10		X		X				
OAS2		X		X				
Randomization		X						

Table 3. Schedule of Activities for Path 2 for Arm A (Filibuvir 600 mg + pegIFN/RBV) and Arm B (Filibuvir 300 mg + pegIFN/RBV), and All Subjects of Arm C (Placebo + pegIFN/RBV)

Protocol Activity	Screen	Day 1/ Week 0	Week 2	Weeks 4, 8, 12, 16, 20, and 24	Weeks 28, 32, 36, 40, and 44	Week 48 End of Treatment	Week 60	Week 72 Final Follow Up/Early Term/ 6-Month Follow-Up[a]
Adverse events assessment		X	X	X	X	X	X	X
Dispense study medication		X		X	X			
Study treatment[p]								
Filibuvir or placebo		X----------X						
PegIFN		X----------X						
RBV		X----------X						

AFP = alpha-fetoprotein; ANA = antinuclear antibody; BID = twice daily; ECG = electrocardiogram; HbA1c = glycosylated hemoglobin A1c; HCV = hepatitis C virus; IP-10 = interferon-inducible protein 10; LH = luteinizing hormone; NS5B = nonstructural 5B protein; OAS2 = 2'5'–oligoadenylate synthase; pegIFN = pegylated interferon-α; PK = pharmacokinetics; RBV = ribavirin; RNA = ribonucleic acid

a. Subjects who had terminated early were to return for a 6-month follow-up visit and repeat the early termination procedures.
b. Targeted physical examination was performed at Weeks 0, 4, 12, 24, 36 and 60.
c. Weight was measured at screening; monthly through the completion of therapy and during the post-treatment follow-up visits occurring at Weeks 60 and 72.
d. Week 2 and 24 only. ECG was conducted at the time of the second filibuvir PK sample collection (30 minutes to 3 hours post dose).
e. For those subjects with liver biopsy outside of the time window (2 years) or for those subjects with no history of liver biopsy, a biopsy was performed prior to randomization, but after the Investigator had determined the subject met all other inclusion/exclusion criteria.
f. Ultrasound was performed within 6 months of screening for those subjects with bridging fibrosis or for those subjects with AFP >50 ng/mL and <100 ng/mL with no evidence of hepatocellular carcinoma. For those subjects with an ultrasound conducted outside the 6-month time window, an ultrasound was performed prior to randomization, but after the Investigator determined the subject met all other inclusion/exclusion criteria.
g. Reproductive hormones in males only (FSH, LH, total testosterone, and inhibin B). Samples were collected between 8:00AM and 12:00 PM.
h. Samples were collected at Week 4, Week 12, and Week 24 only.
i. Week 36 only.
j. Women aged >45 and amenorrheic for >2 years only.
k. Including AFP, ANA, HbA1c, and creatinine clearance.
l. Serum pregnancy test at screening, urine pregnancy test at all other visits for women of child bearing potential only.
m. During the Week 0 (Day 1) and Weeks 2, 12, and 24 visits, the morning dose of filibuvir/placebo was administered in the clinic and 2 venous blood samples were drawn from each subject for filibuvir determination. The times of draws for the 2 samples were as far apart as possible and were separated by at least 30 minutes. It was recommended that the first sample be obtained as soon as possible upon arrival and, if possible, before administering filibuvir/placebo, and that the second sample be obtained immediately prior to leaving the clinic but at least 30 minutes following the administration of filibuvir. During each of the Weeks 4, 8, 16, and 20 visits, 1 venous blood sample was taken from each subject for filibuvir determination.
n. Early termination only if visit occurred ≤24 weeks.
o. Samples for IP-10 and OAS2 biomarkers were collected at Weeks 0 (predose), 4, 8, 12, 16, 20, and 24.
p. Filibuvir or placebo was administered orally, BID through Week 24; pegIFN was administered subcutaneously weekly through Week 48; RBV was administered orally, BID through Week 48.

Number of Subjects (Planned and Analyzed): It was planned to screen approximately 443 subjects in order to randomize 288 subjects to 3 treatment arms in a 1:1:1 ratio of 96 subjects per group. A total of 498 subjects were actually screened, 288 subjects were randomized (96 subjects to each treatment group), and all were treated.

The randomized subjects included 111 in the United States, 44 in Canada, 37 in France, 26 in Spain, 25 in Republic of Korea, 16 in Germany, 15 in Belgium, and 14 in Hungary.

Diagnosis and Main Criteria for Inclusion: Male or female subjects at least 18 years of age who were HCV seropositive with HCV RNA >10,000 IU/mL at screening, and HCV Genotype 1. Subjects infected with a non-genotype 1 strain or mixed genotypes were not eligible. Subjects were to be treatment naïve (no prior treatment with IFN alfa +/ RBV regimens or investigational anti-HCV agents). Subjects were to have had a liver biopsy within 2 years (24 months) of screening with non-cirrhotic fibrosis classification. For those subjects with liver biopsy outside of the time window or for those subjects with no history of liver biopsy, a biopsy had to be performed prior to randomization. Ultrasound within 6 months of screening for 1) those subjects with bridging fibrosis or 2) those subjects with alpha-fetoprotein (AFP) >50 and <100 ng/mL with no evidence of hepatocellular carcinoma. For those subjects with an ultrasound conducted outside the 6 month time window, an ultrasound had to be performed prior to randomization.

Exclusion criteria included pregnant or nursing females, and males whose female partner was pregnant, co-infection with Human Immunodeficiency Virus or hepatitis B virus, liver disease unrelated to HCV infection, evidence of severe or decompensated liver disease, pre-existing medical conditions or laboratory abnormality at screening that made the subject unsuitable for treatment with pegIFN/RBV therapy per product labeling, abnormal electrocardiogram (ECG) suggestive of clinically significant cardiac disease or QT interval corrected for heart rate (QTc) >450 msec, history of organ transplant, use of contraindicated medications being taken by the subject at the time of randomization that had to be continued during the study period, including potent Cytochrome P450 (CYP)3A4 inhibitors, sensitive CYP3A4 substrates, CYP3A4 substrates with narrow therapeutic range and CYP3A4 inducers, and active alcohol or substance abuse sufficient, in the Investigator's judgment, to prevent adherence to study medication and/or follow-up.

Study Treatment: Subjects were randomly assigned to receive either filibuvir (300 or 600 mg BID) or placebo BID for 24 weeks in combination with pegIFN (Pegasys; 180 μg subcutaneously given once weekly) and RBV (Copegus; 1000 mg/day for subjects weighing ≤75 kg; 1200 mg/day for subjects weighing >75 kg; given as divided doses) for 24 or 48 weeks. Treatment with pegIFN/RBV through Week 48 continued based on assessment of viral response.

Efficacy and Pharmacokinetic Endpoints:

Primary Endpoint:

- Proportion of subjects with undetectable HCV RNA (HCV RNA <15 IU/mL) at Week 72 (SVR).

Secondary Endpoints:

- Proportion of subjects with undetectable HCV RNA at Weeks 4 (rapid viral response; RVR), 12 (early viral response; EVR), 24 and 48 (Path 2 only).
- Proportion of subjects with undetectable HCV RNA 12 weeks following the completion of therapy (SVR_{12}).
- Proportion of subjects with undetectable HCV RNA 24 weeks following the completion of therapy (SVR_{24}; Path 1 only).
- Proportion of subjects with breakthrough viremia: >2-log increase from nadir in HCV plasma RNA or HCV RNA that becomes undetectable with treatment but becomes persistently detectable (two or more consecutive viral RNA measurements >1,000 IU/mL) again during treatment.
- Proportion of subjects with relapsed response: HCV RNA that is undetectable at end of treatment (Week 24 or 48) that becomes detectable during the off-treatment follow up period.
- Change in HCV RNA concentrations from Baseline at Week 4, 12 and 24.
- Safety: severity and relationship of adverse events (AEs) to test drug, serious adverse events (SAEs), discontinuations due to AEs, dose reductions due to AEs, and severity of abnormal laboratory values.
- Filibuvir, pegylated interferon (IFN) and ribavirin (RBV) concentrations.

Safety Evaluations: Safety evaluations included vital signs (supine blood pressure [BP], pulse rate, and temperature), 12-lead ECGs, AEs, SAEs, physical examination, laboratory evaluations, reproductive hormones in males, and semen parameters (US male subjects participating in semen sub-study only).

Statistical Methods: The following populations were analyzed in this study:

- Full analysis set (FAS): All randomized subjects who took at least 1 dose of study medication. Subjects in the FAS were analyzed based on the treatment assignment in the randomization scheme. The "FAS analyzed as randomized" was referred to as "Intent-to-Treat" (ITT).
- Per protocol analysis set (PPS): All subjects in the FAS who met the additional criteria of no major protocol violations that could have had an impact on the efficacy endpoints.
- Safety population: All subjects who were randomized and received at least 1 dose of study medication were included in the safety analyses and listings.

Efficacy analyses on HCV RNA data were performed using the ITT population. Additional supportive analyses on the primary endpoint were performed using the PPS. For analysis of

binary data, a responder was a subject with undetectable HCV RNA or who had achieved SVR, SVR_{12}, SVR_{24}, SVR_{last}, or end of treatment (EOT) response.

For all binary endpoints, the specified time points for each treatment group, or subgroups within a treatment group, the following descriptive statistics were presented: sample size (N); number of responders; proportion of responders; and 2-sided 80% confidence intervals (CIs) for the proportion of responders using the normal approximation to the binomial. The final results were expressed in percentages. If the lower confidence limit was <0, it was set to 0. If the upper confidence limit was >100%, it was set to 100%.

The comparison of responders (each filibuvir arm against the placebo arm) was based on constructing the 2-sided 80% CI for the difference in response rates at the specified time points, adjusting for randomization strata (ie, screening HCV RNA <400,000 IU/mL vs ≥400,000 IU/mL), using the normal approximation to the binomial distribution. The stratified analysis involved the use of weighted averages for each endpoint, with the Cochran-Mantel-Haenszel stratum weight.

The continuous endpoint was change from Baseline $\log_{10}$ HCV RNA at Weeks 4, 12, and 24. For the continuous endpoint, the following descriptive statistics were available for baseline, if applicable, and at post-baseline assessment time points: sample size, mean, standard deviation, coefficient of variation, minimum, 25th percentiles, median, 75th percentiles, and maximum. For the semen endpoints, a 2-sided 95% CI was constructed for the median change from baseline using the method of McGill, Tukey, and Larsen.

Adverse events (AEs) were coded by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities version 14.1. ECG abnormalities of prolonged QTc interval were graded according to the Common Terminology Criteria for AEs version 4.03. Laboratory test abnormalities were graded according to the Division of Acquired Immunodeficiency Syndrome Table for Grading the Severity of Adult and Pediatric Adverse Events, version 1.0.

There was no statistical analysis of PK data in this study. The PK results were presented in a separate report.

RESULTS

Subject Disposition and Demography: The numbers of subjects who were treated, completed, and discontinued from the study are summarized for each treatment in Table 4.

Table 4. Subject Disposition and Data Analysis Sets

Number (%) Subjects	Filibuvir 300 mg	Filibuvir 600 mg	Placebo
Screened 498			
Assigned to treatment	96	96	96
Treated	96	96	96
Completed study	39 (40.6)	41 (42.7)	45 (46.9)
Discontinuations			
Related to study treatment	21 (21.9)	17 (17.7)	27 (28.1)
AE	9 (9.4)	8 (8.3)	7 (7.3)
Insufficient virologic response	10 (10.4)	7 (7.3)	12 (12.5)
Virologic breakthrough	2 (2.1)	2 (2.1)	8 (8.3)
Not related to study treatment	36 (37.5)	38 (39.6)	24 (25.0)
AE	1 (1.0)	1 (1.0)	1 (1.0)
Lost to follow-up	10 (10.4)	6 (6.3)	2 (2.1)
No longer willing to participate	6 (6.3)	9 (9.4)	9 (9.4)
Other	0	2 (2.1)	5 (5.2)
Protocol violation	1 (1.0)	0	2 (2.1)
Subject relapsed	18 (18.8)	20 (20.8)	5 (5.2)
Total Discontinuations	57 (59.4)	55 (57.3)	51 (53.1)
Analyzed for efficacy			
Intent-to-treat[a]	96	96	96
Per-protocol analysis set[b]	83 (86.5)	81 (84.4)	84 (87.5)
Analyzed for safety			
Adverse events	96 (100.0)	96 (100.0)	96 (100.0)
Laboratory data	94 (97.9)	96 (100.0)	96 (100.0)
ECG	96 (100.0)	96 (100.0)	96 (100.0)
Vital signs	96 (100.0)	96 (100.0)	96 (100.0)

AE = adverse event; ECG = electrocardiogram; ITT = intent-to-treat; PPS = per-protocol analysis set.

a. The full (ITT) and safety analysis sets consisted of all subjects who received at least 1 dose of study medication.

b. The PPS consisted of subjects in the ITT population who had no major protocol violations that could have had an impact on efficacy endpoints.

A summary of demographic and baseline characteristics is presented in Table 5.

Table 5. Demographic and Baseline Characteristics

Parameters	Filibuvir 300 mg (N=96)	Filibuvir 600 mg (N=96)	Placebo (N=96)
Gender, n (%)			
Male	52 (54.2)	49 (51.0)	52 (54.2)
Female	44 (45.8)	47 (49.0)	44 (45.8)
Age (years)			
Mean [SD]	46.7 [11.0]	48.8 [10.0]	48.0 [10.3]
Range	20-72	19-70	18-67
Race, n (%)			
White	73 (76.0)	77 (80.2)	77 (80.2)
Black	7 (7.3)	5 (5.2)	6 (6.3)
Asian	9 (9.4)	10 (10.4)	11 (11.5)
Other	4 (4.2)	3 (3.1)	1 (1.0)
Unspecified[a]	3 (3.1)	1 (1.0)	1 (1.0)
Region, n (%)			
North America	50 (52.1)	53 (55.2)	52 (54.2)
Europe	39 (40.6)	34 (35.4)	35 (36.5)
Korea	7 (7.3)	9 (9.4)	9 (9.4)
Body weight (kg)			
Mean [SD]	79.1 [16.8]	77.6 [18.9]	78.7 [18.2]
Range	42.0-127.4	47.0-188.6	46.0-124.6
HCV genotype, n (%)			
1A	46 (47.9)	46 (47.9)	52 (54.2)
1B	48 (50.0)	50 (52.1)	43 (44.8)
Other[b]	2 (2.1)	0	1 (1.0)
Liver fibrosis score, n (%)			
No/mild fibrosis	81 (84.4)	77 (80.2)	82 (85.4)
Moderate/severe fibrosis	15 (15.6)	18 (18.8)	14 (14.6)
Screening viral load (IU/mL), n (%)			
≤400,000	18 (18.8)	18 (18.8)	19 (19.8)
>400,000	78 (81.3)	78 (81.3)	77 (80.2)
Log_{10} screening viral load (IU/mL), median (interquatile)	6.3 (5.8, 6.6)	6.2 (5.8, 6.4)	6.3 (5.7, 6.6)

HCV = hepatitis C virus; N = total number of subjects; n = number of subjects with observation; SD = standard deviation

a. Per Belgian privacy law, race was not collected for some subjects; their race was entered as "unspecified".
b. Other includes 1, 1H, and 6.

Efficacy Results:

Primary Endpoint: In the primary analysis of the percentage of subjects in the ITT population with SVR with missing data imputed as failure, 41.7% of subjects in the filibuvir 300 mg group, 39.6% of subjects in the filibuvir 600 mg group, and 45.8% of subjects in the placebo group, achieved SVR. As shown in Table 6, the 80% CIs for the differences in the percentage of subjects with SVR between the filibuvir groups and the placebo group included 0; thus, the primary objective of the study (ie, to determine whether the addition of filibuvir to a regimen of pegIFN/RBV would increase the proportion of subjects who achieved SVR) was not met. Results for the PPS supported those for the ITT population.

Table 6. Percentage of Subjects With SVR by Treatment Group (ITT Population, Method 1 for Missing Data) – Primary Analysis

Treatment Group	N	n (%)	Difference % (80% CI)*
Filibuvir 300 mg	96	40 (41.7)	-4.0 (-13.0, 5.1)
Filibuvir 600 mg	96	38 (39.6)	-6.1 (-15.2, 3.0)
Placebo	96	44 (45.8)	NA

*CMH estimates adjusted for screening HCV RNA (≤400,000 vs >400,000 IU/mL). Difference is the percentage difference between the filibuvir and placebo groups.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; HCV = hepatitis C virus; ITT = intent-to-treat; N = number of subjects in the ITT population; n = number of subjects with SVR; NA = not applicable; RNA = ribonucleic acid; SVR = sustained viral response.

Secondary Endpoints: The percentage of subjects with undetectable HCV RNA at Weeks 4, 12, and 24 by treatment group in the ITT population is presented in Table 7. The percentage of subjects with undetectable HCV RNA at Weeks 4 and 12 in the filibuvir groups was higher than in the placebo group, as the 80% CI for the difference in the percentage between each filibuvir group and the placebo group excluded 0. The percentage of subjects with undetectable HCV RNA at Week 24 in the filibuvir groups was comparable to the placebo group, as the 80% CI for the difference in the percentage between each filibuvir group and the placebo group included 0.

Table 7. Percentage of Subjects With Undetectable HCV RNA at Weeks 4, 12, and 24 (ITT Population)

Visit	Treatment Group	N	n (%)	Difference % (80% CI)•
Week 4	Filibuvir 300 mg	96	56 (58.3)	30.5 (22.1, 38.9)
	Filibuvir 600 mg	96	59 (61.5)	33.7 (25.5, 41.9)
	Placebo	96	27 (28.1)	NA
Week 12	Filibuvir 300 mg	96	73 (76.0)	8.6 (0.5, 16.7)
	Filibuvir 600 mg	96	75 (78.1)	10.6 (2.6, 18.6)
	Placebo	96	65 (67.7)	NA
Week 24	Filibuvir 300 mg	96	71 (74.0)	-3.0 (-10.8, 4.9)
	Filibuvir 600 mg	96	73 (76.0)	-1.0 (-8.7, 6.8)
	Placebo	96	74 (77.1)	NA

•CMH estimates adjusted for screening HCV RNA (≤400,000 vs >400,000 IU/mL). Difference is the percentage difference between the filibuvir and placebo groups.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; HCV = hepatitis C virus; ITT = intent-to-treat; N = number of subjects in the ITT population; n = number of subjects with undetectable HCV RNA; NA = not applicable; RNA = ribonucleic acid.

The percentage of Path 2 subjects with undetectable HCV RNA at Week 48 is presented by treatment group in Table 8. The majority of subjects who were treated with filibuvir maintained viral suppression to Week 48.

Table 8. Percentage of Subjects With Undetectable HCV RNA at Week 48 by Treatment Group (Path 2 Subjects Only)

Treatment Group	N	n (%)
Filibuvir 300 mg	26	19 (73.1)
Filibuvir 600 mg	27	24 (88.9)
Placebo	76	60 (79.0)

HCV = hepatitis C virus; N = number of Path 2 subjects; n = number of subjects with undetectable HCV RNA at Week 48; RNA = ribonucleic acid.

The percentage of subjects with SVR_{12} by treatment group in the ITT population is presented in Table 9. The percentage of subjects with SVR_{12} in the filibuvir groups was comparable to the percentage of subjects with SVR_{12} in the placebo group, as the 80% CI for the difference in the percentage between each filibuvir group and the placebo group included 0.

Table 9. Percentage of Subjects With SVR_{12} (ITT Population)

Treatment Group	N	n (%)	Difference % (80% CI)*
Filibuvir 300 mg	96	41 (42.7)	-2.9 (-12.0, 6.2)
Filibuvir 600 mg	96	43 (44.8)	-0.9 (-10.0, 8.2)
Placebo	96	44 (45.8)	NA

∗CMH estimates adjusted for screening HCV RNA (≤400,000 vs >400,000 IU/mL). Difference is the percentage difference between the filililbuvir and placebo groups.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; N = number of subjects in the ITT population; n = number of subjects with SVR_{12}; NA = not applicable; SVR_{12} = sustained viral response at 12 weeks following the completion of therapy.

The percentage of subjects with SVR_{24} in the ITT population was comparable across treatment groups (42.7%, 42.7%, and 45.8% for the filibuvir 300 mg, filibuvir 600 mg, and placebo groups, respectively; Table 10).

Table 10. Percentage of Subjects With SVR_{24} by Treatment Group - ITT

Treatment Group	N	n (%)	80% CI
Filibuvir 300 mg	96	41 (42.7)	(36.2, 49.2)
Filibuvir 600 mg	96	41 (42.7)	(36.2, 49.2)
Placebo	96	44 (45.8)	(39.3, 52.3)

CI = confidence interval; ITT = intent-to-treat; N = total number of subjects; n = number of subjects with prespecified criteria.

In general, subjects with the host IL28B cytidine-cytidine (CC) genotype had better efficacy (SVR, SVR_{12}, and proportions of undetectable HCV RNA at Weeks 4 and 12) than those with non-CC genotypes.

In the ITT population, there were 4 subjects (4.2%) each in the filibuvir 300 mg and 600 mg groups and 7 subjects (7.3%) in the placebo group with breakthrough viremia (Table 11). Two subjects (2.1%) in each filibuvir group and 8 subjects (8.3%) in the placebo group discontinued the study due to virologic breakthrough (Table 4).

Table 11. Percentage of Subjects With Breakthrough Viremia (Derived) by Treatment Group - ITT

Treatment Group	N	n (%)	80% CI
Filibuvir 300 mg	96	4 (4.2)	(1.6, 6.8)
Filibuvir 600 mg	96	4 (4.2)	(1.6, 6.8)
Placebo	96	7 (7.3)	(3.9, 10.7)

CI = confidence interval; ITT = intent-to-treat; N = total number of subjects; n = number of subjects with prespecified criteria.

Change from Baseline in $\log_{10}$ HCV RNA at each visit up to Week 24 (ITT population) is presented in Table 12. At Week 4, there was a greater mean reduction from Baseline in $\log_{10}$ HCV RNA in the filibuvir groups than in the placebo group (-4.0 in the filibuvir 300 mg group, -4.2 in the filibuvir 600 mg group, and -3.0 in the placebo group). However, the changes were similar between each filibuvir group and the placebo group at Weeks 12 and 24.

Table 12. Summary of Change From Baseline $\log_{10}$ HCV RNA at Each Visit up to Week 24 by Treatment Group -ITT

Week	Treatment Group	N	Mean	SD	Median
Week 2	Filibuvir 300 mg	96	-3.6	1.4	-3.5
	Filibuvir 600 mg	96	-3.9	1.0	-3.9
	Placebo	96	-2.1	1.3	-2.0
Week 4	Filibuvir 300 mg	96	-4.0	1.6	-4.4
	Filibuvir 600 mg	96	-4.2	1.2	-4.5
	Placebo	96	-3.0	1.6	-3.2
Week 8	Filibuvir 300 mg	96	-4.2	1.7	-4.8
	Filibuvir 600 mg	96	-4.3	1.4	-4.7
	Placebo	96	-3.7	1.6	-4.2
Week 12	Filibuvir 300 mg	96	-4.1	1.8	-4.8
	Filibuvir 600 mg	96	-4.2	1.6	-4.9
	Placebo	96	-3.9	1.7	-4.3
Week 16	Filibuvir 300 mg	96	-3.9	2.0	-4.8
	Filibuvir 600 mg	96	-4.0	1.8	-4.7
	Placebo	96	-4.0	1.8	-4.6
Week 20	Filibuvir 300 mg	96	-3.7	2.2	-4.7
	Filibuvir 600 mg	96	-4.0	2.0	-4.9
	Placebo	96	-3.9	1.9	-4.6
Week 24	Filibuvir 300 mg	96	-3.7	2.2	-4.7
	Filibuvir 600 mg	96	-3.8	2.1	-4.8
	Placebo	96	-3.9	2.0	-4.6

Baseline was calculated as the average of Screening and Day 1 pre-dose measurements.
HCV = Hepatitis C virus; ITT = intent-to-treat; N = total number of subjects; n = number of subjects with prespecified criteria; RNA = ribonucleic acid; SD = standard deviation.

The percentage of subjects with EOT response by treatment group in the ITT population is presented in Table 13. The percentage of subjects with EOT response in the filibuvir 600 mg group was higher than the placebo group, as the 80% CI for the difference in the percentage between the filibuvir 600 mg group and the placebo group excluded 0. The percentage of subjects with EOT response in the filibuvir 300 mg group was comparable to the placebo group, as the 80% CI for the difference in the percentage between the filibuvir 300 mg group and the placebo group included 0.

Table 13. Percentage of Subjects With EOT Response (ITT Population)

Treatment Group	N	n (%)	Difference % (80% CI)*
Filibuvir 300 mg	96	64 (66.7)	4.4 (-4.4, 13.1)
Filibuvir 600 mg	96	71 (74.0)	11.6 (3.1, 20.0)
Placebo	96	60 (62.5)	NA

*CMH estimates adjusted for screening HCV RNA (≤400,000 vs >400,000 IU/mL). Difference is the percentage difference between the filibuvir and placebo groups.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EOT = end-of-treatment; HCV = hepatitis C virus; ITT = intent-to-treat; N = number of subjects in the ITT population; n = number of subjects with EOT response; NA = not applicable; RNA = ribonucleic acid.

The percentage of relapsed subjects among EOT completers with EOT HCV RNA <15 IU/mL overall and by subgroup is presented in Table 14. Overall, the percentage of relapsed subjects in the filibuvir groups was higher than in the placebo group. Eighteen subjects (18.8% in the filibuvir 300 mg group, 20 subjects (20.8%) in the filibuvir 600 mg group and 5 subjects (5.2%) in the placebo group discontinued from the study due to relapse (Table 4).

Table 14. Percentage of Relapsed Subjects (Derived) Among EOT Completers With EOT HCV RNA <15 IU/mL

Subgroup	Filibuvir 300 mg		Filibuvir 600 mg		Placebo	
	N	n (%)	N	n (%)	N	n (%)
Overall	64	23 (35.9)	70	30 (42.9)	59	15 (25.4)
Screening viral load						
≤400,000 IU/mL	13	3 (23.1)	12	3 (25.0)	15	3 (20.0)
>400,000 IU/mL	51	20 (39.2)	58	27 (46.6)	44	12 (27.3)
Liver fibrosis score						
No/mild	53	20 (37.7)	59	24 (40.7)	49	12 (24.5)
Moderate/severe	11	3 (27.3)	11	6 (54.6)	10	3 (30.0)
HCV genotype						
1A	25	13 (52.0)	34	14 (41.2)	33	5 (15.2)
1B	39	10 (25.6)	36	16 (44.4)	26	10 (38.5)
Treatment path						
Path 1	45	12 (26.7)	46	16 (34.8)	—	—
Path 2	19	11 (57.9)	24	14 (58.3)	59	15 (25.4)

CI = confidence interval; EOT = end-of-treatment; HCV = hepatitis C virus; N = number of subjects that were EOT completers with EOT HCV RNA <15 IU/mL; n = number of relapsed subjects among EOT completers with EOT HCV RNA <15 IU/mL; RNA = ribonucleic acid.

Safety Results: The incidence of all-causality and treatment-related (which includes any therapy in the regimen [ie, filibuvir/placebo, pegIFN, RBV]) treatment-emergent adverse events (TEAEs) by treatment group is presented in Table 15. At least 1 TEAE was reported by 91.7% of subjects in the filibuvir 300 mg group and 95.8% of subjects each in the filibuvir 600 mg and placebo groups. Twice as many subjects in the filibuvir 300 mg group (14.6%) reported serious TEAEs, as compared to the filibuvir 600 mg and placebo groups (7.3% in each). The majority of TEAEs were assessed as mild or moderate. Severe TEAEs were reported in similar proportions of subjects across treatment groups.

Table 15. Incidence of Treatment-Emergent Adverse Events in Subjects Receiving Any Therapy (All-Causality and Treatment-Related[a])

		Filibuvir 300 mg (N=96)	Filibuvir 600 mg (N=96)	Placebo (N=96)
Number of AEs	All causality	861	920	951
	Treatment-related	661	704	741
Number (%) of subjects:				
With AEs	All causality	88 (91.7)	92 (95.8)	92 (95.8)
	Treatment-related	85 (88.5)	88 (91.7)	91 (94.8)
With SAEs	All causality	14 (14.6)	7 (7.3)	7 (7.3)
	Treatment-related	5 (5.2)	3 (3.1)	1 (1.0)
With severe AEs	All causality	21 (21.9)	15 (15.6)	18 (18.8)
	Treatment-related	14 (14.6)	10 (10.4)	11 (11.5)
Discontinued from study due to AEs	All causality	10 (10.4)	9 (9.4)	8 (8.3)
	Treatment-related	9 (9.4)	8 (8.3)	7 (7.3)
Discontinued any therapy due to AEs	All causality	12 (12.5)	12 (12.5)	12 (12.5)
	Treatment-related	10 (10.4)	9 (9.4)	9 (9.4)
Dose reduced or temporarily discontinued from any therapy due to AEs	All causality	28 (29.2)	22 (22.9)	28 (29.2)
	Treatment-related	26 (27.1)	21 (21.9)	26 (27.1)

With the exception of the number of AEs, subjects are counted once per treatment in each row.
SAE and AE are not separated out in this table.
AE = adverse event; IFN = interferon-α; ITT = intent-to-treat; N = number of subjects in the ITT population; RBV = ribavirin; SAE = serious adverse event.
a. Treatment-related AEs can be related to any therapy in the regimen [ie, filibuvir/placebo, pegIFN, RBV].

Table 16. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥5%

System Organ Class MedDRA Preferred Term	Filibuvir 300 mg n (%)	Filibuvir 600 mg n (%)	Placebo n (%)
Number (%) of subjects: evaluable for AEs	96	96	96
Number (%) of subjects: with AEs	85 (88.5)	89 (92.7)	90 (93.8)
Blood and lymphatic system disorders	26 (27.1)	26 (27.1)	34 (35.4)
Anaemia	15 (15.6)	11 (11.5)	16 (16.7)
Leukopenia	4 (4.2)	5 (5.2)	6 (6.3)
Lymphopenia	5 (5.2)	3 (3.1)	3 (3.1)
Neutropenia	15 (15.6)	11 (11.5)	20 (20.8)
Thrombocytopenia	2 (2.1)	6 (6.3)	3 (3.1)
Ear and labyrinth disorders	3 (3.1)	3 (3.1)	9 (9.4)
Tinnitus	1 (1.0)	0	5 (5.2)
Vertigo	2 (2.1)	3 (3.1)	5 (5.2)
Endocrine Disorders	0	2 (2.1)	6 (6.3)
Hypothyroidism	0	2 (2.1)	6 (6.3)
Eye disorders	5 (5.2)	8 (8.3)	10 (10.4)
Dry eye	2 (2.1)	3 (3.1)	5 (5.2)
Vision blurred	3 (3.1)	5 (5.2)	5 (5.2)
Gastrointestinal disorders	45 (46.9)	57 (59.4)	55 (57.3)
Abdominal pain	6 (6.3)	3 (3.1)	4 (4.2)
Abdominal pain upper	11 (11.5)	10 (10.4)	4 (4.2)
Aphthous stomatitis	2 (2.1)	7 (7.3)	4 (4.2)
Constipation	7 (7.3)	3 (3.1)	10 (10.4)
Diarrhoea	14 (14.6)	10 (10.4)	17 (17.7)
Dry mouth	7 (7.3)	7 (7.3)	4 (4.2)
Dyspepsia	5 (5.2)	6 (6.3)	7 (7.3)
Nausea	20 (20.8)	35 (36.5)	30 (31.3)
Stomatitis	3 (3.1)	2 (2.1)	5 (5.2)
Vomiting	9 (9.4)	11 (11.5)	13 (13.5)
General disorders and administration site conditions	68 (70.8)	71 (74.0)	77 (80.2)
Asthenia	16 (16.7)	19 (19.8)	20 (20.8)
Chills	11 (11.5)	14 (14.6)	12 (12.5)
Fatigue	36 (37.5)	37 (38.5)	36 (37.5)
Influenza like illness	15 (15.6)	14 (14.6)	19 (19.8)
Injection site reaction	4 (4.2)	4 (4.2)	5 (5.2)
Irritability	14 (14.6)	19 (19.8)	15 (15.6)
Oedema peripheral	2 (2.1)	7 (7.3)	4 (4.2)
Pain	4 (4.2)	5 (5.2)	8 (8.3)
Pyrexia	14 (14.6)	14 (14.6)	15 (15.6)
Infections and infestations	7 (7.3)	9 (9.4)	6 (6.3)
Bronchitis	4 (4.2)	5 (5.2)	1 (1.0)
Influenza	3 (3.1)	4 (4.2)	5 (5.2)
Investigations	13 (13.5)	8 (8.3)	10 (10.4)
Weight decreased	13 (13.5)	7 (7.3)	5 (5.2)
White blood cell count decreased	0	1 (1.0)	5 (5.2)
Metabolism and nutrition disorders	20 (20.8)	16 (16.7)	23 (24.0)
Decreased appetite	20 (20.8)	16 (16.7)	23 (24.0)

Table 16. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥5%

System Organ Class MedDRA Preferred Term	Filibuvir 300 mg n (%)	Filibuvir 600 mg n (%)	Placebo n (%)
Musculoskeletal and connective tissue disorders	25 (26.0)	35 (36.5)	35 (36.5)
Arthralgia	13 (13.5)	17 (17.7)	16 (16.7)
Back pain	8 (8.3)	8 (8.3)	8 (8.3)
Myalgia	17 (17.7)	20 (20.8)	25 (26.0)
Nervous system disorders	44 (45.8)	51 (53.1)	43 (44.8)
Disturbance in attention	2 (2.1)	7 (7.3)	1 (1.0)
Dizziness	12 (12.5)	8 (8.3)	12 (12.5)
Dysgeusia	16 (16.7)	24 (25.0)	5 (5.2)
Headache	28 (29.2)	33 (34.4)	35 (36.5)
Syncope	5 (5.2)	1 (1.0)	1 (1.0)
Psychiatric disorders	41 (42.7)	37 (38.5)	39 (40.6)
Anxiety	6 (6.3)	3 (3.1)	7 (7.3)
Depression	21 (21.9)	10 (10.4)	12 (12.5)
Insomnia	24 (25.0)	31 (32.3)	28 (29.2)
Sleep disorder	5 (5.2)	2 (2.1)	4 (4.2)
Respiratory, thoracic and mediastinal disorders	27 (28.1)	35 (36.5)	47 (49.0)
Cough	15 (15.6)	18 (18.8)	21 (21.9)
Dyspnoea	9 (9.4)	9 (9.4)	18 (18.8)
Dyspnoea exertional	6 (6.3)	6 (6.3)	4 (4.2)
Epistaxis	1 (1.0)	5 (5.2)	7 (7.3)
Oropharyngeal pain	3 (3.1)	6 (6.3)	8 (8.3)
Skin and subcutaneous tissue disorders	59 (61.5)	57 (59.4)	61 (63.5)
Alopecia	18 (18.8)	16 (16.7)	24 (25.0)
Dermatitis	0	2 (2.1)	5 (5.2)
Dry skin	20 (20.8)	13 (13.5)	19 (19.8)
Eczema	6 (6.3)	5 (5.2)	2 (2.1)
Erythema	3 (3.1)	5 (5.2)	3 (3.1)
Night sweats	3 (3.1)	1 (1.0)	5 (5.2)
Pruritus	27 (28.1)	29 (30.2)	19 (19.8)
Rash	12 (12.5)	22 (22.9)	18 (18.8)
Rash pruritic	0	3 (3.1)	6 (6.3)

Subjects are only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (version 14.1) coding dictionary applied.
MeDRA = Medical Dictionary for Regulatory Activities; n = subjects with specified criteria.

TEAEs that were considered treatment-related (ie, related to any therapy in the regimen) in subjects in any treatment group are summarized in Table 17.

Table 17. Incidence and Severity of Treatment-Emergent Adverse Events (Treatment Related - Any Therapy) for Events Having a Frequency Rate ≥5%

System Organ Class and MedDRA Preferred Term	Filibuvir 300 mg (N=96) n (%)	Filibuvir 600 mg (N=96) n (%)	Placebo (N=96) n (%)
Blood and lymphatic system disorders	29 (30.2)	26 (27.1)	36 (37.5)
Anaemia	15 (15.6)	11 (11.5)	16 (16.7)
Leukopenia	4 (4.2)	5 (5.2)	6 (6.3)
Lymphopenia	5 (5.2)	3 (3.1)	3 (3.1)
Thrombocytopenia	2 (2.1)	6 (6.3)	3 (3.1)
Neutropenia	15 (15.6)	11 (11.5)	20 (20.8)
Endocrine disorders	1 (1.0)	2 (2.1)	5 (5.2)
Hypothyroidism	0	2 (2.1)	5 (5.2)
Eye disorders	11 (11.5)	10 (10.4)	15 (15.6)
Vision blurred	2 (2.1)	4 (4.2)	5 (5.2)
Gastrointestinal disorders	49 (51.0)	55 (57.3)	54 (56.3)
Abdominal pain upper	10 (10.4)	6 (6.3)	4 (4.2)
Aphthous stomatitis	2 (2.1)	6 (6.3)	2 (2.1)
Constipation	3 (3.1)	1 (1.0)	7 (7.3)
Diarrhoea	10 (10.4)	8 (8.3)	11 (11.5)
Dry mouth	7 (7.3)	6 (6.3)	4 (4.2)
Dyspepsia	5 (5.2)	6 (6.3)	5 (5.2)
Nausea	20 (20.8)	34 (35.4)	26 (27.1)
Vomiting	6 (6.3)	8 (8.3)	11 (11.5)
General disorders and administration site conditions	66 (68.8)	71 (74.0)	79 (82.3)
Asthenia	16 (16.7)	19 (19.8)	20 (20.8)
Chills	10 (10.4)	14 (14.6)	12 (12.5)
Fatigue	34 (35.4)	35 (36.5)	35 (36.5)
Influenza like illness	15 (15.6)	14 (14.6)	19 (19.8)
Injection site reaction	4 (4.2)	3 (3.1)	5 (5.2)
Irritability	14 (14.6)	19 (19.8)	15 (15.6)
Pyrexia	13 (13.5)	14 (14.6)	14 (14.6)
Pain	2 (2.1)	5 (5.2)	8 (8.3)
Investigations	19 (19.8)	14 (14.6)	14 (14.6)
Weight decreased	12 (12.5)	7 (7.3)	5 (5.2)
White blood cell count decreased	0	1 (1.0)	5 (5.2)
Metabolism and nutrition disorders	20 (20.8)	16 (16.7)	25 (26.0)
Decreased appetite	19 (19.8)	15 (15.6)	22 (22.9)
Musculoskeletal and connective tissue disorders	28 (29.2)	29 (30.2)	32 (33.3)
Arthralgia	10 (10.4)	12 (12.5)	13 (13.5)
Myalgia	17 (17.7)	20 (20.8)	24 (25.0)
Nervous system disorders	44 (45.8)	52 (54.2)	47 (49.0)
Disturbance in attention	2 (2.1)	7 (7.3)	1 (1.0)
Dizziness	9 (9.4)	6 (6.3)	11 (11.5)
Dysgeusia	16 (16.7)	24 (25.0)	5 (5.2)
Headache	24 (25.0)	31 (32.3)	31 (32.3)
Psychiatric disorders	45 (46.9)	46 (47.9)	46 (47.9)
Anxiety	6 (6.3)	3 (3.1)	7 (7.3)
Depression	18 (18.8)	9 (9.4)	12 (12.5)
Insomnia	24 (25.0)	31 (32.3)	26 (27.1)
Respiratory, thoracic and mediastinal disorders	22 (22.9)	27 (28.1)	42 (43.8)
Cough	14 (14.6)	12 (12.5)	18 (18.8)

Table 17. Incidence and Severity of Treatment-Emergent Adverse Events (Treatment Related - Any Therapy) for Events Having a Frequency Rate ≥5%

System Organ Class and MedDRA Preferred Term	Filibuvir 300 mg (N=96) n (%)	Filibuvir 600 mg (N=96) n (%)	Placebo (N=96) n (%)
Dyspnoea	5 (5.2)	7 (7.3)	15 (15.6)
Dyspnoea exertional	6 (6.3)	6 (6.3)	4 (4.2)
Epistaxis	0	4 (4.2)	5 (5.2)
Skin and subcutaneous tissue disorders	58 (60.4)	58 (60.4)	60 (62.5)
Alopecia	17 (17.7)	14 (14.6)	23 (24.0)
Dry skin	18 (18.8)	13 (13.5)	18 (18.8)
Erythema	1 (1.0)	5 (5.2)	1 (1.0)
Pruritus	26 (27.1)	29 (30.2)	19 (19.8)
Rash	12 (12.5)	20 (20.8)	18 (18.8)
Rash pruritic	0	3 (3.1)	6 (6.3)

AEs and SAEs are not separated out in this table.
Subjects are counted only once per treatment in each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (version 14.1) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the safety population; n = number of subjects with AEs; SAE = serious adverse event.

Details of SAEs reported during the study are presented in Table 18. None of the reported SAEs were attributed to filibuvir by the Investigator, and none had a fatal outcome.

Table 18. Serious Adverse Events

Serial Number	Therapy Stop Day[a]	Event Onset Day[b]	MedDRA Preferred Term[c]	Causality[d]	Clinical Outcome[e]	Seriousness
Filibuvir 300 mg						
1	183	22	Haematochezia	Unrelated	Resolved	Hospitalization
2	92	106	Cardiac neurosis	Unrelated	Resolved	Hospitalization
3	176	331	Abortion spontaneous	Unrelated	Resolved	Important medical event
4	336	280	BUN/creatinine ratio increased	Unrelated	Resolved	Important medical event
5	224	217	Cerebrovascular accident	Unrelated	Resolved with sequelae	Hospitalization
6	112	50	Rectal haemorrhage	Unrelated	Resolved	Hospitalization
7	112	121	Vertigo	Unrelated	Not resolved	Hospitalization
8	25	21	Gastric cancer	Unrelated	Resolved	Hospitalization
9	296	149	Lymph node tuberculosis	Unrelated	Resolving	Important medical event
10	296	295	Anaemia	Unrelated	Resolved	Life-threatening
11	170	112	Appendicitis	Unrelated	Resolved	Hospitalization, life-threatening, important medical event
12	57	74	Pyoderma gangrenosum	Unrelated	Resolving	Hospitalization
13	169	15	Vestibular disorder	Unrelated	Resolved	Hospitalization
14	96	81	Scapula fracture	Unrelated	Resolved	Hospitalization
15	111	92	Rectal cancer	Unrelated	Unknown	Important medical event
16	169	89	Peritonitis bacterial	Unrelated	Resolved	Hospitalization
Filibuvir 600 mg						
17	93	129	Bacterial abscess central nervous system	Unrelated	Resolved	Hospitalization
18	46	46	Depression	Unrelated	Resolved	Hospitalization
19	133	107	Breast cancer	Unrelated	Not resolved	Important medical event
20	170	11	Loss of consciousness	Unrelated	Resolved	Important medical event
	170	11	Fall	Unrelated	Resolved	Important medical event
21	170	80	Loss of consciousness	Unrelated	Resolved	Hospitalization
22	335	223	Actinomyces test positive	Unrelated	Resolved	Hospitalization
23	146	119	Chronic obstructive pulmonary disease	Unrelated	Resolving	Hospitalization
24	1046	105	Pulmonary calcification	Unrelated	Resolved	Hospitalization
25	146	105	Lung neoplasm malignant	Unrelated	Resolving	Hospitalization

Table 18. Serious Adverse Events

Serial Number	Therapy Stop Day[a]	Event Onset Day[b]	MedDRA Preferred Term[c]	Causality[d]	Clinical Outcome[e]	Seriousness
26	NA	237	Rib fracture[f]	Other: fall after a quad accident	Resolved	NA
Placebo						
27	337	381	Appendicitis perforated	Unrelated	Resolved	Hospitalization
28	334	85	Neutropenia	Unrelated	Resolved	Life-threatening
29	334	57	Neutropenia	Unrelated	Resolved	Life-threatening
30	334	112	Neutropenia	Unrelated	Resolved	Life-threatening
31	55	44	Pulmonary embolism	Unrelated	Resolved	Hospitalization
32	331	332	Sepsis	Unrelated	Resolved	Hospitalization
33	144	144	Cerebral haemorrhage	Unrelated	Resolved	Hospitalization
34	336	92	Ecchymosis	Unrelated	Resolved	Important medical event
35	NA	270	Urosepsis[f]	Other: complications due to prostate biopsy	Resolved	NA
36	NA	266	Pelvic haematoma[f]	Other: complications due to prostate biopsy	Resolved	NA

Four SAEs occurring before randomization were not included.
BUN = blood urea nitrogen; MedDRA = Medical Dictionary for Regulatory Activities; OC = Oracle Clinical; SAE = serious adverse event; SDW = Safety Data Warehouse

a. Therapy stop date is calculated as last active therapy date in OC minus first active therapy date in OC plus one.
b. Onset study day is calculated as the SDW onset date minus first active therapy date in OC plus one.
c. SAEs were coded using MedDRA version 14.1.
d. Causality is relationship to filibuvir/placebo, as assessed by the Investigator.
e. Outcome shortened from “recovered/resolved” to “resolved”; from “recovered/resolved with sequelae” to “resolved with sequelae”; from recovering/resolving” to “resolving”; and from “not recovered/not resolved” to “not resolved.”
f. This SAE was based on the clinical study database, but not included in the centralized safety database because of differences in data that exist between the centralized safety database and the clinical study database.

The number of subjects who had a dose reduction or temporary discontinuation of any therapy due to an all-causality TEAE was similar across treatment groups (28 [29.2%], 22 [22.9%], and 28 [29.2%] in the filibuvir 300 mg, filibuvir 600 mg, and placebo groups, respectively). A higher number of temporary discontinuations from blinded therapy occurred in the filibuvir 600 mg group than in the filibuvir 300 mg and placebo groups (8.3%, 5.2%, and 4.2% of subjects, respectively). The severity distribution of TEAEs leading to temporary discontinuation across treatment groups was similar. There were TEAEs in the filibuvir 300 mg and 600 mg groups that led to temporary discontinuation, which were attributed to filibuvir alone by the Investigator.

TEAEs leading to permanent discontinuation from the study are summarized in Table 19. Similar numbers of subjects across treatment groups were permanently discontinued from the study because of TEAEs (10.4%, 9.4%, and 8.3% of subjects in the filibuvir 300 mg, filibuvir 600 mg, and placebo groups, respectively. There was 1 permanent discontinuation in the filibuvir 600 mg treatment group due to a TEAE of abdominal pain upper, which was attributed to filibuvir alone by the Investigator. The majority of TEAEs leading to permanent discontinuation in the filibuvir 300 mg and 600 mg groups were severe and moderate in severity. The severity of events leading to discontinuation in the placebo group was relatively evenly distributed (mild/moderate/severe). There was 1 subject in each treatment group that discontinued because of an event of rash.

Table 19. Treatment-Emergent Adverse Events Leading to Discontinuation From the Study

Serial Number	MedDRA[a] Preferred Term (Severity)	Start Day[b]	Stop Day[b]	Outcome	Causality
Filibuvir 300 mg					
1	Nausea (moderate)	25	([>35][c]	Still present	pegIFN
2	Rash (severe)	40	[>60]	Still present	pegIFN
3	Autoimmune thyroiditis (moderate)	169	[>176]	Still present	pegIFN
4	Cerebrovascular accident[d] (moderate)	217	407	Resolved	pegIFN
5	Anaemia[d] (severe)	295	300	Resolved	RBV
6	Gastric cancer[d] (severe)	21	50	Resolved	Other
7	Cough (mild)	15	54	Resolved	RBV
8	Neutropenia (severe)	15	[>29]	Still present	pegIFN
9	Blood alkaline phosphatase increased (severe)	113	126	Resolved	FLV/pegIFN/RBV
	GGT increased (severe)	113	[>121]	Still present	FLV/pegIFN/RBV
10	Nausea (moderate)	8	[264]	Resolved	FLV/pegIFN/RBV
Filibuvir 600 mg					
11	Breast cancer[d] (moderate)	107	[>135]	Still present	Other
12	Suicidal ideation (moderate)	108	108	Resolved	pegIFN
13	Asthenia (moderate)	15	167	Resolved	FLV/pegIFN/RBV
14	Vomiting (moderate)	32	211	Resolved	FLV/pegIFN/RBV
15	Depression[d] (severe)	46	58	Resolved	pegIFN
16	Jaundice (mild)	17	21	Resolved	FLV/pegIFN/RBV
17	Irritability (moderate)	110	176	Resolved	pegIFN
18	Rash generalized (moderate)	101	129	Resolved	RBV
19	Abdominal pain upper (severe)	10	17	Resolved	FLV
Placebo					
20	Migraine (severe)	234	291	Resolved	pegIFN
21	Depression (mild)	16	337	Resolved	pegIFN
22	Fatigue (mild)	44	96	Resolved	PBO
	Menorrhagia (moderate)	60	64	Resolved	RBV
	Epistaxis (moderate)	60	64	Resolved	RBV
23	Cerebral haemorrhage[d] (severe)	144	174	Resolved	Other illness
24	Depression (mild)	148	355	Resolved	pegIFN
25	Anaemia (moderate)	17	249	Resolved	RBV
26	Rash (mild)	33	231	Resolved	RBV
27	General physical health deterioration (severe)	64	77	Resolved	PBO/pegIFN/RBV

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; FLV = filibuvir; GGT = gamma-glutamyl transferase; pegIFN = pegylated interferon α; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; PT = preferred term; RBV = ribavirin; SAE = serious adverse event

a. AEs were coded using MedDRA version 14.1.
b. Start day and stop day are the start and stop of the AE relative to the start of the treatment (Day 1).
c. Bracketed [ ] Stop Day values were imputed from incomplete date and time.
d. SAE (according to Investigator's assessment).

There were no deaths in the study.

The rate of Grade 3 or 4 laboratory abnormalities was comparable across treatment groups (39.4%, 47.9%, and 44.8% of subjects in the filibuvir 300 mg, filibuvir 600 mg, and placebo groups, respectively). The rate of Grade 4 laboratory abnormalities was higher in the filibuvir

600 mg group than in the placebo group (11.7%, 16.7%, and 8.3% of subjects in the filibuvir 300 mg, filibuvir 600 mg, and placebo groups, respectively).

ECG abnormalities were similarly distributed across treatment groups. There were no notable changes in vital signs or physical examinations from baseline in any treatment group. There was no differential effect on semen parameters, sperm morphology, or reproductive hormones among the 3 treatment groups.

CONCLUSION(S): Efficacy conclusions:

- Efficacy as measured by the primary endpoint of SVR showed that the addition of 300 mg or 600 mg filibuvir to the pegIFN/RBV regimen did not increase the proportion of subjects who achieved an SVR (41.7%, 39.6%, and 45.8% of subjects in the filibuvir 300 mg, filibuvir 600 mg, and placebo groups, respectively); thus, the primary objective of the study was not met.

- The addition of filibuvir to pegIFN/RBV resulted in higher proportions of subjects achieving undetectable HCV RNA concentrations at Weeks 2 through 12, and comparable proportions at study weeks thereafter, compared to pegIFN/RBV therapy alone. However, this early antiviral activity did not increase the proportion of subjects achieving SVR_{12}, SVR_{24}, and SVR_{last}.

- In general, subjects with the host IL28B CC genotype had better efficacy (SVR, SVR_{12}, and proportions of undetectable HCV RNA at Weeks 4 and 12) than those with non-CC genotypes.

- Few subjects (4 subjects each in the filibuvir 300 mg and 600 mg groups and 7 subjects in the placebo group) experienced breakthrough viremia on treatment.

- A higher proportion of subjects in the filibuvir 600 mg group achieved EOT response compared to pegIFN/RBV alone.

- Subjects in the filibuvir 300 mg and 600 mg groups had higher rates of relapse off treatment (35.9% and 42.9%, respectively) than subjects treated with pegIFN/RBV alone (25.4%). The lack of increase in the rate of filibuvir-treated subjects who achieved SVR was driven primarily by this higher than expected off-treatment relapse rate.

Safety conclusions:

- Based on the safety data, it is concluded that the addition of filibuvir to a regimen of pegIFN/RBV has an acceptable safety profile for the treatment of subjects with hepatitis C.

- No deaths occurred during the study. The number of subjects reporting SAEs in the filibuvir 300 mg group was twice that of the filibuvir 600 mg and placebo groups, but the SAEs did not appear to be dose-related and overall SAE rate was low (14 subjects in the filibuvir 300 mg group and 7 subjects each in the filibuvir 600 mg and placebo groups). There were no SAEs attributed to filibuvir by the Investigator.

- The most frequently reported all-causality TEAEs were fatigue, headache, and insomnia, occurring in similar proportions in each treatment group. The incidence of pruritis, dysgeusia, and abdominal pain upper was higher in the filibuvir groups than in the placebo group (pruritis: 28.1%, 30.2%, and 19.8% in the filibuvir 300 mg, filibuvir 600 mg, and placebo groups, respectively; dysgeusia: 16.7%, 25.0%, and 5.2% in the filibuvir 300 mg, filibuvir 600 mg, and placebo groups, respectively; and abdominal pain upper: 11.5%, 10.4%, and 4.2% in the filibuvir 300 mg, filibuvir 600 mg, and placebo groups respectively). The majority of TEAEs were mild in severity and the rate of severe TEAEs was similar across treatment groups.

- The number of subjects who discontinued from the study was similar across treatment groups (59.4%, 57.3%, and 53.1% in the filibuvir 300 mg, filibuvir 600 mg, and placebo groups, respectively). The number of subjects who discontinued from the study due to AEs was low and similar across treatment groups (10.4%, 9.4%, and 8.3% of subjects in the filibuvir 300 mg, filibuvir 600 mg, and placebo groups, respectively). The rate of SAEs and TEAEs leading to discontinuation from the study was similar across treatment groups, as was the number of subjects who were dose reduced or temporarily discontinued from any therapy in the regimen due to AEs.

- The rate of Grade 3 or 4 laboratory abnormalities was comparable across treatment groups (39.4%, 47.9%, and 44.8% of subjects in the filibuvir 300 mg, filibuvir 600 mg, and placebo groups, respectively). The rate of Grade 4 laboratory abnormalities was higher in the filibuvir groups than in the placebo group (11.7%, 16.7%, and 8.3% of subjects in the filibuvir 300 mg, filibuvir 600 mg, and placebo groups, respectively).

- ECG abnormalities were similarly distributed across treatment groups. There were no notable changes in vital signs or physical examinations from baseline in any treatment group.

- There was no differential effect on semen parameters, sperm morphology, or reproductive hormone levels among the 3 treatment groups.