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: Daclatasvir (BMS-790052)		

SYNOPSIS

Final Clinical Study Report for Study AI444031

TITLE OF STUDY: A Phase 2b Pilot Study of Short-Term Treatment of BMS-790052 in Combination with Peg-Interferon Alfa-2a and Ribavirin in Treatment Naive Subjects with Chronic Hepatitis C Genotype 2 or 3 Infection

INVESTIGATORS/STUDY CENTERS: 26 sites (United States, Australia, Canada, Denmark, France, and Italy) enrolled subjects

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 20-Dec-2010 **CLINICAL PHASE:** 2b

Study Completion Date: 13-Sep-2012

OBJECTIVES:

Primary: The primary objective was to assess antiviral activity, as determined by the proportion of subjects who achieved sustained virologic response at follow-up Week 24 (SVR24) for each hepatitis C virus (HCV) genotype (GT), defined in the protocol as undetectable HCV ribonucleic acid (RNA) (but referred to in this clinical study report [CSR] as HCV RNA less than the lower limit of quantitation [< LLOQ], target not detected [TND]) at follow-up Week 24.

Secondary:

- To assess safety, as measured by the frequency of serious adverse events (SAEs) and discontinuations due to AEs.
- To assess the proportion of subjects with rapid virologic response (RVR: defined as HCV RNA < LLOQ, TND at Week 4) for each HCV GT.
- To assess the proportion of subjects with sustained virologic response at follow-up Week 12 (SVR12: defined as HCV RNA < LLOQ, TND at follow-up Week 12) for each HCV GT.
- To describe resistant variants associated with virologic failure for each HCV GT.

METHODOLOGY: This was a Phase 2b, randomized, placebo-controlled, response-guided study. Subjects were randomized 1:1:1 to either daclatasvir (DCV)/ peginterferon alfa plus ribavirin (pegIFNα/RBV) for 12 weeks, DCV/pegIFNα/RBV for 16 weeks, or placebo/pegIFNα/RBV for 24 weeks (control group) (Figure 1). Randomization was stratified by HCV GT determined at screening (-2 or -3) and was capped at approximately 50% for each HCV GT.

Subjects randomized to receive 12 or 16 weeks of treatment were evaluated for a protocol-defined response (PDR).

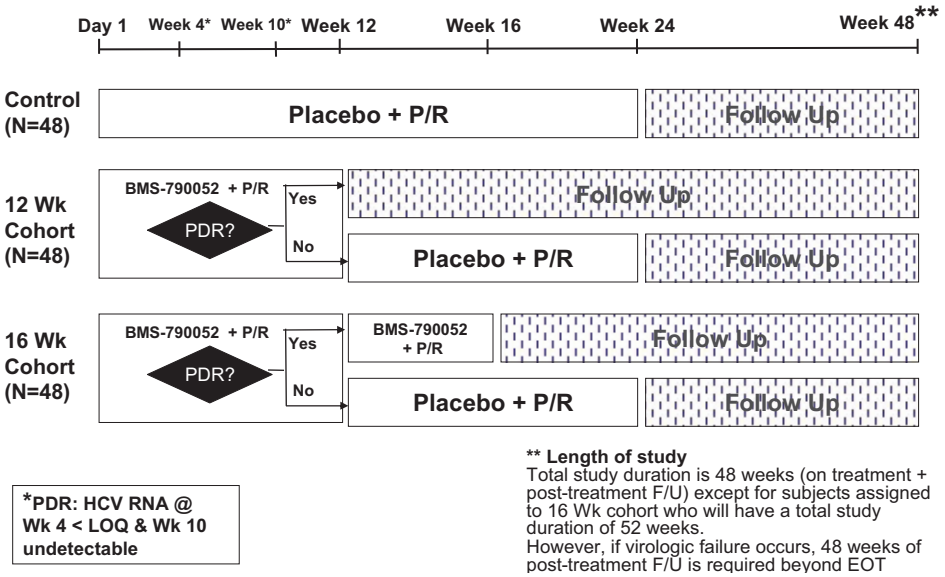
- Subjects who achieved a PDR (defined as HCV RNA < LLOQ, target detected [TD] or TND at Week 4 and HCV RNA at < LLOQ, TND at Week 10) completed 12 or 16 weeks of DCV/pegIFNα/RBV therapy based on their initial randomization and proceeded to post-treatment follow-up.
- Subjects who did not achieve a PDR were required to receive 24 weeks of therapy. At Week 12 of DCV/pegIFNα/RBV treatment, these subjects received an additional 12 weeks of placebo/pegIFNα/RBV. The change in treatment regimen was administered via the interactive voice response system (IVRS).

Subjects in the control group received 24 weeks of pegIFNα/RBV irrespective of response during therapy.

Subjects participated in the study for a total of approximately 48 weeks (or 52 weeks for subjects assigned to the 16-week cohort), irrespective of their treatment duration (e.g., subjects who received shorter treatment had a longer post-treatment follow-up). The purpose of longer follow up for subjects who completed shorter durations of therapy was to allow assessment of the durability of SVR for these regimens.

Any subject randomized to DCV who demonstrated virologic failure (regardless of length of treatment) required a total of 48 weeks of post-treatment follow-up to monitor for drug-resistant HCV variants. Thus, the maximum amount of time on study for any subject was 72 weeks.

Figure 1: Study Design



PDR is defined as HCV RNA < LLOQ, TD or TND at Week 4 and < LLOQ, TND at Week 10. In the figure, HCV RNA < LOQ is the same as HCV RNA < LLOQ, TD or TND.

BMS-790052 - daclatasvir (DCV), EOT - end of treatment, F/U - follow-up, HCV - hepatitis C virus, LLOQ - lower limit of quantitation, PDR - protocol-defined response, P/R - peginterferon alfa + ribavirin, RNA - ribonucleic acid, TD - target detected, TND - target not detected

NUMBER OF SUBJECTS: Of the 196 subjects enrolled, 152 subjects were randomized, and 151 subjects were treated:

- 50 to 12 weeks of treatment with DCV/pegIFNα/RBV: 24 with GT-2, 26 with GT-3
- 50 to 16 weeks of treatment with DCV/pegIFNα/RBV: 23 with GT-2, 27 with GT-3
- 51 to 24 weeks of treatment with placebo/pegIFNα/RBV: 24 with GT-2, 27 with GT-3.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Adult men and women 18 to 70 years of age with 1) chronic HCV GT-2 or -3 infection, 2) an HCV RNA viral load of $\geq 10^5$ IU/mL (100,000 IU/mL), 3) no previous exposure to interferon, pegIFNα, or RBV, and 4) no evidence of hepatocellular carcinoma (HCC), decompensated cirrhosis, or chronic liver disease (other than hepatitis C). Subjects with compensated liver cirrhosis were included (compensated cirrhotics were capped at approximately 10% of the randomized population).

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: DCV 60 mg once daily (QD) in tablet form for 12 or 16 weeks (Table 1).

Table 1: Investigational Product Identification

Drug Product	Formulation	Product Batch Number
DCV 30 mg	Film-coated tablet	9L51069
Placebo	Film-coated tablet	0B61213
Ribavirin	Film-coated tablet	1B63344, 0D60446, 0F59067, 0J64930
Peginterferon	Prefilled syringes	0D59456, B1191

CRITERIA FOR EVALUATION:

Efficacy: The primary efficacy variable was the proportion of subjects for each HCV GT with SVR24, defined as HCV RNA < LLOQ, TND at follow-up Week 24.

Secondary efficacy endpoints included RVR: HCV RNA < LLOQ, TND at Week 4, SVR12: HCV RNA < LLOQ, TND at follow-up Week 12, and the frequency of genotypic substitutions associated with virologic failure for each HCV genotype.

Other endpoints included the proportion of subjects for each HCV GT with extended rapid virologic response (eRVR): HCV RNA < LLOQ, TND at both Weeks 4 and 12, the proportion of subjects for each HCV GT with early virologic response (EVR), defined as ≥ 2 log10 decrease in HCV RNA from baseline or HCV RNA < LLOQ, TD or TND at Week 12 on treatment, proportion of subjects for each HCV genotype with complete early virologic response (cEVR) defined as HCV RNA < LLOQ, TND at Week 12, proportion of subjects for each HCV genotype with PDR defined as HCV RNA < LLOQ, TD or TND at Week 4 and HCV RNA < LLOQ, TND at Week 10, proportion of subjects for each HCV genotype with SVR4, defined as HCV RNA < LLOQ, TND at follow-up Week 4, and exploring the relationship between endpoints of safety and/or antiviral activity and exposure to DCV when co-administered with pegIFNα/RBV.

Virologic failure 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. Measurements were to be confirmed within 2 weeks of receipt of initial HCV RNA measurement or at the next scheduled visit, whichever was sooner.
  - Subjects were to discontinue DCV/placebo but were to continue pegIFNα/RBV at the discretion of the investigator to complete a total duration of therapy of 24 weeks regardless of PDR status.
- < 1 log10 decrease in HCV RNA from baseline at Week 4 of treatment
  - Subjects were to discontinue DCV/placebo but were to continue pegIFNα/RBV at the discretion of the investigator.
- Failure to achieve EVR: < 2 log10 decrease in HCV RNA from baseline and HCV RNA ≥ LLOQ at Week 12 of treatment
  - Subjects were to discontinue all study drugs.
- HCV RNA ≥ LLOQ or < LLOQ, TD at EOT (including early discontinuation)
- Relapse, defined as HCV RNA ≥ LLOQ or < 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.

Other: HCV Resistance Testing: 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 analyses. The following safety endpoints were summarized by treatment group for treated subjects by study period (on-treatment and follow-up): SAEs; AEs leading to discontinuation of study therapy; AEs (related and regardless of relationship to study therapy); laboratory abnormalities by toxicity grade. 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. Response rates were presented with 2-sided 80% exact binomial confidence intervals (CIs). Viral genotypic substitutions at baseline and newly emergent viral genotypic substitutions on treatment or during follow-up were summarized.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics:

12-week DCV/pegIFNα/RBV Group

A total of 45 (90.0%) subjects completed 12 weeks of DCV/pegIFNα/RBV; this includes 23 (95.8%) subjects with GT-2 and 22 (84.6%) subjects with GT-3. Overall, the most common reason for not completing the treatment period was due to an AE. Of the 49 subjects who entered follow-up, 48 (98.0%) subjects completed the follow-up period.

16-week DCV/pegIFNα/RBV Group

A total of 44 (88.0%) subjects completed 16 weeks of DCV/pegIFNα/RBV; this includes 20 (87.0%) subjects with GT-2 and 24 (88.9%) subjects with GT-3. Overall, the most common reasons for not completing the treatment period were lost to follow-up and the subject requesting to discontinue study treatment. Of the 47 subjects who entered follow-up, 41 (87.2%) subjects completed the follow-up period.

Placebo/pegIFNα/RBV Group

A total of 42 (82.4%) subjects completed 24 weeks of placebo/pegIFNα/RBV treatment; this includes 19 (79.2%) subjects with GT-2 and 23 (85.2%) subjects with GT-3. The most common reason for not completing the treatment period was due to lack of efficacy. Of the 49 subjects who entered follow-up 39 (79.6%) subjects completed the follow-up period.

Baseline/Demographic and Disease Characteristics

Baseline demographics were generally balanced across the treatment groups. Overall, the majority of subjects were male (63.6%); however, there was a higher proportion of female subjects in the placebo group compared with the DCV groups (47.1% vs 26.0% - 36.0%) (Table 2). The mean age in this study was 47.9 years; 1 subject in the 16-week DCV group was ≥ 65 years of age (67 years). Most subjects were white (85.4%) and a small proportion were Asian other (5.3%), black/African American (2.6%), or Asian/Indian (2.6%). The distribution of subjects across the 3 BMI categories (< 25, 25 to < 30, and ≥ 30 kg/m^2) was similar in all 3 treatment groups.

Baseline demographics were generally similar in subjects with GT-2 and subjects with GT-3, with a few exceptions. There were a higher proportion of female subjects with GT-2 compared with GT-3 (45.1% vs 28.8%). Subjects with GT-2 (mean ages: 49.0 - 52.7 years) tended to be older than subjects with GT-3 (mean ages: 45.3 - 46.2 years). Overall, a higher proportion of subjects with GT-2 were from North America compared with subjects with GT-3 (48% vs 28%) and a lower proportion of subjects with GT-2 were from Europe compared with subjects with GT-3 (30% vs 51%).

Baseline HCV disease characteristics were similar across the treatment groups. Mean HCV RNA level ranged from 6.4 to 6.6 $\log_{10}$ IU/mL. Most (83.4%) subjects had a high baseline viral load (≥ 800,000 IU/mL). All subjects were infected with HCV RNA GT-2 (N = 71) or GT-3 (N = 80). The proportion of subjects with cirrhosis at baseline was 14.0%, 8.0%, and 15.7% in the 12-week DCV/pegIFNα/RBV, 16-week DCV/pegIFNα/RBV, and placebo/pegIFNα/RBV groups, respectively. Overall, a higher proportion of subjects had the IL-28B rs12979860 non-CC genotypes (61.6%) compared with the IL-28B CC genotype (37.1%).

Baseline characteristics were generally similar in subjects with GT-2 and subjects with GT-3, with a few exceptions. There were a higher proportion of female subjects with GT-2 compared with GT-3 (45.1% vs 28.8%). Subjects with GT-2 (mean ages: 49.0 - 52.7 years) tended to be older than subjects with GT-3 (mean ages: 45.3 - 46.2 years). Baseline liver cirrhosis was more common in subjects with GT-3 compared with GT-2 (22.5% vs 1.4%). A higher proportion of GT-3 subjects compared with GT-2 subjects had an IL-28B rs12979860 CC genotype (41.3% vs 32.4%).

Table 2: Demographic and Baseline Disease Characteristics - All Treated Subjects

	DCV/ pegIFNα/RBV 12 weeks N = 50	DCV/ pegIFNα/RBV 16 weeks N = 50	Placebo/ pegIFNα/RBV 24 weeks N = 51
Age (years)			
Mean	47.5	47.5	48.8
Min, Max	28, 64	25, 67	20, 63
Age Categorization (n, %)			
< 65 years	50 (100.0)	49 (98.0)	50 (98.0)
≥ 65 years	0	1 (2.0)	0
Gender (n, %)			
Male	32 (64.0)	37 (74.0)	27 (52.9)
Female	18 (36.0)	13 (26.0)	24 (47.1)
HCV RNA (log10 IU/mL)			
Mean	6.4	6.6	6.6
HCV RNA Distribution (n, %)			
< 800,000 IU/ML	12 (24.0)	7 (14.0)	6 (11.8)
≥ 800,000 IU/ML	38 (76.0)	43 (86.0)	45 (88.2)
HCV Genotype (n, %)			
2	24 (48.0)	23 (46.0)	24 (47.1)
3	26 (52.0)	27 (54.0)	27 (52.9)
Liver Cirrhosis (n, %)			
Absent	43 (86.0)	43 (86.0)	41 (80.4)
Present	7 (14.0)	4 (8.0)	8 (15.7)
Not Reported	0	3 (6.0)	2 (3.9)
IL-28B Genotype (n, %)			
CC	20 (40.0)	19 (38.0)	17 (33.3)
CT	20 (40.0)	26 (52.0)	30 (58.8)
TT	9 (18.0)	4 (8.0)	4 (7.8)

HCV - hepatitis C virus, IFN/RBV - interferon plus ribavirin, RNA - ribonucleic acid

Extent of Exposure: The mean duration of study therapy was 13.0, 16.2, and 22.1 weeks in the 12-week DCV/pegIFNα/RBV, 16-week DCV/pegIFNα/RBV, and placebo/pegIFNα/RBV groups, respectively. The median duration of therapy was 12.1, 16.1, and 24.0 weeks in the 12-week DCV/pegIFNα/RBV, 16-week DCV/pegIFNα/RBV, and placebo/pegIFNα/RBV groups, respectively. The median daily DCV doses in each DCV group, as well as the median daily pegIFNα and RBV doses were consistent with the protocol-specified doses.

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 88.0%, 76.0%, and 70.6% in the 12-week DCV/pegIFNα/RBV, 16-week DCV/pegIFNα/RBV, and placebo/pegIFNα/RBV groups, respectively. The high

adherence of subjects who received the shorter duration of therapy (12-week DCV/pegIFNα/RBV group) illustrates the high tolerability of DCV.

Efficacy Results:

In treatment-naive subjects with HCV GT-2/-3, virologic response rates with 12 weeks or 16 weeks of treatment DCV/pegIFNα/RBV were higher than those for placebo/pegIFNα/RBV given for 24 weeks. SVR24 (HCV RNA < LLOQ, TND) rates were similar between the DCV/pegIFNα/RBV 12-week and 16-week groups (Table 3). SVR rates were higher in subjects with GT-2 compared with those for subjects with GT-3. The overall efficacy summary statements are based on the modified ITT analysis.

Primary efficacy endpoint:

- For treatment-naive subjects with either GT-2 or GT-3, SVR24 rates were comparable (≤ 5% difference) in the DCV/pegIFNα/RBV (12-week and 16-week) groups and higher compared with placebo/pegIFNα/RBV given for 24 weeks. SVR24 rates were higher in subjects with GT-2 compared with those for subjects with GT-3.
    - GT-2: SVR24 was 83.3% and 82.6% in the DCV/pegIFNα/RBV 12-week and 16-week groups, respectively, and 62.5% in the placebo group.
    - GT-3: SVR24 was 69.2% and 66.7% in the DCV/pegIFNα/RBV 12-week and 16-week groups, respectively, and 59.3% in the placebo group.

Secondary and other efficacy endpoints:

- In subjects with GT-2 and in subjects with GT-3, most virologic response rates on-treatment and during follow-up [sustained]), including RVR and SVR12, were numerically higher in the DCV/pegIFNα/RBV groups (12-week and 16-week) compared with the placebo/pegIFNα/RBV group.
- More than 78% of subjects in the 12-week and 16-week DCV/pegIFNα/RBV groups achieved the PDR and were therefore treated for a shortened duration of therapy, only 12 to 16 weeks compared with 24 weeks of treatment in the placebo group.
- Among DCV/pegIFNα/RBV-treated subjects with HCV RNA results at both follow-up Weeks 12 and 24, concordance between SVR12 and SVR24 rates was 100% in subjects with GT-2 and 96% in subjects with GT-3.
    - Two subjects with GT-3 (1 in the 12-week DCV/pegIFNα/RBV group and 1 in the 16-week DCV/pegIFNα/RBV group) were not concordant because they had missing HCV RNA at follow-up Week 12.
- DCV/pegIFNα/RBV demonstrated efficacy in all subgroups of subjects.
    - Subjects with baseline cirrhosis had lower SVR rates than those without cirrhosis.
    - Subjects treated with DCV/pegIFNα/RBV (for 12 or 16 weeks) appeared to be less sensitive to pegIFNα and/or RBV dose reduction than subjects treated with placebo/pegIFNα/RBV.
- Virologic failure was higher in subjects with GT-3 compared with subjects with GT-2, mainly due to higher rates of relapse in subjects with GT-3 (15 total with GT-3: 12 DCV/pegIFNα/RBV relapsers and 3 placebo/pegIFNα/RBV relapsers).
    - All of the GT-3 relapsers had a baseline HCV RNA level ≥ 800,000 IU/mL.
    - 33% (5/15) of GT-3 relapsers had baseline liver cirrhosis.
    - IL-28B rs12979860 non-CC genotype did not appear to be associated with relapse in subjects with GT-3.
    - Baseline NS5A resistance-associated polymorphisms (alanine [A]30 lysine [K] or tyrosine [Y]93 histidine [H]) may be loosely associated with virologic failure in subjects infected with GT-3; 4/8 (50%) of subjects with A30K or Y93H relapsed.
    - Virologic failure (VBT and relapse) was associated with the detection of NS5A resistance-associated variants at the time of failure: asparagine (N)62 aspartic acid (D)-Y93H in subjects with GT-2 and A30K and Y93H in subjects with GT-3.

Table 3: Efficacy Results- All Treated Subjects

Modified Intent to Treat Responder/Evaluable	DCV/ pegIFNα/RBV 12 weeks	DCV/ pegIFNα/RBV 16 weeks	Placebo/ pegIFNα/RBV 24 weeks
Genotype 2	**N =24**	**N = 23**	**N =24**
RVR	87.5 (21/24)	73.9 (17/23)	41.7 (10/24)
80% CI	(78.8, 96.2)	(62.2, 85.6)	(28.8, 54.6)
cEVR	91.7 (22/24)	82.6 (19/23)	75.0 (18/24)
80% CI	(84.4, 98.9)	(72.5, 92.7)	(63.7, 86.3)
PDR	87.5 (21/24)	78.3 (18/23)	66.7 (16/24)
80% CI	(78.8, 96.2)	(67.2, 89.3)	(54.3, 79.0)
SVR12	87.5 (21/24)	82.6 (19/23)	70.8 (17/24)
80% CI	(78.8, 96.2)	(72.5, 92.7)	(58.9, 82.7)
SVR24 (Primary Endpoint)	83.3 (20/24)	82.6 (19/23)	62.5 (15/24)
80% CI	(73.6, 93.1)	(72.5, 92.7)	(49.8, 75.2)
On-Treatment Virologic Failure	1 (4.2)	4 (17.4)	2 (8.3)
Virologic Breakthrough	0	1 (4.3)	1 (4.2)
< 1 $\log_{10}$ HCV RNA decr. from BL at Wk 4	0	1 (4.3)	0
HCV RNA < LLOQ, TD or ≥ LLOQ at EOT	1 (4.2)	2 (8.7)	1 (4.2)
Relapse (in subjects with HCV RNA < LLOQ, TND at EOT)	1/23 (4.3)	0/21	1/22 (4.5)
Genotype 3	**N = 26**	**N = 27**	**N = 27**
RVR	84.6 (22/26)	74.1 (20/27)	37.0 (10/27)
80% CI	(75.5, 93.7)	(63.3, 84.9)	(25.1, 48.9)
cEVR	80.8 (21/26)	88.9 (24/27)	59.3 (16/27)
80% CI	(70.9, 90.7)	(81.1, 96.6)	(47.1, 71.4)
PDR	84.6 (22/26)	81.5 (22/27)	40.7 (11/27)
80% CI	(75.5, 93.7)	(71.9, 91.1)	(28.6, 52.9)
SVR12	69.2 (18/26)	77.8 (21/27)	51.9 (14/27)
80% CI	(57.6, 80.8)	(67.5, 88.0)	(39.5, 64.2)
SVR24 (Primary Endpoint)	69.2 (18/26)	66.7 (18/27)	59.3 (16/27)
80% CI	(57.6, 80.8)	(55.0, 78.3)	(47.1, 71.4)
On-Treatment Virologic Failure	1 (3.8)	3 (11.1)	7 (25.9)
Virologic Breakthrough	0	0	1 (3.7)
< 1 $\log_{10}$ HCV RNA decr. from BL at Wk 4	0	1 (3.7)	3 (11.1)
HCV RNA < LLOQ, TD or > LLOQ at EOT	1 (3.8)	2 (7.4)	3 (11.1)
Relapse (in subjects with HCV RNA < LLOQ, TND at EOT)	6/25 (24.0)	6/24 (25.0)	3/21 (14.3)

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:

DCV/pegIFNα/RBV therapy for 12 or 16 weeks was generally well tolerated in treatment-naive subjects with HCV GT-2/-3 with a safety profile that was consistent with that for placebo/pegIFNα/RBV (Table 4).

- No deaths were reported in this study.
- On-treatment, SAEs regardless of relationship to study drug were reported for ≤ 8% of subjects per group. Serious adverse events were reported for 2 subjects in the 12-week DCV/pegIFNα/RBV during the follow-up period.
- On-treatment AEs leading to discontinuation of study therapy were reported for ≤ 8% of subjects per group.
- There were no clinically relevant trends in AEs on-treatment. The most commonly reported AEs (> 15% in all dose groups) were headache, fatigue, pruritus, rash, nausea, and insomnia. These AEs are commonly 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 of 12 weeks of DCV/pegIFNα/RBV and 16 weeks of DCV/pegIFNα/RBV treatment.
- DCV/pegIFNα-2a/RBV appeared to have a similar safety profile to pegIFNα-2a/RBV alone in the small subgroup of subjects with baseline liver cirrhosis.
- No clinically relevant trends in laboratory abnormalities, electrocardiograms (ECGs) or vital signs were observed on-treatment or during follow-up. The most common laboratory abnormalities were hematologic abnormalities, which are frequently observed for pegIFNα/RBV.

Table 4: On-treatment Safety: All Treated Subjects

	Number (%) of Subjects		
	DCV/pegIFNα/RBV 12 weeks (N = 50)	**DCV/pegIFNα/RBV 16 weeks (N = 50)**	**Placebo/pegIFNα/RBV 24 weeks (N = 51)**
Adverse Events			
SAEs	4 (8.0)	0	3 (5.9)
AEs Leading to Discontinuation of Study Drugs	4 (8.0)	3 (6.0)	2 (3.9)
Grade 3/4 AEs	7 (14.0)	4 (8.0)	6 (11.8)
Most Common AEs (> 15% in all 3 groups)			
Headache	15 (30.0)	15 (30.0)	9 (17.6)
Fatigue	23 (46.0)	12 (24.0)	19 (37.3)
Pruritus	14 (28.0)	13 (26.0)	14 (27.5)
Rash	13 (26.0)	12 (24.0)	12 (23.5)
Nausea	10 (20.0)	12 (24.0)	8 (15.7)
Insomnia	11 (22.0)	8 (16.0)	17 (33.3)

Table 4: On-treatment Safety: All Treated Subjects

	Number (%) of Subjects		
	DCV/pegIFNα/RBV 12 weeks (N = 50)	**DCV/pegIFNα/RBV 16 weeks (N = 50)**	**Placebo/pegIFNα/RBV 24 weeks (N = 51)**
Measured Grade 3/4 Laboratory Abnormalities			
Hemoglobin	3 (6.0)	0	3 (5.9)
WBC	4 (8.0)	6 (12.0)	4 (7.8)
Neutrophils	10 (20.0)	12 (24.0)	16 (31.4)
Lymphocytes	5 (10.0)	7 (14.3)	4 (7.8)
Platelets	1 (2.0)	2 (4.0)	4 (7.8)
ALT	1 (2.0)	1 (2.0)	0
AST	1 (2.0)	1 (2.0)	1 (2.0)
Total Bilirubin	2 (4.0)	0	0
Lipase	2 (4.0)	1 (2.0)	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

Pharmacokinetic Results:

The PK parameters for DCV were comparable in the 2 DCV/pegIFNα/RBV treatment groups (12-week and 16-week groups). Both groups had a median time of maximum observed plasma concentration (Tmax) of 2 hours, a maximum observed plasma concentration (Cmax, geometric mean) of 981 to 1021 ng/mL, and a trough plasma concentration observed pre-dose (C0, geometric mean) of 161 to 162 ng/mL.

Pharmacodynamic Results:

DCV/pegIFNα/RBV led to a rapid decline in mean HCV RNA that was faster compared with the placebo/pegIFNα/RBV group. At the first treatment visit, Week 1, this decline was notable. This mean improvement in HCV RNA was maintained through Week 24 for all treatment groups.

There were no clinically relevant trends in AEs or laboratory abnormalities associated with DCV. The decline in mean hemoglobin or ANC over time was comparable for both DCV/pegIFNα/RBV groups and the placebo/pegIFNα/RBV group.

Other Results:

HCV Drug Resistance

- The baseline NS5A resistance-associated polymorphism leucine (L)31 methionine(M) was detected in the majority of GT-2 subjects (23/44 with sequence data) and did not impact response rates.
- There may be a loose association with baseline NS5A resistance-associated polymorphisms detected by population sequencing and virologic failure in subjects infected with GT-3; 4/8 (50%) of subjects with A30K or Y93H relapsed.
- Only 1/47 GT-2 subjects experienced VBT with the emergence of NS5A-N62D-Y93H while on treatment, although this subject ultimately achieved SVR24 with 24 weeks of treatment.
- In GT-3 subjects experiencing virologic failure (3 on-treatment, 12 relapsers), A30K (2/15 subjects) and Y93H (12/15 subjects) was detected at the time of failure.

- In general, the GT-3 NS5A resistance-associated variants persisted out to follow-up Week 24 (detected in 8/9 subjects monitored).

CONCLUSIONS:

In summary, the following conclusions regarding the antiviral activity and safety of DCV/pegIFNα/RBV therapy in treatment-naive subjects with HCV RNA GT-2 and GT-3 may be made based on data obtained from the current study:

- DCV 60 mg QD/pegIFNα/RBV for 12 or 16 weeks demonstrated higher SVR rates among subjects infected with HCV GT-2 and GT-3 compared with pegIFNα/RBV for 24 weeks.
  - SVR rates were similar between DCV/pegIFNα/RBV treatment for 12 weeks and 16 weeks in subjects with GT-2 or GT-3.
  - DCV 60 mg QD/pegIFNα/RBV for 12 or 16 weeks demonstrated rapid antiviral activity (RVR) in subjects with HCV GT-2 and GT-3 (81% and 79%).
  - More than 78% of subjects achieved the PDR in the 12-week and 16-week DCV/pegIFNα/RBV groups and were therefore treated for a shortened duration of therapy of only 12 to 16 weeks compared with 24 weeks of treatment in the placebo group.
- SVR24 rates were higher in subjects with GT-2 compared with those for subjects with GT-3.
- Among DCV/pegIFNα/RBV-treated subjects with HCV RNA results at both follow-up Weeks 12 and 24, concordance between SVR12 and SVR24 rates was 100% in subjects with GT-2 and 96% in subjects with GT-3.
- The majority of virologic failures were due to relapse in subjects with GT-3 in the study.
  - Baseline liver cirrhosis and baseline NS5A resistant variants (A30K or Y93H) may be predisposing factors for relapse in subjects infected with GT-3.
- DCV 60 mg/pegIFNα/RBV was well tolerated when given for up to 16 weeks in treatment-naive subjects.
  - The safety profile of DCV/pegIFNα/RBV was consistent with pegIFNα/RBV alone.
  - There did not appear to be a difference in the safety profile of 12 weeks of DCV/pegIFNα/RBV and 16 weeks of DCV/pegIFNα/RBV treatment.
  - No unique AEs were identified for DCV in this study.
  - In the DCV/pegIFNα/RBV groups, there was no increase rash, GI events (including ano-rectal events) and no apparent increase in bone marrow suppression compared with pegIFNα/RBV alone.
  - There was no apparent difference between DCV/pegIFNα/RBV and pegIFNα/RBV alone with regard to hematologic parameters, liver function tests, ECGs, and vital signs.
- The PK of DCV observed in this study is similar to what has previously been observed with DCV in combination with pegIFNα/RBV.

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