Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product:		
Name of Active Ingredient: NS5A Replication Co-Factor Inhibitor (BMS-790052)		

SYNOPSIS

Final Clinical Study Report for Study AI444011

TITLE OF STUDY: A Phase 2B Study of BMS-790052 in Combination with Peginterferon Alfa-2a and Ribavirin in Chronic Hepatitis C Genotype 1 Infected Subjects Who are Null or Partial Responders to Prior Treatment with Peginterferon Alfa Plus Ribavirin Therapy

INVESTIGATORS/STUDY CENTERS: A total of 69 sites enrolled subjects: 3 in Argentina, 6 in Australia, 5 in Canada, 3 in Denmark, 7 in France, 4 in Germany, 2 in Italy, 3 in Mexico, 1 in Puerto Rico, 2 in Sweden, and 33 in the United States (US).

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 12-Aug-2010 **CLINICAL PHASE:** 2b

Study Completion Date: 20-Dec-2012

PURPOSE:

The purpose of this clinical study report (CSR) is to present the efficacy and safety results of Study AI444011.

OBJECTIVES:

Primary:

- Antiviral activity, as determined by the proportion of subjects with extended rapid virologic response (eRVR) in each cohort (prior partial responders and prior null responders), defined as undetectable hepatitis C virus (HCV) ribonucleic acid (RNA) at both Weeks 4 and 12
- Antiviral activity, as determined by the proportion of subjects with 24-week sustained virologic response (SVR24) in each cohort (prior partial responders and prior null responders), defined as undetectable HCV RNA at follow-up Week 24
- Safety, as measured by the frequency of serious adverse events (SAEs) and discontinuations due to adverse events (AEs)

Secondary:

- To assess the proportion of subjects in each cohort (prior partial responders and prior null responders) with rapid virologic response (RVR), i.e., undetectable HCV RNA at Week 4
- To assess the proportion of subjects in each cohort (prior partial responders and prior null responders) with complete early virologic response (cEVR), i.e., undetectable HCV RNA at Week 12
- To assess the proportion of subjects in each cohort (prior partial responders and prior null responders) with 12-week sustained virologic response (SVR12), i.e., undetectable HCV RNA at follow-up Week 12
- To describe resistant variants associated with virologic failure

Other:

- To describe the relationship between antiviral activity endpoints and the duration of therapy ("24 triple" versus "24 triple plus 24 pegIFNα2a/RBV")
- To describe the pharmacokinetics (PK) of daclatasvir (DCV), a hepatitis C virus NS5A replication complex inhibitor (BMS-790052), RBV, and pegIFNα-2a

In this synopsis, "24 triple" will be referred hereafter as, 24 W DCV/pegIFNα/RBV, and "24 triple plus 24 pegIFNα2a/RBV" will be referred hereafter as, 24 W DCV plus 24 W pegIFNα/RBV.

METHODOLOGY: This is a randomized, double-blind, placebo-controlled, multicenter, Phase 2b study conducted in prior null responders (defined as, < 1 $\log_{10}$ decrease in HCV RNA from baseline at or after 4 weeks, or < 2 $\log_{10}$ decrease from baseline at Week 12 of interferon [IFN]-based therapy) and prior partial responder (defined as, > 2 $\log_{10}$ decrease in HCV RNA from baseline by Week 12 of IFN-based therapy, but detectable HCV RNA when therapy was discontinued) subjects that were infected with HCV genotype (GT)-1. Prior null responders were randomized 1:1 to either 20-mg or 60-mg DCV once daily (QD) in combination with pegylated interferon alfa-2a (PEGASYS®; pegIFNα-2a) plus ribavirin (RBV) (pegIFNα-2a/RBV). Prior partial responders were randomized 4:4:1 to either 20-mg or 60-mg DCV or placebo QD, in combination with pegIFNα-2a/RBV (Figure 1). Randomization was stratified by prior non-response status (null or partial) and was capped so that neither cohort comprised more than approximately 66% of the total number of randomized subjects.

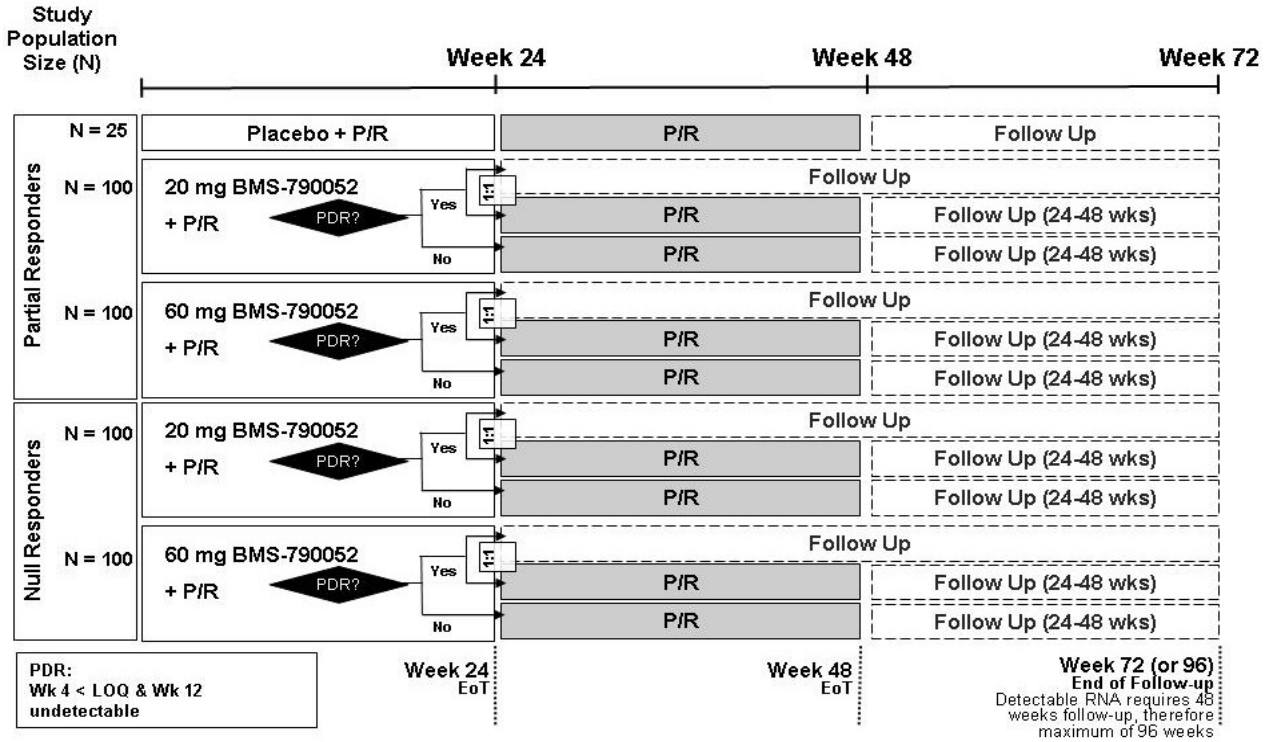
All subjects received combination therapy with DCV/peginterferon α-2a (pegIFNα-2a)/ribavirin (RBV) or placebo plus pegIFNα-2a/RBV (placebo/pegIFNα-2a/RBV) through Week 24. A second randomization occurred at Week 24 for subjects initially assigned to 20-mg DCV/pegIFNα-2a/RBV or 60-mg DCV/pegIFNα-2a/RBV who achieved a protocol-defined response (PDR), defined as HCV RNA < LOQ at Week 4 and undetectable HCV RNA at Week 12. Subjects who achieved a PDR (PDR+) were randomized (1:1) to either:

- Complete therapy at Week 24 and enter posttreatment follow-up for 48 weeks (24 W DCV/pegIFNα/RBV group) or
- Continue therapy with pegIFNα-2a/RBV alone for an additional 24 weeks before entering posttreatment follow-up for 24 weeks (24 W DCV plus 24 W pegIFNα/RBV group)

Subjects who were randomized to DCV who did not achieve a PDR (non-PDR) and subjects randomized to placebo (regardless of PDR status) received an additional 24 weeks of pegIFNα-2a/RBV alone for a total of 48 weeks of therapy, followed by a posttreatment follow-up period for 24 weeks.

Total study duration was a minimum of 72 weeks for DCV-treated subjects who achieved a PDR randomized to either the 24 W DCV/pegIFNα/RBV group or the 24 W DCV plus 24 W pegIFNα/RBV group (24 W DCV/pegIFNα/RBV group had a 48-week posttreatment follow-up period to assess sustained virologic response [SVR] durability). However, any subject with detectable HCV RNA at either end of treatment (EOT) or during posttreatment follow-up were required to have a total of 48 weeks of posttreatment follow-up to monitor for the persistence of drug-resistant HCV variants; thus, the maximum amount of time on-study for any subject in any group may have been 96 weeks.

Figure 1: AI444011 Study Design



Abbreviations: EoT, end of treatment; LOQ, limit of quantitation; PDR, protocol-defined response; P/R, pegylated interferon alfa plus ribavirin; RNA, ribonucleic acid; Wk, week.

NUMBER OF SUBJECTS (Planned and Analyzed): The planned number of subjects to be randomized was a total of 425 prior non-responders, consisting of approximately 200 prior null responders and 225 prior partial responders (including 25 subjects in the placebo group). A total of 203 [133 prior null responders and 70 prior partial responders], 199 [132 prior null responders and 67 prior partial responders], and 17 subjects were randomized and treated in the DCV 20 mg/pegIFNα/RBV, DCV 60 mg/pegIFNα/RBV, and placebo/pegIFNα/RBV groups, respectively.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: The study population comprised adult men and women 18 to 70 years of age with chronic HCV GT-1 infection and who had an HCV RNA viral load of $\geq 10^5$ IU/mL (100,000 IU/mL), and no evidence of hepatocellular carcinoma or evidence of decompensated cirrhosis based on radiologic criteria or biopsy results and clinical criteria. Failure of prior pegIFNα/RBV therapy was documented by HCV RNA obtained:

- Between Week 4 to 12 on therapy that demonstrated < 1 $\log_{10}$ decrease from pre-treatment value, or, at or after Week 12 on therapy that demonstrated < 2 $\log_{10}$ decrease from pre-treatment value (Week 12 HCV RNA may have been obtained up to 1 week prior to Week 12 or anytime after as long as the subject was on pegIFNα/RBV therapy at the time of collection) for prior null responders
- After a minimum of 12 weeks of therapy (not meeting criteria for null responder) that demonstrated detectable virus at the time treatment was discontinued for prior partial responders

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Subjects received DCV doses of 20 or 60 mg given orally QD with pegIFNα/RBV for 24 weeks. Subjects who were PDR+ either received an additional 24 weeks of DCV (20 or 60 mg)/pegIFNα/RBV or entered follow-up for 48 weeks. Subjects who did not achieve PDR (non-PDR) at Week 24 received an additional 24 weeks of pegIFNα/RBV for a total of 48 weeks of therapy. Investigational product information is presented in Table 1.

Table 1: Investigational Product Identification

Drug Product	Formulation	Product Batch Number
DCV 10 mg	Film-coated tablet	8J43343, 0D56662
DCV 30 mg	Film-coated tablet	9L51069, 0H51832
Placebo for 10 mg and 30 mg	Film-coated tablet	0B61212, 0B61213, 9B54029, 9H42143

Abbreviation: DCV, daclatasvir.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Subjects received treatment with placebo given QD with pegIFNα/RBV for 24 weeks and an additional 24 weeks of pegIFNα/RBV (total treatment duration of 48 weeks).

All subjects received pegIFNα-2a/RBV treatment for HCV infection: 180 μg pegIFNα given once weekly (qw) and RBV either 400 mg (subjects < 75 kg: 2 tablets) or 600 mg (subjects ≥ 75 kg: 3 tablets) in the morning with food and 600 mg (3 tablets) in the evening with food.

Bristol-Myers Squibb Company (BMS) supplied sufficient marketed pegIFNα and RBV product as follows:

- pegIFNα-2a as 1 mL, pre-filled syringes (PEGASYS) containing 180 μg/0.5 mL, manufactured by Roche Laboratories, Inc, batch numbers B1143 and B1191
- RBV as 200-mg film-coated tablets (COPEGUS®) manufactured by Roche Laboratories, Inc, batch numbers 0D60446, 0L58093, 0F59067, and 1B63344

CRITERIA FOR EVALUATION:

Efficacy: The primary endpoints were the proportions of subjects with eRVR and SVR24. Secondary endpoints included the proportions of subjects with rapid virologic response (RVR), complete early virologic response (cEVR), and sustained virologic response at follow-up Week 12 (SVR12). Other endpoints included the relationship between antiviral activity endpoints and the duration of DCV therapy.

Virologic failure, for the purpose of the study, was defined as:

- Virologic breakthrough (VBT): confirmed > 1 $\log_{10}$ increase in HCV RNA over nadir or confirmed HCV RNA ≥ LOQ after confirmed undetectable HCV RNA while on-treatment. Measurements were confirmed at the next scheduled visit.
- < 1 $\log_{10}$ decrease in HCV RNA from baseline at Week 4 of treatment
- Failure to achieve early virologic failure (EVR): < 2 $\log_{10}$ decrease in HCV RNA from baseline and HCV RNA ≥ limit of quantitation (LOQ) at Week 12 of treatment
- Detectable HCV RNA at Week 12 and HCV RNA ≥ LOQ at Week 24 of treatment
- Detectable HCV RNA at EOT (including early discontinuation)
- Relapse, defined as detectable HCV RNA during follow-up after undetectable HCV RNA at EOT

Safety: Key safety endpoints included deaths, SAE, AEs leading to discontinuation, Grade 3 or 4 AEs, and Grade 3 or 4 laboratory abnormalities.

Other: Resistance testing of variants associated with clinical failure was a secondary endpoint. Testing was performed on all baseline samples and in all subjects with HCV RNA ≥ 1000 IU/mL who had virologic failure.

STATISTICAL CONSIDERATIONS: Safety and antiviral activity were assessed for treated subjects using descriptive and exploratory analyses. Binary antiviral activity endpoints were assessed using modified intent-to-treat (ITT) and observed values. In both analyses, the numerator was based on subjects meeting the response criteria. For modified ITT, the denominator was based on all treated subjects. For observed values, the denominator was based on subjects with available measurements at the analysis week(s). Response rates were presented with 2-sided 80% exact binomial confidence intervals (CIs). To evaluate the concordance (agreement) between SVR12 and SVR24, a cross-tabulation of posttreatment Week 12 data and posttreatment Week 24 data was presented for subjects who had non-missing data at both timepoints. Cohort safety stopping rules were assessed as described in the protocol.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics:

Of the 512 subjects enrolled, 419 were randomized and treated:

- 203 to DCV 20 mg/pegIFNα/RBV
- 199 to DCV 60 mg/pegIFNα/RBV
- 17 to placebo/pegIFNα/RBV

Overall, a numerically higher proportion of treated subjects in the DCV 20 and 60 mg/pegIFNα/RBV groups (37.4% and 44.2%, respectively) completed the treatment period than the placebo/pegIFNα/RBV group (29.4%) (Table 2). This was mainly due to a higher proportion of subjects in the placebo/pegIFNα/RBV group compared with the DCV/pegIFNα/RBV groups who discontinued due to a lack of efficacy, an AE, and subject request to discontinue study treatment.

A higher proportion of subjects in the DCV 20 and 60 mg/pegIFNα/RBV groups who entered the follow-up period completed the study compared with the placebo/pegIFNα/RBV group: 80.3% and 85.9% vs 60.0% (Table 2). The observed difference between the DCV treatment groups and placebo/pegIFNα/RBV group was mainly due to a higher proportion of subjects in the placebo/pegIFNα/RBV group (17.6%) who discontinued due to AEs than the DCV/pegIFNα/RBV groups (5.4% and 6.0% in the DCV 20 and 60 mg/pegIFNα/RBV groups, respectively). Lack of efficacy was the main reason that subjects did not complete the period.

Table 2: Subject Disposition - All Treated Subjects

	Number (%) of Subjects			
	DCV 20 mg/ pegIFNα/RBV	**DCV 60 mg/ pegIFNα/RBV**	**Placebo/ pegIFNα/RBV**	**Total**
Subjects Randomized and Treated	203	199	17	419
Completed Treatment Period	76 (37.4)	88 (44.2)	5 (29.4)	169 (40.3)
Not completing the treatment period	127 (62.6)	111 (55.8)	12 (70.6)	250 (59.7)
Reason for not completing treatment period				
Lack of efficacy	96 (47.3)	91 (45.7)	7 (41.2)	194 (46.3)
Adverse event	11 (5.4)	12 (6.0)	3 (17.6)	26 (6.2)
Subject withdrew consent	2 (1.0)	1 (0.5)	0	3 (0.7)
Lost to follow-up	1 (0.5)	1 (0.5)	1 (5.9)	3 (0.7)
Subjects no longer met study criteria	0	1 (0.5)	0	1 (0.2)
Subject requested to discontinue treatment	7 (3.4)	3 (1.5)	1 (5.9)	11 (2.6)
Completed 24-week treatment period only	10 (4.9)	2 (1.0)	0	12 (2.9)

Table 2: Subject Disposition - All Treated Subjects

	Number (%) of Subjects			
	DCV 20 mg/ pegIFNα/RBV	DCV 60 mg/ pegIFNα/RBV	Placebo/ pegIFNα/RBV	Total
Number of subjects entering follow-up	198	192	15	405
Subjects completing follow-up	159 (80.3)	165 (85.9)	9 (60.0)	333 (82.2)
Subjects not completing follow-up	39 (19.7)	27 (14.1)	6 (40.0)	72 (17.8)
Reason for not completing follow-up				
Subject withdrew consent	14 (7.1)	10 (5.2)	2 (13.3)	26 (6.4)
Death	2 (1.0)	2 (1.0)	0	4 (1.0)
Lost to follow-up	13 (6.6)	8 (4.2)	1 (6.7)	22 (5.4)
Other	10 (5.1)	7 (3.6)	3 (20.0)	20 (4.9)

Abbreviations: DCV, daclatasvir; pegIFNα/RBV, pegylated interferon alfa plus ribavirin.

Baseline demographics were balanced across the treatment groups (Table 3). Overall, the majority of subjects were male (65.2%). The mean age in this study was 52.4 years; 5.5% of subjects were ≥ 65 years of age. Most subjects were white (89.5%) and a small proportion were black/African American (8.6%), "Other" race (0.7%; includes the following: Aboriginal, Hispanic, and Puerto Rico), or Chinese (0.5%).

Baseline HCV disease characteristics were similar across the treatment groups (Table 3). The mean HCV RNA level was 6.6 $\log_{10}$ IU/mL. Most (92.6%) subjects had a high baseline viral load (≥ 800,000 IU/mL). The mean HCV RNA level was 6.6 $\log_{10}$ IU/mL. Most (92.6%) subjects had a high baseline viral load (≥ 800,000 IU/mL). All subjects were infected with GT-1, except 1 subject randomized to the DCV 20 mg/pegIFNα/RBV group who had a GT that was reported as missing: 64.0% had GT-1 subtype a (GT-1a) and 34.8% had GT-1 subtype b (GT-1b). The proportion of subjects with cirrhosis at baseline was 17.7%, 17.1%, and 17.6% in the DCV 20 mg/pegIFNα/RBV, DCV 60 mg/pegIFNα/RBV, and placebo/pegIFNα/RBV groups, respectively. Overall, 7.2% (30/419) and 92.6% (388/419) of subjects had the interleukin (IL)-28B CC and non-CC genotypes, respectively. In the DCV 20 mg/pegIFNα/RBV and the DCV 60 mg/pegIFNα/RBV groups, respectively, there were 133 (65.5%) and 132 (66.3%) prior null responders, and 70 (34.5%) and 67 (33.7%) prior partial responders. The placebo/pegIFNα/RBV group was comprised of prior partial responders only (100.0%).

Table 3: Baseline Demographic and Disease Characteristics

	DCV 20 mg/ pegIFNα/RBV (N = 203)	DCV 60 mg/ pegIFNα/RBV (N = 199)	Placebo/ pegIFNα/RBV (N = 17)	Total (N = 419)
Age (years)				
Mean	52.1	52.7	52.5	52.4
Min, Max	24, 68	21, 70	34, 66	21, 70
Age Categorization (n, %)				
21 to < 65 years	192 (94.6)	189 (95.0)	15 (88.2)	396 (94.5)
≥ 65 years	11 (5.4)	10 (5.0)	2 (11.8)	23 (5.5)
Gender (n, %)				
Male	133 (65.5)	127 (63.8)	13 (76.5)	273 (65.2)
Female	70 (34.5)	72 (36.2)	4 (23.5)	146 (34.8)

Table 3: Baseline Demographic and Disease Characteristics

	DCV 20 mg/ pegIFNα/RBV (N = 203)	DCV 60 mg/ pegIFNα/RBV (N = 199)	Placebo/ pegIFNα/RBV (N = 17)	Total (N = 419)
Race (n, %)				
White	177 (87.2)	183 (92.0)	15 (88.2)	375 (89.5)
Black/African American	22 (10.8)	13 (6.5)	1 (5.9)	36 (8.6)
American indian/Alaska native	1 (0.5)	0	0	1 (0.2)
Asian indian	0	1 (0.5)	0	1 (0.2)
Chinese	1 (0.5)	1 (0.5)	0	2 (0.5)
Asian other	0	1 (0.5)	0	1 (0.2)
Other	2 (1.0)	0	1 (5.9)	3 (0.7)
HCV RNA (log_{10} IU/mL)				
Mean	6.7	6.6	6.7	6.6
HCV RNA Distribution (n, %)				
< 800,000 IU/ML	11 (5.4)	18 (9.0)	2 (11.8)	31 (7.4)
≥ 800,000 IU/ML	192 (94.6)	181 (91.0)	15 (88.2)	388 (92.6)
HCV Genotype (n, %)				
1	2 (1.0)	2 (1.0)	0	4 (1.0)
1a	135 (66.5)	126 (63.3)	7 (41.2)	268 (64.0)
1b	65 (32.0)	71 (35.7)	10 (58.8)	146 (34.8)
Missing	1 (0.5)	0	0	1 (0.2)
Cirrhosis (n, %)				
Absent	167 (82.3)	165 (82.9)	14 (82.4)	346 (82.6)
Present	36 (17.7)	34 (17.1)	3 (17.6)	73 (17.4)
IL-28B Genotype (n, %) (RS12979860)				
CC	12 (5.9)	17 (8.5)	1 (5.9)	30 (7.2)
CT	138 (68.0)	132 (66.3)	11 (64.7)	281 (67.1)
TT	53 (26.1)	50 (25.1)	4 (23.5)	107 (25.5)
Not reported	0	0	1 (5.9)	1 (0.2)
Randomization Stratum (%)				
Prior null response	133 (65.5)	132 (66.3)	0	265 (63.2)
Prior partial response	70 (34.5)	67 (33.7)	17 (100.0)	154 (36.8)

Abbreviations: DCV, daclatasvir; pegIFNα/RBV, pegylated interferon alfa plus ribavirin; HCV, hepatitis C virus; RNA, ribonucleic acid.

Treatment Adherence: The proportion of subjects who received ≥ 90% of planned treatment duration and ≥ 90% of target daily/weekly dose for all drugs in the treatment regimen was similar in the DCV treatment groups: 63.5% and 66.8% in the DCV 20 mg/pegIFNα/RBV and DCV 60 mg/pegIFNα/RBV groups, respectively, and 35.3% in the placebo/pegIFNα/RBV group. The proportion of subjects who received < 80% of planned treatment duration and < 80% of target daily/weekly dose for all drugs in the treatment regimen that was observed was lowest in the DCV 60 mg/pegIFNα/RBV group (9.5% + 8.0%, 17.5%) than the DCV 20 mg/pegIFNα/RBV (7.9% + 14.8%; 22.7%) and placebo/pegIFNα/RBV (5.9% + 41.2%; 47.1%) groups.

Efficacy Results:

Primary and secondary antiviral activity and efficacy endpoints, based on the modified ITT analysis, and virologic failure are summarized in Table 4.

Table 4: Efficacy Results - Modified Intent-to-Treat Analysis, All Treated Subjects

	Prior Null Responder		Prior Partial Responder		
Virologic Endpoints	**DCV 20 mg/ pegIFNα/ RBV N = 133**	**DCV 60 mg/ pegIFNα/ RBV N = 132**	**DCV 20 mg/ pegIFNα/ RBV N = 70**	**DCV 60 mg/ pegIFNα/ RBV N = 67**	**Placebo/ pegIFNα/ RBV N = 17**
Co-primary Antiviral/Efficacy Endpoints					
eRVR					
% (Responder/N)	18.0 (24/133)	19.7 (26/132)	25.7 (18/70)	35.8 (24/67)	0/17
80% CI	(13.8, 22.3)	(15.3, 24.1)	(19.0, 32.4)	(28.3, 43.3)	(0.0, 0.0)
SVR24					
% (Responder/N)	18.8 (25/133)	22.0 (29/132)	24.3 (17/70)	43.3 (29/67)	0/17
80% CI	(14.5, 23.1)	(17.4, 26.6)	(17.7, 30.9)	(35.5, 51.0)	(0.0, 0.0)
Secondary Antiviral Activity/ Efficacy Endpoints					
RVR					
% (Responder/N)	21.8 (29/133)	21.2 (28/132)	25.7 (18/70)	38.8 (26/67)	0/17
80% CI	(17.2, 26.4)	(16.7, 25.8)	(19.0, 32.4)	(31.2, 46.4)	(0.0, 0.0)
cEVR					
% (Responder/N)	30.1 (40/133)	34.1 (45/132)	44.3 (31/70)	56.7 (38/67)	0/17
80% CI	(25.0, 35.2)	(28.8, 39.4)	(36.7, 51.9)	(49.0, 64.5)	(0.0, 0.0)
PDR					
% (Responder/N)	24.1 (32/133)	30.3 (40/132)	38.6 (27/70)	52.2 (35/67)	0/17
80% CI	(19.3, 28.8)	(25.2, 35.4)	(31.1, 46.0)	(44.4, 60.1)	(0.0, 0.0)
EOTR					
% (Responder/N)	33.8 (45/133)	36.4 (48/132)	38.6 (27/70)	59.7 (40/67)	4/17 (23.5)
80% CI	(28.6, 39.1)	(31.0, 41.7)	(31.1, 46.0)	(52.0, 67.4)	(10.3, 36.7)
SVR4					
% (Responder/N)	24.1 (32/133)	28.0 (37/132)	30.0 (21/70)	50.7 (34/67)	0/17
80% CI	(19.3, 28.8)	(23.0, 33.0)	(23.0, 37.0)	(42.9, 58.6)	(0.0, 0.0)
SVR12					
% (Responder/N)	19.5 (26/133)	23.5 (31/132)	25.7 (18/70)	47.8 (32/67)	0/17
80% CI	(15.1, 24.0)	(18.8, 28.2)	(19.0, 32.4)	(39.9, 55.6)	(0.0, 0.0)

Table 4: Efficacy Results - Modified Intent-to-Treat Analysis, All Treated Subjects

	Prior Null Responder		Prior Partial Responder		
Virologic Endpoints	**DCV 20 mg/ pegIFNα/ RBV N = 133**	**DCV 60 mg/ pegIFNα/ RBV N = 132**	**DCV 20 mg/ pegIFNα/ RBV N = 70**	**DCV 60 mg/ pegIFNα/ RBV N = 67**	**Placebo/ pegIFNα/ RBV N = 17**
Virologic Failure, On-Treatment[a] % (N)	66.2 (88)	63.6 (84)	60.0 (42)	40.3 (27)	76.5 (13)
Virologic breakthrough	36.1 (48)	41.7 (55)	32.9 (23)	26.9 (18)	5.9 (1)
Week 4 Futility Criteria[b]	9.8 (13)	6.1 (8)	1.4 (1)	1.5 (1)	35.3 (6)[c]
Detectable HCV RNA at EOT	10.5 (14)	6.8 (9)	17.1 (12)	7.5 (5)	23.5 (4)
Relapse Rate[d]	44.4 (20/45)	37.5 (18/48)	33.3 (9/27)	30.0 (12/40)	75.0 (3/4)

Abbreviations: cEVR, complete early virologic response (undetectable HCV RNA at Week 12); CI, confidence interval; DCV, daclatasvir; EOT, end of treatment; eRVR, extended rapid virologic response (undetectable HCV RNA at both Week 4 and 12); HCV, hepatitis C virus; < LLOQ, less than the lower limit of quantitation; < LOQ, less than the limit of quantitation; N, number; PDR, protocol-defined response (HCV RNA < LOQ at Week 4 and undetectable HCV RNA at Week 12); pegIFNα, peginterferon alfa; RBV, ribavirin; RNA, ribonucleic acid; RVR, rapid virologic response (undetectable at Week 4); SVR12, sustained virologic response at follow-up Week 12; SVR24, sustained virologic response at follow-up Week 24; SVR4, sustained virologic response at follow-up Week 4; TD, target detected; TND, target not detected.

[a] Virologic failure was defined as 1) virologic breakthrough: confirmed > 1 $\log_{10}$ increase in HCV RNA over nadir or confirmed HCV RNA ≥ LOQ after confirmed undetectable HCV RNA while on treatment, measurements were confirmed at the next scheduled visit; < 1 $\log_{10}$ decrease in HCV RNA from baseline at Week 4 of treatment; failure to achieve EVR: < 2 $\log_{10}$ decrease in HCV RNA from baseline and HCV RNA ≥ LOQ at Week 12 of treatment; detectable HCV RNA at Week 12 and HCV RNA ≥ LOQ at Week 24 of treatment; detectable HCV RNA at EOT (including early discontinuation); or relapse, defined as detectable HCV RNA during follow-up after undetectable HCV RNA at EOT.

[b] Defined as < 1 $\log_{10}$ decrease in HCV RNA from baseline at Week 4 of treatment

[c] One subject was counted as a relapser at follow-up Week 24.

[d] In subjects with undetectable HCV RNA at EOT; the numerator is based on subjects meeting the response criteria, i.e., undetectable HCV RNA during the follow-up period.

The following summary points for efficacy are primarily based on Table 4:

- Virologic response rates during treatment and SVR rates during follow-up for subjects who were prior null and prior partial responders and treated with DCV 20 mg/pegIFNα/RBV or DCV 60 mg/pegIFNα/RBV were numerically higher than those for placebo/pegIFNα/RBV.
  - Extended RVR and SVR24 rates were numerically higher in the DCV 60 mg/pegIFNα/RBV group than the DCV 20 mg/pegIFNα/RBV group.
  - Earlier virologic response was observed in the DCV/pegIFNα/RBV treatment groups. However, the co-primary objective of eRVR was not met for either prior null or prior partial responders in the study.
    - Extended RVR rates were numerically higher for subjects in the DCV 60 mg/ pegIFNα/RBV group than the DCV 20 mg/pegIFNα/RBV group and numerically higher in prior partial responders than prior null reponders; eRVR was not achieved by any subject in the placebo/pegIFNα/RBV group.
      - Extended RVR rates were 18.0% and 25.7% for prior null responders or prior partial responders, respectively, in the DCV 20 mg/pegIFNα/RBV group.

    - Extended RVR rates were 19.7% and 35.8% for prior null responders or prior partial responders in the DCV 60 mg/pegIFNα/RBV group, respectively.
  - SVR24 rates with DCV 20 or 60 mg/pegIFNα/RBV were numerically higher in the subjects who received the placebo control. The co-primary objective of SVR24 was met by prior partial responders in the DCV 60 mg/pegIFNα/RBV group, but was not met for both prior null and prior partial responders in the DCV 20 mg/pegIFNα/RBV group in the study.
    - 18.8% and 24.3% of prior null responders and prior partial responders, respectively, in the DCV 20 mg/pegIFNα/RBV group achieved SVR24.
    - 22.0% and 43.3% of prior null responders and prior partial responders, respectively, in the DCV 60 mg/pegIFNα/RBV group achieved SVR24.
- A PDR in the DCV-treated subjects was achieved by a numerically higher proportion of subjects in the prior partial responder cohorts compared with the prior null responder cohorts.
  - 38.6% and 52.2% subjects in the prior partial responder cohorts compared with 24.1% and 30.3% in the prior null responder cohorts in the DCV 20 mg/pegIFNα/RBV and DCV 60 mg/pegIFNα/RBV groups, respectively, achieved a PDR.
  - DCV/pegIFNα/RBV-treated subjects who achieved PDR were 53.6% to 72.2% more likely to have an SVR24 response compared with 4.1% to 7.9% who did not achieve a PDR.
  - SVR24 rates in subjects who received 24 weeks of DCV/pegIFNα/RBV followed by 24 weeks of pegIFNα/RBV were generally comparable to those in subjects who received a total of 24 weeks of treament with DCV/pegIFNα/RBV. Prior null responders generally responded better to a longer DCV treatment duration than prior partial responders.
- Among subjects with HCV RNA results at both follow-up Weeks 12 and 24, there was 98.2% to 100.0% concordance (defined as [number of responders at both timepoints + number of non-responders at both timepoints] divided by total number of subjects with non-missing data at both timepoints) between SVR12 with SVR24 rates in the DCV 20 mg/pegIFNα/RBV and DCV 60 mg/pegIFNα/RBV groups.
- DCV/pegIFNα/RBV demonstrated efficacy in all subgroups of subjects:
  - SVR24 rates were numerically higher in subjects with GT-1b compared with GT-1a.
  - SVR24 rates were numerically lower in subjects with baseline cirrhosis than in subjects without baseline cirrhosis.
- Virologic failure was more frequent in the placebo/pegIFNα/RBV group compared with the DCV/pegIFNα/RBV groups.
  - In the placebo/pegIFNα/RBV group, virologic failure was primarily due to a higher proportion of subjects meeting the Week 4 futility criteria (< 1 $\log_{10}$ decrease in HCV RNA from baseline at Week 4 of treatment) and having detectable HCV RNA at EOT.
  - Observed virologic failures in the DCV 20 and 60 mg/pegIFNα/RBV were due to on-treatment VBT and relapse off-treatment, and were higher for prior null responders than prior partial responders.
  - In the DCV/pegIFNα/RBV groups, within both 20-mg and 60-mg dose groups and prior response cohorts, virologic failure was more frequent in subjects with GT-1a (59.5% to 77.6%) compared with those with GT-1b (16.7% to 53.7%), mainly due to a higher rate of VBT.

Based on SVR24 outcomes analysis, 87 (65.4%) and 83 (62.9%) prior null responders in the DCV 20 mg/pegIFNα/RBV and DCV 60 mg/pegIFNα/RBV groups, respectively, had virologic failure on-treatment. Forty-two (60.0%) and 26 (38.8%) prior partial responders in the DCV 20 mg/pegIFNα/RBV and DCV 60 mg/pegIFNα/RBV groups, respectively, had virologic failure on-treatment. Relapse rates (among subjects who had HCV RNA < LLOQ, TND at EOT) were 44.4% (20/45) and 37.5% (18/48) for prior null responders in the DCV 20 mg/pegIFNα/RBV and DCV 60 mg/pegIFNα/RBV groups, respectively, and 29.6% (8/27) and 25.0% (10/40) prior partial responders in the DCV 20 mg/pegIFNα/RBV and DCV 60 mg/pegIFNα/RBV groups, respectively. Subjects infected with GT-1b had numerically higher SVR24 rates (29.3% to 55.0%) compared with subjects infected with GT-1a (9.4% to 35.1%).

Safety Results:

Daclatasvir 20 mg or 60 mg/pegIFNα/RBV therapy was well tolerated in prior non-responders infected with HCV GT-1 and exhibited a safety profile that was consistent with that for placebo/pegIFNα/RBV.

The following summary points for safety are presented hereafter and Table 5:

- There were 5 deaths (2 in the DCV 20 mg/pegIFNα/RBV group, 2 in the DCV 60 mg/pegIFNα/RBV group, and 1 in the placebo/pegIFNα/RBV group). One subject in the placebo/pegIFNα/RBV group (pancytopenia and metabolic acidosis) died during the on-treatment period, and 4 during follow-up (infiltrative hepatocellular carcinoma, intraventricular haemorrhage, liver and kidney failure, and hemoperitoneum due to hepatocellular carcinoma). Deaths by infiltrative hepatocellular carcinoma, pancytopenia and metabolic acidosis, and liver and kidney failure were considered related to study therapy by investigator assessment.
- On-treatment, SAEs regardless of relationship to study drug were reported for 6.9%, 5.5%, and 17.6% of subjects in the DCV 20 mg/pegIFNα/RBV, DCV 60 mg/pegIFNα/RBV, and placebo/pegIFNα/RBV groups, respectively.
- On-treatment AEs leading to discontinuation of study therapy were more frequent in the placebo/pegIFNα/RBV group (17.6%) compared with the DCV/pegIFNα/RBV groups (5.4% and 6.0%, in the DCV 20 mg/pegIFNα/RBV and DCV 60 mg/pegIFNα/RBV groups, respectively).
- There were no clinically relevant trends in AEs on-treatment. The most frequently (> 20% in any treatment group) reported AEs (Grade 1 to 4) in the 3 treatment groups were fatigue, headache, pruritus, dry skin, insomnia, nausea, asthenia, anaemia, diarrhoea, influenza like illness, dyspnoea, cough, alopecia, decreased appetite, myalgia, irritability, neutropenia, and chills. These AEs are frequently associated with pegIFNα/RBV therapy.
- No unique AEs were identified for DCV in this study.
- There did not appear to be a difference in the safety profile between DCV 20 mg/pegIFNα/RBV and DCV 60 mg/pegIFNα/RBV groups. The observed AEs in the study were consistent with pegIFNα/RBV therapy.
- Daclatasvir was not observed to increase the frequency and/or severity of events known to be associated with other approved direct-acting antiviral agent (DAA) therapies and no clinical meaningful signal for any special search categories was detected. Two subjects had reported pancytopenia composite. Neutropenia followed by infection events (7.4%, 7.0%, and 11.8% subjects in the DCV 20 mg/pegIFNα/RBV, DCV 60 mg/pegIFNα/RBV, and placebo/pegIFNα/RBV groups, respectively) were reported. Gastrointestinal and ano-rectal disorders were infrequently reported in all dose groups. Grade 1 to 4 rash (composite) and psychiatric disorders were similar in frequency between the DCV and placebo groups.
- In cirrhotics, DCV 20 mg and 60 mg/pegIFNα/RBV groups had an observed safety profile that was similar to that expected with pegIFNα-2a/RBV alone.
- No clinically relevant trends in laboratory abnormalities were observed on-treatment or during follow-up. The most frequent laboratory abnormalities were hematologic abnormalities, which are frequently observed for pegIFNα/RBV.

Table 5: On-Treatment Safety - All Treated Subjects

	Number (%) of Subjects		
	DCV 20 mg/ pegIFNα/RBV (N = 203)	**DCV 60 mg/ pegIFNα/RBV (N = 199)**	**Placebo/ pegIFNα/RBV (N = 17)**
Adverse Events			
Death[a]	0	0	1
SAEs	14 (6.9)	11 (5.5)	3 (17.6)
AEs Leading to Discontinuation of Study Drugs	11 (5.4)	12 (6.0)	3 (17.6)

Table 5: On-Treatment Safety - All Treated Subjects

	Number (%) of Subjects		
	DCV 20 mg/ pegIFNα/RBV (N = 203)	**DCV 60 mg/ pegIFNα/RBV (N = 199)**	**Placebo/ pegIFNα/RBV (N = 17)**
Grade 3 to 4 AEs	37 (18.2)	32 (16.1)	7 (41.2)
Most Frequent AEs (> 20% in any group)			
Fatigue	81 (39.9)	91 (45.7)	10 (58.8)
Headache	71 (35.0)	63 (31.7)	7 (41.2)
Pruritus	55 (27.1)	63 (31.7)	3 (17.6)
Dry skin	39 (19.2)	65 (32.7)	4 (23.5)
Insomnia	53 (26.1)	53 (26.6)	5 (29.4)
Nausea	55 (27.1)	45 (22.6)	3 (17.6)
Asthenia	55 (27.1)	38 (19.1)	1 (5.9)
Anaemia	43 (21.2)	28 (14.1)	5 (29.4)
Diarrhoea	26 (12.8)	32 (16.1)	5 (29.4)
Influenza like illness	55 (27.1)	59 (29.6)	1 (5.9)
Dyspnoea	46 (22.7)	39 (19.6)	4 (23.5)
Cough	35 (17.2)	47 (23.6)	3 (17.6)
Alopecia	36 (17.7)	42 (21.1)	1 (5.9)
Decreased appetite	38 (18.7)	36 (18.1)	4 (23.5)
Myalgia	40 (19.7)	33 (16.6)	4 (23.5)
Irritability	29 (14.3)	42 (21.1)	3 (17.6)
Neutropenia	31 (15.3)	31 (15.6)	4 (23.5)
Chills	16 (7.9)	27 (13.6)	4 (23.5)
On-Treatment Grade 3 to 4 Laboratory Abnormalities			
Neutrophils	57 (28.2) N = 202	46 (23.1) N = 199	7 (43.8) N = 16
Lymphocytes	33 (16.3) N = 202	31 (15.7) N = 198	3 (18.8) N = 16
WBC	31 (15.3) N = 202	29 (14.6) N = 199	3 (18.8) N = 16
Hemoglobin	9 (4.5) N = 202	8 (4.0) N = 199	3 (18.8) N = 16
Platelets	6 (3.0) N = 202	8 (4.0) N = 199	2 (12.5) N = 16
AST	9 (4.5) N = 202	6 (3.0) N = 199	0 N = 16
Lipase	8 (4.0) N = 202	4 (2.0) N = 199	0 N = 16

Table 5: On-Treatment Safety - All Treated Subjects

	Number (%) of Subjects		
	DCV 20 mg/ pegIFNα/RBV (N = 203)	**DCV 60 mg/ pegIFNα/RBV (N = 199)**	**Placebo/ pegIFNα/RBV (N = 17)**
ALT	5 (2.5) N = 202	2 (1.0) N = 199	0 N = 16
Total bilirubin	2 (1.0) N = 202	2 (1.0) N = 199	2 (12.5) N = 16

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCV, daclatasvir; pegIFNα/RBV, peginterferon alfa plus ribavirin; SAE, serious adverse event; WBC, white blood cell.

[a] An additional 4 deaths occurred in the follow-up period

Pharmacokinetics Results:

Daclatasvir geometric mean maximum observed plasma concentration (Cmax) following administration of oral doses of 20 and 60 mg were ~288 and ~1044 ng/mL, respectively, within the range of Cmax values previously observed in HCV-infected subject.

- The time of maximum observed plasma concentration (Tmax) mean value after administration of oral doses of 20 and 60 mg were 2.2 and 1.4 hours, respectively, which were comparable with the data previously reported.
- Daclatasvir trough plasma concentration observed pre-dose (C0) values were ~39 and ~120 ng/mL following administration of oral doses of 20 and 60 mg, respectively, which were slightly lower than the range of trough values previously observed.
- The pegINFα geometric mean value of Ctrough ranged from 6.11 to 11.43 ng/ml in the DCV 20 mg/pegIFNα/RBV group, from 5.46 to 9.49 ng/mL in the DCV 60 mg/pegIFNα/RBV group, and 5.50 to 11.72 ng/mL in the placebo/pegINFα/RBV group.
- The RBV geometric mean value of Ctrough ranged from 1390 to 2077 ng/ml in the DCV 20 mg/pegIFNα/RBV group, from 1460 to 2126 ng/mL in the DCV 60 mg/pegIFNα/RBV group, and from 1658 to 2527 ng/mL in the placebo/pegINFα/RBV group.

Pharmacodynamic Results: The PK data obtained from this study will be pooled with data from other DCV studies to perform an integrated population PK analysis to explore selected safety and antiviral activity endpoints; that analysis will be reported separately.

Other Results:

Resistance: A brief summary of the results is provided hereafter.

Nonstructural protein 5A (NS5A) resistance associated polymorphisms (RAPs) were detected in 32% (118/374) of subjects:

- GT-1a (N = 247):
  - 36 of 247 subjects had baseline NS5A RAPs; GT-1a samples included methionine (M)28 leucine (L)/threonine (T)/valine (V), glutamine (Q)30 histidine (H), L31M, H54 tyrosine (Y), H58 cysteine (C)/aspartate (D)/asparagine (N)/proline (P)/Q, glutamate (E)62D, and Y93C
- GT-1b (N = 127):
  - 82 of 127 subjects had baseline NS5A RAPs; GT-1b samples included L28M/V, arginine (R)30H/Q, L31M, Q54H/N/Y, P58A/Q/Serine (S), Q62E/lysine (K)/N/R/S, alanine (A)/92T/V, and Y93 phenylalanine (F)/H

The most prevalent baseline NS5A RAP in subjects with GT-1a was L31M, detected in 25% (9/36) of subjects; 6 of 9 were prior null responders and 3 of 9 were prior partial responders. One-hundred percent (9/9) of subjects with the L31M RAP failed treatment. The most prevalent baseline NS5A RAP in subjects with GT-1b was Q54H, detected in 59% (48/82) of subjects; 33 of 48 were prior null responders and 15 of 48 were prior partial responders. Sixty-five percent (31/48) of subjects with the Q54H RAP failed treatment.

Analysis of the effects of pre-existing signature DCV-resistant variants indicated there may be an association between GT-1a NS5A RAPs (M28V/L/T, L31M, H58C/D/N/P/Q, and Y93C) and virologic failure since 96% (25/26) of subjects with these variants failed treatment.

Of GT-1a virologic failures, emergent substitutions at M28A/glycine (G)/S/T/V, Q30D/E/G/H/K/N/R/T, L31 isoleucine (I)/M/V, H54R/Y, H58D/N/P/Q/V, A92P, and Y93C/H/N/R/S were detected. Q30 variants were detected most frequently either alone or in combination with other NS5A RAVs at amino acid positions 28, 31, 58, and 93 (91%; 180/197 failures). Of GT-1b virologic failures, emergent substitutions at L28M, P29X, R30H/K/L/P/Q/R/S, L31F/I/M/V, P32X, Q54H/Y, P58S, A92E/K/T, and Y93H were detected. Y93H combined with variants at L31 (L31I/M/V) predominated and was detected in 81% (57/70) of GT-1b failures with NS5A sequence.

Replacement or partial replacement of emergent NS5A RAVs was observed in subjects when monitored out to follow-up Week 48. Of the 148 subjects with GT-1a examined at follow-up Week 48, replacement or partial replacement of these NS5A variants was observed in 2% (3/148) and 25% (36/148) of subjects, respectively; in 2 subjects who relapsed with emergent Y93H, reversion/outgrowth by baseline sequence was observed.

CONCLUSIONS:

The following are the conclusions from this study:

- Daclatasvir, 20 mg or 60 mg QD in combination with pegIFNα-2a/RBV demonstrated rapid antiviral activity and increased rates of SVR24 in prior non-responders compared with pegIFNα/RBV alone.
  - eRVR rates, as well as all other on-treatment virologic response rates, overall were highest in the DCV 60 mg/pegIFNα/RBV group and both DCV-treatment groups were higher than pegIFNα/RBV alone; early, on-treatment response was a good predictor of SVR, with eRVR having the greatest correlation numerically.
  - The SVR24 rates for the 20-mg and 60-mg DCV/pegIFNα/RBV dose groups were numerically higher than the SVR24 rate for the placebo/pegIFNα/RBV group.
    - The SVR24 rates overall were numerically higher in DCV-treated prior partial responders than prior null responders.
    - SVR24 rates among subjects with GT-1b were numerically higher than those with GT-1a in the DCV/pegIFNα/RBV groups.
    - SVR24 rates were better in subjects without baseline cirrhosis than in those with baseline cirrhosis in the DCV/pegIFNα/RBV groups.
  - Concordance between SVR12 and SVR24 was high in the 20-mg and 60-mg DCV/pegIFNα-2a/RBV dose groups.
  - SVR rates were similar in PDR+ subjects treated with either DCV pegIFNα-2a/RBV for a total of 24 weeks or 24 weeks of DCV/pegIFNα-2a/RBV plus 24 weeks of pegIFNα-2a/RBV; in prior null responders, SVR24 in PDR+ subjects was slightly better with a total of 48 weeks of treatment.
  - The majority of virologic failures were due to VBT and relapse in the DCV-treatment groups and treatment futility or detectable HCV RNA at EOT in the placebo/pegIFNα/RBV group.
  - Subjects who were ≥ 80% treatment compliant were more likely to achieve SVR24 than those who were noncompliant (< 80%).

- Daclatasvir was well tolerated at doses of 20 and 60 mg when given in combination with pegIFNα-2a/RBV for up to 24 weeks in prior null and prior partial responders.
  - The safety profile of DCV/pegIFNα-2a/RBV treatment groups were comparable and the safety profile of DCV/pegIFNα-2a/RBV was consistent with pegIFNα-2a/RBV alone, thereby demonstrating that there is no added toxicity when DCV is combined with pegIFNα-2a/RBV.

  - No unique AEs were identified for DCV in this study.
  - There was no apparent difference between DCV/pegIFNα-2a/RBV and pegIFNα-2a/RBV alone with regard to the decline of hemoglobin, neutrophils, lymphocytes, or platelets.
  - DCV/pegIFNα-2a/RBV had a similar safety profile to pegIFNα-2a/RBV alone in cirrhotics.
- In general, virologic failure to DCV/pegIFNα/RBV was associated with the emergence of DCV-resistant variants that were GT-specific. Emergent NS5A variants generally persisted to the end of the study.
  - In GT-1a failures, Q30 variants predominantly emerged either alone or in combination with other NS5A RAVs and pre-existing NS5A-L31M may be associated with virologic failure.
  - In GT-1b failures, L31I/M/V plus Y93H variants were most frequently detected, and pre-existing NS5A-Y93H may be associated with virologic failure.

DATE OF REPORT: 19-Aug-2013