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 AI444010

TITLE OF STUDY: A Phase 2b Study of BMS-790052 in Combination with Peg-Interferon Alfa-2a and Ribavirin in Treatment Naive Subjects with Chronic Hepatitis C Genotype 1 and 4 Infection

INVESTIGATORS/STUDY CENTERS: 64 sites enrolled subjects: 6 in Australia, 5 in Canada, 3 in Denmark, 2 in Egypt, 5 in France, 4 in Germany, 2 in Italy, 1 in Mexico, 1 in Puerto Rico, 2 in Sweden and 33 in the US.

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 14-Jul-2010 **CLINICAL PHASE:** 2b
Study Completion Date: 29-Aug-2012

OBJECTIVES:

Primary:

- Antiviral activity, as determined by the proportion of hepatitis C virus (HCV) genotype (GT)-1 subjects with extended rapid virologic response (eRVR) defined as HCV ribonucleic acid (RNA) < lower limit of quantitation (< LLOQ), target not detected (TND) at both Weeks 4 and 12 on treatment.
- Antiviral activity, as determined by the proportion of HCV GT-1 subjects with sustained virologic response at follow-up Week 24 (SVR24), defined as HCV RNA < LLOQ, TND at follow-up Week 24.
- Safety, as measured by the frequency of serious adverse events (SAEs) and discontinuations due to adverse events (AEs).

Secondary:

- Proportion of HCV GT-1 subjects with rapid virologic response (RVR), i.e., HCV RNA < LLOQ, TND at Week 4 on treatment.
- Proportion of HCV GT-1 subjects with complete early virologic response (cEVR), i.e., HCV RNA < LLOQ, TND at Week 12 on treatment.
- Proportion of HCV GT-1 subjects with sustained virologic response at follow-up Week 12 (SVR_{12}), i.e., HCV RNA < LLOQ, TND at follow-up Week 12.
- Describe resistant variants associated with virologic failure.

Other:

- Relationship between antiviral activity endpoints and the duration of daclatasvir (DCV) + peginterferon alfa-2a (pegIFNα) + ribavirin (RBV) for GT-1 subjects on 24-week DCV regimens: 12 weeks of DCV/pegIFNα/RBV plus 12 weeks of pegIFNα/RBV vs 24 weeks of DCV/pegIFNα/RBV.
- Antiviral activity endpoints for HCV GT-4 subjects.

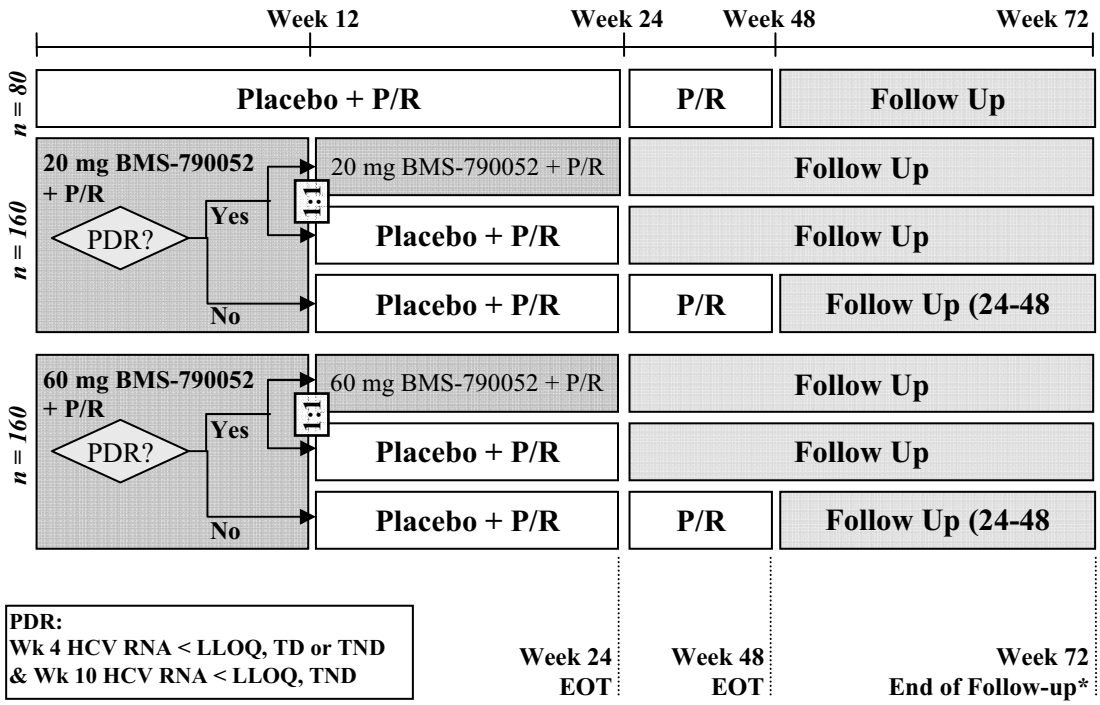
- Relationship between endpoints of safety or antiviral activity and exposure to DCV when co-administered with pegIFNα/RBV.
- Relationship between antiviral activity endpoints and single nucleotide polymorphisms (SNPs) in genes encoding proteins of the interferon lambda (IFNλ) family (IL-28A, IL-28B, IL-29).
- Relationship between antiviral activity endpoints and the changes from baseline in Hepatitis C Physical Symptom Severity (HPSS) Questionnaire score over time for HCV GT-1 subjects.

METHODOLOGY: This is a randomized, double-blind, placebo-controlled, multicenter study conducted in treatment naive, GT-1 and -4 HCV-infected subjects. Subjects were randomized 2:2:1 to either DCV 20 mg, DCV 60 mg, or placebo, plus pegIFNα/RBV (Figure 1). Randomization was stratified by HCV GT determined at screening (GT-1 or -4). Randomization of subjects with HCV GT-4 infection and subjects with compensated cirrhosis were each capped at 10%.

All subjects received DCV or placebo plus pegIFNα/RBV through Week 12. A second randomization (1:1) occurred at Week 12 for subjects initially randomized to 20 mg or 60 mg DCV who achieved a protocol defined response (PDR: HCV RNA < LLOQ, target detected [TD] or TND at Week 4 and HCV RNA < LLOQ, TND at Week 10). These subjects either received an additional 12 weeks of DCV (20 or 60 mg)/pegIFNα/RBV or 12 weeks of placebo/pegIFNα/RBV.

Subjects randomized to DCV, who did not achieve PDR at Week 12, received an additional 36 weeks of therapy (12 weeks placebo/pegIFNα/RBV followed by 24 weeks of pegIFNα/RBV) for a total of 48 weeks of therapy. Subjects randomized to placebo received an additional 36 weeks of therapy (12 weeks placebo/pegIFNα/RBV followed by 24 weeks of pegIFNα/RBV only) regardless of their PDR status, for a total of 48 weeks of therapy.

Figure 1: AI444010 Study Design



BMS-790052 - daclatasvir, EOT - end of treatment, P/R - peginterferon alfa plus ribavirin, PDR - protocol defined response, TD - target detected, TND - target not detected

* Subjects assigned to 48-week DCV regimens had 24 weeks of follow-up; however, if HCV RNA was detectable at EOT or post treatment, 48 weeks of follow-up was required

NUMBER OF SUBJECTS (Planned and Analyzed): The planned number of subjects to be randomized was 160 subjects per DCV treatment group (20 and 60 mg) and 80 subjects in the placebo group. A total of 159, 158, and 78 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: Adult men and women 18 to 70 years of age with chronic HCV GT-1 or -4 infection (GT-4 was capped at 10% of the randomized study population) who: 1) had an HCV RNA viral load of $\geq 10^5$ IU/mL (100,000 IU/mL); 2) no previous exposure to interferon, pegIFNα, or RBV; 3) had a liver biopsy to detect presence or absence of cirrhosis (compensated cirrhotics [based on clinical criteria] with HCV GT-1 infection were eligible, but capped at 10% of the randomized study population); 4) no evidence of hepatocellular carcinoma (HCC) or chronic liver disease; and 5) body mass index (BMI) of 18 to 35 kg/m^2, inclusive.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Subjects received DCV doses of 20 or 60 mg given orally once daily (QD) with pegIFNα/RBV for 12 weeks. Subjects who achieved a PDR either received an additional 12 weeks of DCV (20 or 60 mg)/pegIFNα/RBV or 12 weeks of placebo/pegIFNα/RBV. Subjects who did not achieve PDR at Week 12, received an additional 36 weeks of therapy (12 weeks placebo/pegIFNα/RBV followed by 24 weeks of pegIFNα/RBV) for a total of 48 weeks of therapy. Investigational Product Information appears 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	9B54029, 9H42143, 0B61212, 0B61213

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/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 (BMS) supplied sufficient marketed pegIFNα and RBV product as follows:

- pegIFNα as 1 mL, pre-filled syringes containing 180 μg/0.5 mL, manufactured by Roche Laboratories, Inc, batch number B1116 (expiration: 30-Jun-2011), 0D59456 and B1143 (both expirations : 31-Mar-2012) and B1191 (expiration 30-Jun-2013)
- RBV as 200-mg film-coated tablets (Copegus®) manufactured by Roche Laboratories, Inc, batch numbers 0D60446, 0G59739, 0F59067 (expiration: 30-Apr-2012) and 1B63344 (expiration: 31-Mar-2012).

CRITERIA FOR EVALUATION:

Efficacy: The primary endpoints were the proportions of HCV GT-1 subjects with eRVR and SVR24. Secondary endpoints included the proportions of subjects with RVR, cEVR, and SVR12. Other endpoints included the relationship between antiviral activity endpoints and the duration of DCV therapy, antiviral activity endpoints for HCV GT-4 subjects, relationship between antiviral activity endpoints and SNPs in genes encoding proteins of the IFNλ family (IL-28A, IL-28B, IL-29), and relationship between antiviral activity endpoints and the changes from baseline in HPSS Questionnaire score over time for HCV GT-1 subjects.

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 ≥ LLOQ after confirmed HCV RNA < LLOQ, TND 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 response (EVR): < 2 $\log_{10}$ decrease in HCV RNA from baseline and HCV HCV RNA ≥ LLOQ at Week 12 of treatment
- HCV RNA < LLOQ, TD or ≥ LLOQ at Week 12 and ≥ LLOQ at Week 24
- HCV RNA < LLOQ, TD or ≥ LLOQ at EOT (including early discontinuation)
- Relapse, defined as HCV RNA ≥ LLOQ or HCV RNA < LLOQ, TD during follow-up after HCV RNA < LLOQ, TND 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.

Pharmacokinetics: Determination of the following PK parameters of DCV:

Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
C0	Trough plasma concentration pre-observed dose

Pharmacodynamics: Pharmacodynamic (PD) analyses of the relationship between measures of safety/antiviral activity and exposure to DCV when co-administered with pegIFNα/RBV.

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). Cohort safety stopping rules were assessed as described in the protocol.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics:

Of the 558 subjects enrolled, 395 were randomized and treated:

- 159 to DCV 20 mg/pegIFNα/RBV (147 with GT-1, 12 with GT-4)
- 158 to DCV 60 mg/pegIFNα/RBV (146 with GT-1, 12 with GT-4)
- 78 to placebo/pegIFNα/RBV (72 with GT-1, 6 with GT-4)

A higher proportion of treated subjects in the DCV 20 and 60 mg/pegIFNα/RBV groups completed the treatment period compared with the placebo/pegIFNα/RBV group: 80.5% and 77.8% vs 47.4% (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: 86.8% and 90.2% vs 78.4%. This was mainly due to a higher proportion of subjects in the placebo pegIFNα/RBV group compared with the DCV/pegIFNα/RBV groups who withdrew consent and discontinued due to other reasons that included initiating alternative anti-HCV medications or enrolling in the BMS open-label roll-over study AI444026.

Table 2: Subject Disposition: All Treated Subjects

	Number (%) of Subjects		
	DCV 20 mg/ pegIFNα/RBV	**DCV 60 mg/ pegIFNα/RBV**	**Placebo/ pegIFNα/RBV**
Subjects Randomized and Treated	**159**	**158**	**78**
Completed Treatment Period	**128 (80.5)**	**123 (77.8)**	**37 (47.4)**
Reason for not Completing Treatment Period			
Lack of efficacy	15 (9.4)	18 (11.4)	25 (32.1)
Adverse event	7 (4.4)	8 (5.1)	8 (10.3)
Subject withdrew consent	3 (1.9)	1 (0.6)	1 (1.3)
Death	1 (0.6)	0	0
Lost to follow-up	1 (0.6)	2 (1.3)	1 (1.3)
Poor/non-compliance	0	1 (0.6)	0
Subject requested to discon. treatment	1 (0.6)	3 (1.9)	4 (5.1)
Other	1 (0.6)	1 (0.6)	0
Completed 24-wk treatment period only	2 (1.3)	1 (0.6)	2 (2.6)
Number of Subjects Entering Follow-up	**152**	**153**	**74**
Subjects Completing Follow-up	**132 (86.8)**	**138 (90.2)**	**58(78.4)**
Reason for not Completing Follow-up			
Subject withdrew consent	3 (2.0)	2 (1.3)	5 (6.8)
Death	1 (0.7)	0	0
Lost to follow-up	12 (7.9)	9 (5.9)	6 (8.1)
Other	4 (2.6)	4 (2.6)	5 (6.8)

DCV - daclatasvir, HCV - hepatitis C virus, pegIFNα/RBV **-** peginterferon alfa plus ribavirin

Baseline demographics were balanced across the treatment groups (Table 3). Overall, the majority of subjects were male (67.1%). The mean age in this study was 48.8 years; 2.5% of subjects were ≥ 65 years of age. Most subjects were white (80.8%) and a small proportion were black/African American (11.4%), "other" race (5.6%), or Asian (2.1%). "Other" race includes the following: other mixed race, other Caucasian, other Arabs/Arabic, other Latin America, other Hispanic, and other Egyptian.

Baseline HCV disease characteristics were similar across the treatment groups (Table 3). The mean HCV RNA level was 6.5 $\log_{10}$ IU/mL. Most (80.3%) subjects had a high baseline viral load (≥ 800,000 IU/mL). All subjects had HCV RNA GT-1 (N = 364) or -4 (N = 31). Of the subjects with GT-1, 69.6% had GT-1a and 22.3% had GT-1b. The proportion of subjects with cirrhosis at baseline was 8.2%, 5.1%, and 10.3% in the DCV 20 mg/pegIFNα/RBV, DCV 60 mg/pegIFNα/RBV, and placebo/pegIFNα/RBV groups, respectively. Overall, 30.4% (120/395) and 63.8% (252/395) of subjects had the IL-28B CC and non-CC genotypes, respectively.

Table 3: Baseline Demographic and Disease Characteristics

	DCV 20 mg/ pegIFNα/RBV (N = 159)	DCV 60 mg/ pegIFNα/RBV (N = 158)	Placebo/ pegIFNα/RBV (N = 78)
Age (years)			
Mean	49.1	48.3	49.5
Min, Max	22, 70	18, 67	25, 66
Age Categorization (n, %)			
< 65 years	154 (96.9)	154 (97.5)	77 (98.7)
≥ 65 years	5 (3.1)	4 (2.5)	1 (1.3)
Gender (n, %)			
Male	107 (67.3)	103 (65.2)	55 (70.5)
Female	52 (32.7)	55 (34.8)	23 (29.5)
Race (n, %)			
White	132 (83.0)	127 (80.4)	60 (76.9)
Black/African American	15 (9.4)	21 (13.3)	9 (11.5)
Asian	5 (3.1)	2 (1.3)	1 (1.3)
Other	7 (4.4)	8 (5.1)	8 (10.3)
HCV RNA (log_{10} IU/mL)			
Mean	6.5	6.5	6.4
HCV RNA Distribution (n, %)			
< 800,000 IU/ML	26 (16.4)	35 (22.2)	17 (21.8)
≥ 800,000 IU/ML	133 (83.6)	123 (77.8)	61 (78.2)
HCV Genotype (n, %)			
1	147 (92.5)	146 (92.4)	72 (92.3)
4	12 (7.5)	12 (7.6)	6 (7.7)
Cirrhosis (n, %)			
Absent	146 (91.8)	149 (94.3)	70 (89.7)
Present	13 (8.2)	8 (5.1)	8 (10.3)
Not reported	0	1 (0.6)	0
IL-28B Genotype (n, %)			
CC	53 (33.3)	44 (27.8)	23 (29.5)
CT	82 (51.6)	86 (54.4)	38 (48.7)
TT	17 (10.7)	18 (11.4)	11 (14.1)
Missing	7 (4.4)	10 (6.3)	6 (7.7)

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 all 3 treatment groups: 66.7%, 72.8%, and 66.7% of subjects in the DCV 20 mg/pegIFNα/RBV, DCV 60 mg/pegIFNα/RBV, and placebo/pegIFNα/RBV groups, respectively. 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 was lowest in the DCV

60 mg/pegIFNα/RBV group (15.8%) compared with the DCV 20 mg/pegIFNα/RBV (19.5%) and placebo/pegIFNα/RBV (23.1%) groups.

Efficacy Results: The following summary points for efficacy are based on the modified ITT analysis (Tables 4 and 5):

- In treatment-naive subjects with HCV GT-1, virologic response rates during treatment and SVR rates during follow-up with DCV 20 mg/pegIFNα/RBV and DCV 60 mg/pegIFNα/RBV were comparable and higher than those for placebo/pegIFNα/RBV.
    - Earlier and persistent virologic response was observed in the DCV/pegIFNα/RBV groups. Extended RVR rates (HCV RNA < LLOQ, TND at both Weeks 4 and 12 on treatment) with DCV 20 or 60 mg/pegIFNα/RBV were 40% higher compared with placebo/pegIFNα/RBV.
    - SVR24 rates (HCV RNA < LLOQ, TND at follow-up Week 24) with DCV 20 or 60 mg/pegIFNα/RBV were 22% higher compared with placebo/pegIFNα/RBV.
    - SVR24 rates in subjects who received 12 weeks of DCV/pegIFNα/RBV followed by 12 weeks of pegIFNα/RBV were generally comparable to those in subjects who received 24 weeks of DCV/pegIFNα/RBV.
- A PDR (HCV RNA < LLOQ, TD or TND at Week 4 and HCV RNA < LLOQ, TND at Week 10) was achieved by a higher proportion of GT-1 subjects in the DCV/pegIFNα/RBV groups compared with the placebo/pegIFNα/RBV group, resulting in a shorter duration of therapy for the majority of GT-1 subjects treated with DCV.
    - DCV/pegIFNα/RBV-treated subjects who achieved PDR were roughly 3 to 4.5 times more likely to have an SVR24 response compared with PDR failures. DCV/pegIFNα/RBV-treated subjects with a PDR had SVR24 rates of 73% to 75% compared with 20% to 24% in PDR failures.
- Among GT-1 subjects with HCV RNA results at both follow-up Weeks 12 and 24, there was 96.8% to 99.2% concordance between SVR12 and SVR24 rates in the DCV/pegIFNα/RBV groups.
- DCV/pegIFNα/RBV demonstrated efficacy in all subgroups of subjects with GT-1.
    - SVR24 rates were comparable in subjects with and without baseline cirrhosis.
    - SVR24 rates were higher in subjects with HCV GT-1b compared with GT-1a.
    - SVR24 rates were higher in subjects who received DCV/pegIFNα/RBV compared with those who received placebo/pegIFNα/RBV for all IL-28B rs12979860 genotypes (CC, CT, or TT).
- Virologic failure in treatment-naive subjects with GT-1 was more common in the placebo/pegIFNα/RBV group compared with the DCV/pegIFNα/RBV groups, mainly due to a higher proportion of subjects who met the Week 4 futility rule (< 1 $\log_{10}$ decrease in HCV RNA from baseline at Week 4 of treatment).
    - In the DCV/pegIFNα/RBV groups, virologic failure was more common in subjects with GT-1a compared with those with GT-1b, mainly due to a higher rate of VBT.
    - Baseline nonstructural protein 5A (NS5A) polymorphisms at leucine (L)31 isoleucine (I)/valine (V)/methionine (M) and tyrosine (Y)93 histidine (H)/asparagine (N)/serine (S) in GT-1a subjects may be loosely associated with virologic failure, especially when combined with a non-CC IL-28B GT.
    - In all subjects who failed with HCV RNA ≥ 1000 IU/mL and an available NS5A sequence, NS5A resistance variants were detected; substitutions at glutamine (Q)30 predominated in GT-1a, substitutions at L31-Y93 predominated in GT-1b, and substitutions at L28-L30 predominated in GT-4.
- SVR24 rates for treatment-naive subjects with GT-4 were higher in the DCV/pegIFNα/RBV groups (66.7% in the DCV 20 mg and 100% in the DCV 60 mg groups) compared with 50% in the placebo/pegIFNα/RBV group.

Table 4: Efficacy Results: All Treated Subjects with HCV Genotype-1

Modified ITT	DCV 20 mg/ pegIFNα/RBV N = 147	DCV 60 mg/ pegIFNα/RBV N = 146	Placebo/ pegIFNα/RBV N = 72
Virologic Endpoints % (Responder /N)			
Co-primary Endpoints			
eRVR	54.4 (80/147)	54.1 (79/146)	13.9 (10/72)
80% CI	49.2, 59.7	48.8, 59.4	8.7, 19.1
SVR24	59.2 (87/147)	59.6 (87/146)	37.5 (27/72)
80% CI	54.0, 64.4	54.4, 64.8	30.2, 44.8
SVR24 in PDR responders	73.3 (77/105)	75.2 (79/105)	-
SVR24 in PDR non-responders	23.8 (10/42)	19.5 (8/41)	-
Secondary and Other Efficacy Endpoints			
RVR	59.9 (88/147)	56.8 (83/146)	15.3 (11/72)
80% CI	54.7, 65.0	51.6, 62.1	9.8, 20.7
cEVR	77.6 (114/147)	75.3 (110/146)	43.1 (31/72)
80% CI	73.1, 82.0	70.8, 79.9	35.6, 50.5
PDR	72.1 (106/147)	72.6 (106/146)	18.1 (13/72)
80% CI	67.4, 76.8	67.9, 77.3	12.2, 23.9
EOTR	81.0 (119/147)	79.5 (116/146)	56.9 (41/72)
80% CI	76.8, 85.1	75.2, 83.7	49.5, 64.4
SVR4	70.7 (104/147)	67.1 (98/146)	43.1 (31/72)
80% CI	65.9, 75.6	62.1, 72.1	35.6, 50.5
SVR12	64.6 (95/147)	60.3 (88/146)	36.1 (26/72)
80% CI	59.6, 69.7	55.1, 65.5	28.9, 43.4
On-Treatment Virologic Failure	**19.0 (28/147)**	**19.9 (29/146)**	**40.3 (29/72)**
Virologic Breakthrough	8.2 (12/147)	10.3 (15/146)	2.8 (2/72)
Week 4 Futility Rule	2.0 (3/147)	2.1 (3/146)	25.0 (18/72)
Detectable HCV RNA at EOT	7.5 (11/147)	6.8 (10/146)	5.6 (4/72)
Other	1.4 (2/147)	< 0.1 (1/146)	6.9 (5/72)
Relapse (in subjects with HCV RNA < LLOQ, TND at EOT)	**18.5 (22/119)**	**19.0 (22/116)**	**22.0 (9/41)**

cEVR - complete early virologic response (HCV RNA < LLOQ, TND at Week 12), CI - confidence interval, DCV - daclatasvir, EOT - end of treatment, eRVR - extended rapid virologic response (HCV RNA < LLOQ, TND at both Week 4 and 12), HCV - hepatitis C virus, < LLOQ - less than the lower limit of quantitation, PDR - protocol defined response (HCV RNA < LLOQ, TD or TND at Week 4 and HCV RNA < LLOQ, TND at Week 10), pegIFNα/RBV - peginterferon alfa + ribavirin, RNA - ribonucleic acid, RVR - rapid virologic response (HCV RNA < LLOQ, TND at Week 4), SVR4/SVR12/SVR24 - sustained virologic response (< LLOQ, TND HCV RNA) at follow-up Weeks 4, 12, and 24, respectively, TD - target detected, TND - target not detected

Table 5: Efficacy Results: All Treated Subjects with HCV Genotype-4

Modified ITT	DCV 20 mg/ pegIFNα/RBV N = 12	DCV 60 mg/ pegIFNα/RBV N = 12	Placebo/ pegIFNα/RBV N = 6
Virologic Endpoints % (Responder /N)			
RVR	25.0 (3/12)	33.3 (4/12)	0 (0/6)
80% CI	9.0, 41.0	15.9, 50.8	0, 0
cEVR	75.0 (9/12)	100.0 (12/12)	50.0 (3/6)
80% CI	59.0, 91.0	100.0, 100.0	23.8, 76.2
eRVR	16.7 (2/12)	33.3 (4/12)	0 (0/6)
80% CI	2.9, 30.5	15.9, 50.8	0, 0
PDR	66.7 (8/12)	100.0 (12/12)	33.3 (2/6)
80% CI	49.2, 84.1	100.0, 100.0	8.7, 58.0
EOTR	83.3 (10/12)	100.0 (12/12)	66.7 (4/6)
80% CI	69.5, 97.1	100.0, 100.0	42.0, 91.3
SVR4	75.0 (9/12)	100.0 (12/12)	33.3 (2/6)
80% CI	59.0, 91.0	100.0, 100.0	8.7, 58.0
SVR12	75.0 (9/12)	100.0 (12/12)	50.0 (3/6)
80% CI	59.0, 91.0	100.0, 100.0	23.8, 76.2
SVR24	66.7 (8/12)	100.0 (12/12)	50.0 (3/6)
80% CI	49.2, 84.1	100.0, 100.0	23.8, 76.2
On-Treatment Virologic Failure	**16.7 (2/12)**	**0**	**33.3 (2/6)**
Virologic Breakthrough	1 (8.3)	0	0
Week 4 Futility Rule	1 (8.3)	0	33.3 (2/6)
Relapse (in subjects with HCV RNA < LLOQ, TND at EOT)	**20.0 (2/10)**	**0 (0/12)**	**25.0 (1/4)**

cEVR - complete early virologic response (HCV RNA < LLOQ, TND at Week 12), CI - confidence interval, DCV - daclatasvir, EOT - end of treatment, eRVR - extended rapid virologic response (HCV RNA < LLOQ, TND at both Week 4 and 12), HCV - hepatitis C virus, < LLOQ - less than the lower limit of quantitation, PDR - protocol defined response (HCV RNA < LLOQ, TD or TND at Week 4 and HCV RNA < LLOQ, TND at Week 10), pegIFNα/RBV - peginterferon alfa + ribavirin, RNA - ribonucleic acid, RVR - rapid virologic response (HCV RNA < LLOQ, TND at Week 4), SVR4/SVR12/SVR24 - sustained virologic response (< LLOQ, TND HCV RNA) at follow-up Weeks 4, 12, and 24, respectively, TD - target detected, TND - target not detected

Safety Results:

Daclatasvir 20 mg or 60 mg/pegIFNα/RBV therapy was well tolerated in treatment-naive subjects with HCV GT-1 and GT-4 with a safety profile that was consistent with that for placebo/pegIFNα/RBV (Table 6).

- Two subjects in the DCV 20 mg/pegIFNα/RBV group died: 1 during the treatment period (sudden death due to unknown causes) and 1 during follow-up (cardiopulmonary failure exacerbated by asthma). Both deaths were unrelated to study therapy by investigator assessment.
- On-treatment, SAEs regardless of relationship to study drug were reported in approximately 8% of subjects in each treatment group.
- On-treatment AEs leading to discontinuation of study therapy were more common in the placebo/pegIFNα/RBV group (10%) compared with the DCV/pegIFNα/RBV groups (4%).

- There were no clinically relevant trends in AEs on-treatment. The most commonly reported AEs in all dose groups were fatigue, headache, pruritus, nausea, insomnia, rash, influenza-like illness and myalgia. These AEs are commonly associated with pegIFNα/RBV therapy.
- No unique AEs were identified for DCV in this study.
- There were no differences observed in the safety profile of 12 weeks of DCV/pegIFNα/RBV plus 12 weeks of pegIFNα/RBV and 24 weeks of DCV/pegIFNα/RBV treatment.
- DCV/pegIFNα-2a/RBV had a similar safety profile to pegIFNα-2a/RBV alone in cirrhotics.
- No clinically relevant trends in laboratory abnormalities were observed on-treatment or during follow-up. The most common laboratory abnormalities were hematologic abnormalities, which are frequently observed for pegIFNα/RBV.

Table 6: On-treatment Safety: All Treated Subjects

	Number (%) of Subjects		
	DCV 20 mg/ pegIFNα/RBV (N = 159)	**DCV 60 mg/ pegIFNα/RBV (N = 158)**	**Placebo/ pegIFNα/RBV (N = 78)**
Adverse Events			
Death	1 (0.6)[a]	0	0
SAEs	12 (7.5)	13 (8.2)	6 (7.7)
AEs Leading to Discontinuation of Study Drugs	7 (4.4)	7 (4.4)	8 (10.3)
Grade 3/4 AEs	32 (20.1)	23 (14.6)	18 (23.1)
Most Common AEs (> 30% in any group)			
Fatigue	88 (55.3)	86 (54.4)	46 (59.0)
Headache	68 (42.8)	68 (43.0)	36 (46.2)
Pruritus	56 (35.2)	63 (39.9)	26 (33.3)
Nausea	56 (35.2)	53 (33.5)	20 (25.6)
Insomnia	49 (30.8)	53 (33.5)	30 (38.5)
Rash	54 (34.0)	40 (25.3)	25 (32.1)
Influenza-like illness	45 (28.3)	49 (31.0)	16 (20.5)
Myalgia	45 (28.3)	43 (27.2)	25 (32.1)
Measured Grade 3/4 Laboratory Abnormalities			
Hemoglobin	9 (5.7)	10 (6.4)	5 (6.6)
WBC	24 (15.1)	19 (12.1)	7 (9.2)
Neutrophils	42 (26.4)	46 (29.3)	20 (26.3)
Lymphocytes	21 (13.2)	21 (13.4)	9 (11.8)
Platelets	2 (1.3)	5 (3.2)	2 (2.6)
ALT	0	6 (3.8)	1 (1.3)
AST	0	4 (2.5)	2 (2.6)
Total Bilirubin	1 (0.6)	0	1 (1.3)
Lipase	5 (3.1)	1 (0.6)	0

AEs - adverse events, ALT - alanine aminotransferase, AST - aspartate aminotransferase, DCV daclatasvir, pegIFNα/RBV - peginterferon alfa plus ribavirin, SAEs - serious adverse events, WBC - white blood cell

[a] An additional subject in the DCV 20 mg/pegIFNα/RBV group died due to cardiopulmonary failure exacerbated by asthma at follow-up Week 12.

Patient Reported Outcomes: Based on an analysis of scores from Hepatitis Physical Symptom Severity Diary (HPSS-D), overall symptom severity in the DCV treatment groups was comparable to the placebo group, indicating that addition of DCV to pegIFNα/RBV did not impact the symptom severity of physical or flu-like symptoms.

HPSS-D is a novel patient-reported outcome instrument developed by Bristol-Myers Squibb (BMS) to measure presence and severity of physical symptoms associated with HCV and related treatments on a daily basis. The HPSS-D is a 14-item self-report instrument designed for daily assessment of physical symptoms commonly reported by HCV patients, especially those undergoing treatment.

Pharmacokinetics Results: Pharmacokinetic parameters Cmax, Tmax and C0 were assessed for subjects participating in the semi-intense PK sampling at Week 2.

- DCV geometric mean Cmax values following administration of oral doses of 20 and 60 mg were ~ 389 and ~ 1347 ng/mL, respectively.
- DCV C0 geometric mean values were ~ 61 and ~ 194 ng/mL following administration of oral doses of 20 and 60 mg, respectively.
- DCV Tmax geometric mean value was 1.5 hours following administration of oral doses of 20 and 60 mg.

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 below:

- Baseline NS5A polymorphisms at L31I/V/M and Y93H/N/S in GT-1a subjects may be loosely associated with virologic failure, especially when combined with a non-CC IL-28B GT. A correlation could not be determined for baseline NS5A polymorphisms at M28 or Q30.
  - Any potential correlation with baseline NS5A polymorphisms at 28, 30, 31, or 93 and GT-1b and GT-4 failures was less apparent.
  - IL-28B GT did appear to be more predictive of failure against subjects infected with GT-1b and GT-4.
- In all available subjects who failed with HCV RNA ≥ LLOQ, NS5A resistance variants were detected; substitutions at Q30 predominated in GT-1a, substitutions at L31-Y93 predominated in GT-1b, and substitutions at L28-L30 predominated in GT-4.
- A greater number of GT-1a subjects (46%, 101/220) did not achieve SVR24 than GT-1b subjects (25%, 18/72) or GT-4 subjects (16%, 4/25).
  - The resistance barrier to DCV in GT-1a subjects was lower than for GT-1b and GT-4 in that one emergent substitution could confer high level resistance to DCV in GT-1a whereas at least 2 substitutions were generally required in GT-1b and GT-4.
  - Pre-existence of a GT-1a NS5A resistance-associated variant may increase a subject's chance of failure to DCV/pegIFNα/RBV treatment, although this observation is based on a limited number of cases.
- Irrespective of GT or emergent variant, the emergent NS5A resistance variants were fit and generally persisted out to follow-up Week 48.
- The commercially available VERSANT HCV Genotype 2.0 (LiPA) genotyping kit was shown to be reliable for GT-1 sub-typing of baseline samples from 317 subjects; mis-genotyping, as determined by NS5A sequence alignment with GT-1a (H77c) and GT-1b (Con1) reference strains, was only detected in ~ 1% of samples.

CONCLUSIONS:

The following are the conclusions from this study:

- DCV at 20 mg and 60 mg QD in combination with pegIFNα-2a/RBV demonstrated rapid antiviral activity and increased rates of SVR24 in treatment-naïve subjects with GT-1 and GT-4 HCV compared with pegIFNα-2a/RBV alone.
  - The SVR24 rates for the 20 mg and 60-mg DCV/pegIFNα-2a/RBV dose groups for the treatment-naïve GT-1 subjects were 22% higher than the SVR24 rate for the placebo/pegIFNα-2a/RBV group.
    - SVR24 rates among subjects with GT-1b were higher than those with GT-1a in the DCV/pegIFNα-2a/RBV groups.
    - SVR24 rates were comparable in subjects with and without baseline cirrhosis.
    - SVR24 rates were higher in subjects who received DCV/pegIFNα/RBV compared with those who received placebo/pegIFNα/RBV for all IL-28B rs12979860 genotypes (CC, CT, or TT).
  - eRVR rates as well as all other on-treatment virologic response rates were consistent with this finding; eRVR rates were 40% higher in both DCV/pegIFNα-2a/RBV groups compared with placebo/pegIFNα-2a/RBV.
  - In the 20-mg and 60-mg DCV/pegIFNα-2a/RBV dose groups in subjects with GT-1, concordance between SVR12 and SVR24 was high.
  - A high proportion of subjects achieved PDR in the DCV/pegIFNα-2a/RBV groups and were treated with only 24 weeks of therapy.
    - SVR rates were similar in PDR subjects treated with either 12 or 24 weeks of DCV and with 24 weeks of pegIFNα-2a/RBV.
  - The majority of virologic failures were due to VBT and relapse in the treatment-naive subjects with GT-1.
  - The SVR24 rates for treatment-naive subjects with GT-4 were higher in the DCV/pegIFNα/RBV groups compared with the placebo/pegIFNα/RBV group.
- DCV was well tolerated at doses of 20 and 60 mg when given in combination with pegIFNα-2a/RBV for up to 24 weeks in treatment-naïve subjects with GT-1 and GT-4 HCV.
  - The safety profile of DCV/pegIFNα-2a/RBV was consistent with pegIFNα-2a/RBV alone.
  - 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.
  - Hepatic laboratory abnormalities were minimal in this study with no Grade 4 AST, ALT or bilirubin increases reported. Improved ALT values from baseline were reported in all treatment groups.
  - DCV/pegIFNα-2a/RBV had a similar safety profile to pegIFNα-2a/RBV alone in cirrhotics.

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