BRISTOL-MYERS SQUIBB COMPANY

DACLATASVIR

Final Clinical Study Report for Study AI444052

A Phase 3 Evaluation of BMS-790052 (Daclatasvir) Compared with Telaprevir in Combination with Peg-Interferon Alfa-2a and Ribavirin in Treatment-Naive Patients with Chronic Hepatitis-C

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THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:
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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 AI444052

TITLE OF STUDY: A Phase 3 Evaluation of BMS-790052 (Daclatasvir) Compared with Telaprevir in Combination with Peg-Interferon Alfa-2a and Ribavirin in Treatment-Naive Patients with Chronic Hepatitis-C

INVESTIGATORS/STUDY CENTERS: 90 sites in 15 countries (Argentina, Austria, Australia, Canada, Denmark, France, Germany, Israel, Italy, Poland, Russia, Spain, Switzerland, the United Kingdom, and the United States) randomized 605 subjects.

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 22-Feb-2012 **CLINICAL PHASE:** 3
Study Completion Date: 20-Mar-2014

RESEARCH HYPOTHESIS: In treatment-naive patients chronically infected with hepatitis C virus (HCV) genotype 1b (GT-1b), treatment with daclatasvir (DCV) plus peg-interferon alfa-2a (pegIFNα-2a)/ribavirin (RBV) ("DCV/P/R") has similar SVR12 rates (sustained virologic response at 12 weeks after the last dose of study drug) to telaprevir (TVR) plus pegIFNα-2a/RBV ("TVR/P/R").

OBJECTIVES:

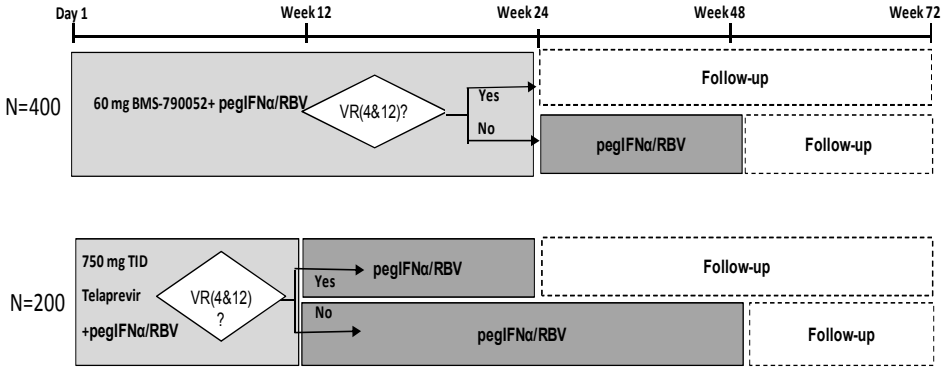
Primary: To compare rates of SVR12, defined as HCV RNA < limit of quantitation (LOQ) (target detected [TD] or target not detected [TND]) at follow-up Week 12, for GT-1b subjects treated with either DCV or TVR in combination with pegIFNα-2a/RBV.

Secondary:

- To compare the proportion of GT-1b subjects with hemoglobin laboratory value < 10 g/dL during the first 12 weeks of treatment;
- To compare the proportion of GT-1b subjects with rash-related dermatologic "events of special interest" reported during the first 12 weeks of treatment;
- To compare the proportion of GT-1b subjects with HCV RNA < LLOQ, TND at Week 12;
- To compare the proportion of GT-1b subjects with HCV RNA < LLOQ, TND at Week 4;
- To compare the proportion of GT-1b subjects with HCV RNA < LLOQ, TND at Weeks 4 and 12;
- To compare the proportion of GT-1b subjects with SVR24, defined as HCV RNA < LOQ (TD or TND) at follow-up Week 24;
- To compare the proportion of GT-1b subjects with SVR12 by IL28B rs12979860 SNP genotype.
- To compare rates of SVR12 for GT-1a subjects treated with either DCV or TVR in combination with pegIFNα-2a/RBV.

METHODOLOGY: This was a Phase 3, randomized, open-label, multicenter study conducted in treatment-naive subjects infected with HCV GT-1. A schematic of the AI444052 study design is shown in Figure 1.

Figure 1: AI444052 Study Design



**Two thirds of all patients in each arm must have genotype 1b. The number of genotype 1a subjects will be capped at one-third of the total number of patients per arm.*

For Response Guided Therapy (RGT):

VR(4&12) is defined as HCV RNA undetectable at Weeks 4 and 12

Six-hundred subjects were to be randomized 2:1 to receive DCV or TVR. Randomization was stratified according to IL28B rs12979860 host genotype (CC or non-CC), HCV subtype (GT-1b or GT-1a), and baseline cirrhosis status (absent or present). The number of GT 1a subjects was capped at 200. The total duration of this study was 72 weeks (on treatment phase plus follow-up). Both DCV- and TVR-assigned subjects who achieved a virologic response [VR (4&12)], also referred to as eRVR in the literature, defined as HCV RNA < LLOQ, TND at both Week 4 and Week 12, were to complete therapy at Week 24 and were to be evaluated for an additional 48 weeks of post-treatment follow-up. Both DCV- and TVR-assigned subjects who achieved HCV RNA < LLOQ, TND but not VR (4&12) were to receive an additional 24 weeks of pegIFNα-2a/RBV for a total treatment duration of 48 weeks, and were evaluated for 24 weeks in the post-treatment follow-up period. Subjects were to discontinue all study drugs in the event of treatment futility, defined for the DCV/P/R arm as virologic breakthrough (VBT, confirmed > 1 $\log_{10}$ increase in HCV RNA over nadir or confirmed HCV RNA ≥ LOQ after confirmed HCV RNA < LLOQ, TND while on treatment beginning at Week 2 of therapy), Week 12 HCV RNA > 1,000 IU/mL, and Week 24 HCV RNA ≥ LOQ; and for the TVR/P/R arm as Week 4 or 12 HCV RNA > 1000 IU/mL, and Week 24 HCV RNA detectable confirmed.

NUMBER OF SUBJECTS (Planned and Analyzed): The planned number of subjects to be randomized was 600. To ensure that approximately 400 of the subjects were GT-1b infected, randomization of subjects with GT-1a infection was to be capped at approximately 200. Seven hundred and ninety three subjects were enrolled, 605 of whom were randomized. Of the 605 subjects randomized, 602 were treated.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: The study population was to consist of adult men and women ≥18 years of age chronically infected with HCV GT-1a or -1b who had an HCV RNA viral load of ≥ 10^4 IU/mL (10,000 IU/mL); no previous exposure to an interferon formulation (ie, IFNα, pegIFNα), RBV, or HCV direct antiviral agent (protease, polymerase inhibitor, etc); seronegative for human immunodeficiency virus and hepatitis B surface antigen (HBsAg); and no evidence of hepatocellular carcinoma. Subjects with compensated cirrhosis were permitted (capped at approximately 25% of treated population).

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: DCV 60 mg once daily (QD) tablet was self-administered by mouth for 24 weeks. All subjects received pegIFNα-2a/RBV treatment for HCV infection: 180 µg pegIFNα given once weekly (QW); and RBV (for subjects weighing < 75 kg the total dose was 1000 mg per day and for those weighing ≥ 75 kg the dose was 1200 mg per day; therefore, subjects were to take either 400 mg [2 tablets for subjects < 75 kg] or 600 mg [3 tablets for subjects ≥ 75 kg] in the morning with food and 600 mg [3 tablets] in the evening with food). Information on investigational product administered during the treatment phase of the study is presented in Table 1.

Table 1: Investigational Product Identification

Drug Product	Formulation	Product Batch Numbers
BMS-790052-05 60 mg (as the free base)	Film-coated tablet	1D65922, 1G66006, 1G66009, 1J67801
Telaprevir (INCIVEK™); Vertex Pharmaceuticals Inc.	750 mg film-coated tablet	224180, 244035, 244049
Telaprevir (INCIVO™); Janssen-Cilag	750 mg film coated tablet	BJL2Z01
Peginterferon alfa-2a (Pegasys®); F. Hoffmann-La Roche LTD	0.5 mL, pre-filled syringes containing 180 µg/0.5 mL	B1191, B1221, B1233, B1240
Ribavirin (Copegus®); Hoffmann-La Roche Inc, or Patheon, Inc.	200 mg film-coated tablets	123650, 134919, 134977, 899756, 899761, 899762, 899765, 913114, 914595, 964713

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Telaprevir 750 mg three times daily (TID) was self-administered by mouth approximately 7-9 hours apart for 12 weeks. All subjects received pegIFNα-2a/RBV treatment for HCV infection: 180 µg pegIFNα given QW; and RBV (for subjects weighing < 75 kg the total dose was 1000 mg per day and for those weighing ≥ 75 kg the dose was 1200 mg per day; therefore, subjects were to take either 400 mg [2 tablets for subjects < 75 kg] or 600 mg [3 tablets for subjects ≥ 75 kg] in the morning with food and 600 mg [3 tablets] in the evening with food).

CRITERIA FOR EVALUATION:

Efficacy: The HCV RNA collected at follow-up Week 12 was used for the primary objective, the comparison of proportions of GT-1b subjects in each treatment arm with SVR12, defined as HCV RNA < LOQ at follow-up Week 12. The HCV RNA collected at Weeks 4, 12, and follow-up Week 24 was used for the secondary antiviral assessments in this study.

Safety: Safety endpoints included deaths, SAEs, AEs leading to discontinuation, Grade 3 or 4 AEs, and Grade 3 or 4 laboratory abnormalities

Pharmacokinetics: Pharmacokinetic (PK) trough samples were collected from all subjects assigned to DCV at randomization at Weeks 2, 4, 8, and 12 for DCV, and Weeks 4, 8, and 12 for RBV and pegIFNα-2a concentrations.

Other: HCV Resistance Testing: Resistance testing of variants associated with virologic failure was done. Stored plasma samples for possible resistance testing were collected at study visits indicated in the study protocol. Resistance testing was performed in subjects receiving DCV/P/R by population sequencing on all baseline samples and in all subjects with HCV RNA ≥ 1000 IU/mL who had virologic failure or relapse.

STATISTICAL CONSIDERATIONS: Demography, baseline characteristics, and efficacy analyses were presented on treated subjects grouped by arm assigned at randomization (also referred to "modified ITT"). Safety, extent of exposure, and PK were presented on treated subjects, grouped by arm, as treated (also referred to "as received").

The primary hypothesis to be tested was that the SVR12 rate in GT-1b subjects receiving DCV/P/R was similar to, ie, non-inferior to, the rate in GT-1b subjects receiving TVR/P/R. The secondary hypotheses were that:

- the rate of hemoglobin < 10 g/dL through Week 12 in GT-1b subjects receiving DCV/P/R was less than the rate in GT-1b subjects receiving TVR/P/R
- the rate of rash-related dermatologic events through Week 12 in GT-1b subjects receiving DCV/P/R was less than the rate in GT-1b subjects receiving TVR/P/R
- the rate of cEVR in GT-1b subjects receiving DCV/P/R was non-inferior to the rate in GT-1b subjects receiving TVR/P/R

- the rate of RVR in GT-1b subjects receiving DCV/P/R was non-inferior to the rate in GT-1b subjects receiving TVR/P/R
- the rate of eRVR in GT-1b subjects receiving DCV/P/R was non-inferior to the rate in GT-1b subjects receiving TVR/P/R
- the SVR24 rate in GT-1b subjects receiving DCV/P/R was non-inferior to the rate in GT-1b subjects receiving TVR/P/R
- the SVR12 rate in GT-1b, IL28B rs129798860 non-CC subjects receiving DCV/P/R was non-inferior to the rate in similar subjects receiving TVR/P/R
- the SVR12 rate in GT-1a subjects receiving DCV/P/R was non-inferior to the rate in GT-1a subjects receiving TVR/P/R.

Individual tests were carried out at the 5% significance level. Tests were conducted in hierarchical order (order listed) in order to limit the type 1 error rate for the group of tests as a whole to 5%. Efficacy tests were carried out using stratified Mantel-Haenszel 95% confidence intervals for differences in rates -- DCV/P/R minus TVR/P/R. (The stratification factors were IL28B rs12979860 SNP, CC vs non-CC, and cirrhosis status at baseline.) If the lower bound of the confidence interval for the difference exceeded -12%, DCV/P/R was considered to be non-inferior to TVR/P/R, at the 5% significance level, provided all prior tests were significant as well. Safety tests were carried out using unstratified 95% confidence intervals for the difference in event rates -- DCV/P/R minus TVR/P/R. For safety testing, if the upper bound of the 95% confidence interval was less than 0, DCV/P/R was considered to be significantly less toxic than TVR/P/R.

Efficacy results are presented by GT (1b versus 1a) while safety results are pooled across GT, except in the case of the tests for safety mentioned above. In addition, key safety analyses were repeated by GT. The frequencies of the following safety events were summarized by study period (on-treatment and follow-up) for treated subjects: SAEs, AEs leading to discontinuation of study therapy (regardless of onset) (only for the on-treatment period); AEs by intensity (as determined by the investigator); laboratory abnormalities by toxicity grade.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics:

Of the 793 subjects enrolled, 605 (76.3%) were randomized to treatment. A total of 188 enrolled subjects did not enter the treatment period because they no longer met study entry criteria during the screening period, withdrew consent, had an AE, or were not randomized due to administrative or other reasons. Three subjects were randomized but never received study therapy. Two hundred and sixty eight (268) and 134 GT-1b subjects were randomized and treated in the DCV/P/R and TVR/P/R treatment arms, respectively, and 134 and 66 GT-1a subjects were randomized and treated in the DCV/P/R and TVR/P/R treatment arms, respectively (Table 2). The treatment period was completed by 85.4% and 85.1% of GT-1b subjects in the DCV/P/R and TVR/P/R arms, respectively, and by 67.2% and 69.7% of GT-1a subjects in the DCV/P/R and TVR/P/R arms, respectively. Lack of efficacy and AEs were the most frequent reasons for treatment discontinuation. A total of 575 subjects entered post-treatment follow-up, 384 in the DCV/P/R and 191 in TVR/P/R arm. Of these subjects, 359 (93.5%) in the DCV/P/R arm and 181 (94.8%) in the TVR/P/R arm completed the study.

Among GT-1b subjects, 57.5% were male and the median age was 47 years; most subjects were white (92.5%), black or African American (4.7%), or Asian (2.0%). Among GT-1a subjects, 72.5% were male and the median age was 50 years; most subjects were white (91.5%), black or African American (6.5%), or Asian (0.5%). Most subjects had IL-28B rs12979860 non-CC genotype (80.1% of subjects with GT-1b and 69.0% with GT-1a). Overall, 10.2% of GT-1b and 12.5% of GT-1a subjects had compensated cirrhosis at baseline. Demographics were comparable between the DCV/P/R and TVR/P/R treatment arms within each GT-1 cohort (Table 3).

Table 2: Subject Disposition - Treated Subjects

	GT-1b			GT-1a		
	DCV/P/R	**TVR/P/R**	**Total**	**DCV/P/R**	**TVR/P/R**	**Total**
No. of Subjects Treated	268	134	402	134	66	200
No. of Subjects Completed Therapy	229 (85.4)	114 (85.1)	343 (85.3)	90 (67.2)	46 (69.7)	136 (68.0)
No. of Subjects Discontinued Therapy[a]	39 (14.6)	20 (14.9)	59 (14.7)	44 (32.8)	20 (30.3)	64 (32.0)
Lack of Efficacy	15 (5.6)	0	15 (3.7)	23 (17.2)	5 (7.6)	28 (14.0)
Adverse Event	14 (5.2)	17 (12.7)	31 (7.7)	11 (8.2)	8 (12.1)	19 (9.5)
Subject Request	6 (2.2)	0	6 (1.5)	1 (0.7)	3 (4.5)	4 (2.0)
Subject Withdrew Consent	1 (0.4)	2 (1.5)	3 (0.7)	0	0	0
Death	0	0	0	0	1 (1.5)	1 (0.5)
Lost to Follow-up	3 (1.1)	1 (0.7)	4 (1.0)	6 (4.5)	3 (4.5)	9 (4.5)
All Other Reasons	0	0	0	3 (2.2)	0	3 (1.5)

[a] Reflects discontinuation of all study medication.

Table 3: Baseline and Demographic Characteristics

	GT-1b			GT-1a		
	DCV/P/R N = 268	**TVR/P/R N = 134**	**Total N = 402**	**DCV/P/R N = 134**	**TVR/P/R N = 66**	**Total N = 200**
Age, yrs, median (range)	46.0 (18, 71)	48.0 (19, 69)	47.0 (18, 71)	49.0 (19, 67)	51.5 (28, 69)	50.0 (19, 69)
Male, n (%)	159 (59.3)	72 (53.7)	231 (57.5)	98 (73.1)	47 (71.2)	145 (72.5)
Race, n (%)						
White	243 (90.7)	129 (96.3)	372 (92.5)	120 (89.6)	63 (95.5)	183 (91.5)
African American/Black	16 (6.0)	3 (2.2)	19 (4.7)	11 (8.2)	2 (3.0)	13 (6.5)
Asian	6 (2.2)	2 (1.5)	8 (2.0)	1 (0.7)	0	1 (0.5)
Other	3 (1.1)	0	3 (0.7)	2 (1.5)	1 (1.5)	3 (1.5)
HCV RNA, $\log_{10}$ IU/mL, mean (SD)	6.23 (0.701)	6.23 (0.577)	6.23 (0.662)	6.30 (0.637)	6.31 (0.636)	6.31 (0.635)
HCV RNA, n (%)						
< 800,000 IU/mL	72 (26.9)	37 (27.6)	109 (27.1)	30 (22.4)	15 (22.7)	45 (22.5)
≥ 800,000 IU/mL	196 (73.1)	97 (72.4)	293 (72.9)	104 (77.6)	51 (77.3)	155 (77.5)
IL28B Genotype (rs12979860), n (%)						
CC	53 (19.8)	27 (20.1)	80 (19.9)	42 (31.3)	20 (30.3)	62 (31.0)
CT	161 (60.1)	86 (64.2)	247 (61.4)	73 (54.5)	37 (56.1)	110 (55.0)
TT	53 (19.8)	21 (15.7)	74 (18.4)	19 (14.2)	9 (13.6)	28 (14.0)
Not Reported	1 (0.4)	0	1 (0.2)	0	0	0
Cirrhosis, n (%)						
Absent	242 (90.3)	119 (88.8)	361 (89.8)	118 (88.1)	57 (86.4)	175 (87.5)
Present	26 (9.7)	15 (11.2)	41 (10.2)	16 (11.9)	9 (13.6)	25 (12.5)

Hypothesis Test Results:

Results of hypothesis tests are given in Table 4.

- The primary objective, to show that the SVR12 rate among GT-1b subjects in the DCV/P/R arm was similar to (non-inferior to) the rate in the TVR/P/R arm, was met. (Lower bound of the 95% CI for the difference of DCV/P/R minus TVR/P/R, -3.3%, exceeded the -12% non-inferiority margin.)
- The first secondary objective, which was to show that the incidence of hemoglobin < 10 g/dL among GT-1b subjects was lower in the DCV/P/R arm than in the TVR/P/R arm, was also met. (The upper bound of the 95% CI for the difference [DCV/P/R-TVR/P/R], -19.4%, was less than 0.)
- The next secondary objective, however, was not met. This was to show that incidence of grade 3-4 rash, rash qualifying as an SAE, or rash leading to discontinuation among GT-1b subjects was lower in the DCV/P/R arm than in the TVR/P/R arm. Although the observed rate of rash in the DCV/P/R (1.9%) was lower than in the TVR/P/R arm (5.2%), the difference did not achieve significance, with the upper bound of the confidence interval, 0.7%, just exceeding 0.
- All subsequent tests are, by definition, non-significant as well.

Efficacy Results:

Efficacy results are presented in Table 4.

- **Primary Endpoint:** SVR12 (HCV RNA < LLOQ, TD or TND at follow-up Week 12) among GT-1b subjects in the DCV/P/R arm (85.1%) was similar (non-inferior) to the rate in the TVR/P/R arm (81.3%). The lower bound of the 95% CI for the difference of DCV/P/R minus TVR/P/R, -3.3%, exceeded the -12% non-inferiority margin.
- **Secondary Efficacy Endpoints:**
  - RVR (< LLOQ, TND at Week 4) in GT-1b: 77.2% of subjects DCV/P/R subjects achieved RVR versus 79.1% TVR/P/R subjects.
  - eRVR (< LLOQ, TND at Weeks 4 and 12) in GT1b: 75.0% of DCV/P/R subjects achieved eRVR versus 73.1% of TVR/P/R subjects.
  - cEVR (< LLOQ, TND at Week 12) in GT1b: 90.7 % of DCV/P/R subjects achieved cEVR versus 90.3% of TVR/P/R subjects.
  - SVR24 (< LLOQ, TND or TD at follow-up Week 24) in GT-1b: 84.3% of DCV/P/R subjects achieved SVR24 versus 80.6% of TVR/P/R subjects.
  - In GT-1a subjects, SVR12 (< LLOQ, TND or TD at follow-up Week 12) was achieved by 64.9% of DCV/P/R subjects and 69.7% of TVR/P/R subjects.
- **Virologic Failures:**
  - Treatment futility in GT-1b: 1.1% of subjects in the DCV/P/R arm and 0% of subjects in the TVR/P/R arm. VBT: 4.1% of subjects in the DCV/P/R arm.
  - Other on-treatment failure in GT-1b: 2.6% of subjects in the DCV/P/R arm and 2.2% of subjects in the TVR/P/R arm had detectable HCV RNA at EOT.
  - Confirmed relapse in GT-1b: 4.9% of subjects in the DCV/P/R arm and 15.3% of subjects in the TVR/P/R arm.

Table 4: Primary and Key Secondary Endpoints and Comparisons

	GT-1b		GT-1a	
	DCV/P/R N = 268 n/N (%)	**TVR/P/R N = 134 n/N (%)**	**DCV/P/R N = 134 n/N (%)**	**TVR/P/R N = 66 n/N (%)**
SVR12 (<LOQ at F/U Week 12)	228/268 (85.1)	109/134 (81.3)	87/134 (64.9)	46/66 (69.7)
95% CI	(80.2, 89.1)	(73.7, 87.5)	(56.2, 73.0)	(57.1, 80.4)
Difference and 95% CI	4.3 (-3.3, 11.9)*		-3.5 (-15.9, 8.9)[a]	
Hemoglobin <10 g/dL through Week 12	49/268 (18.3)	63/133 (47.4)		
95% CI	(13.8, 23.4)	(38.7, 56.2)		
Difference and 95% CI	-29.1 (-38.8,-19.4)*			
Rash through Week 12	5/268 (1.9)	7/134 (5.2)		
95% CI	(0.6, 4.3)	(2.1, 10.5)		
Difference and 95% CI	-3.4 (-7.5, 0.7)			
cEVR (TND at Week 12)	243/268 (90.7)	121/134 (90.3)		
95% CI	(86.5, 93.9)	(84.0, 94.7)		
Difference and 95% CI	0.6 (-5.5, 6.6)			
RVR (TND at Week 4)	207/268 (77.2)	106/134 (79.1)		
95% CI	(71.7, 82.1)	(71.2, 85.6)		
Difference and 95% CI	-1.5 (-9.8, 6.8)			
eRVR (TND at Week 4 and 12)	201/268 (75.0)	98/134 (73.1)		
95% CI	(69.4, 80.1)	(64.8, 80.4)		
Difference and 95% CI	2.2 (-6.8, 11.2)			
SVR24 (<LOQ at F/U Week 24)	226/268 (84.3)	108/134 (80.6)		
95% CI	(79.4, 88.5)	(72.9, 86.9)		
Difference and 95% CI	4.4 (-3.5, 12.2)			
SVR12 (<LOQ at F/U Week 12) in IL28B rs12979860 Non-CC	177/215 (82.3)	86/107 (80.4)		
95% CI	(76.6, 87.2)	(71.6, 87.4)		
Difference and 95% CI	1.8 (-7.3, 10.8)			

Abbreviations: cEVR, complete early virologic response (HCV RNA < LOQ, TND at Week 12 of treatment); CI, confidence interval; eRVR, extended rapid virologic response (HCV RNA < LOQ, TND at both Weeks 4 and 12 of treatment); F/U, follow-up; GT, genotype; HCV, hepatitis C virus; IVRS, LOQ, limit of quantitation; RVR, rapid virologic response (HCV RNA < LOQ, TND at Week 4 of treatment); SVR12, sustained virologic response at follow-up Week 12; SVR24, sustained virologic response at follow-up Week 24; TD, target detected; TND, target not detected.

[a] Comparison of SVR12 between arms among GT-1a subjects is the last secondary objective in the testing hierarchy.

* Indicates a significant difference according to the hierarchical testing procedure. Non-inferiority tested for efficacy endpoints (lower bound of the 95% CI > -12%) while superiority tested for safety endpoints (upper bound of 95% confidence interval < 0%).

Note: Differences and CIs for differences are presented for primary and key secondary comparisons only.

Safety Results: Safety results are summarized in Table 5.

- One on-treatment death was reported in the TVR/P/R arm (sepsis secondary to cirrhosis), and one post treatment death was reported in the DCV/P/R arm (trauma, multiple fractures, and subdural hematoma from a fall). Both were unrelated to study therapy.
- On-treatment SAEs, regardless of relationship to study drug, were reported for 6.5% of subjects treated with DCV/P/R and 10.0% of subjects treated with TVR/P/R; SAEs in 3.5% and 8.0% of subjects, respectively, were considered related to study therapy.
- On-treatment AEs leading to discontinuation (of one or more study therapies) were reported for 7.0% of subjects treated with DCV/P/R and 18.5% of subjects treated with TVR/P/R; AEs in 6.0% and 18.0% of subjects, respectively, were considered related to study therapy by the investigator.
- Differences in Grade 3/4 treatment-emergent laboratory abnormalities between DCV/P/R and TVR/P/R arms were most prominent in hemoglobin levels (6% and 21%, respectively); neutropenia, lymphopenia, and thrombocytopenia rates were similar between treatment arms.
- No potential drug-induced liver injury (DILI) was observed.

Table 5: On-treatment Safety - Treated Subjects

	Number (%) of Subjects	
	DCV/P/R N = 402	**TVR/P/R N = 200**
Adverse Events		
Death	1 (0.2)	1 (0.5)
SAEs	26 (6.5)	20 (10.0)
AEs Leading to Discontinuation of Study Therapy	28 (7.0)	37 (18.5)
Grade 3/4 AEs	96 (23.9)	72 (36.0)
AEs (Grade 1-4) ≥ 20%		
Fatigue	140 (34.8)	81 (40.5)
Headache	137 (34.1)	57 (28.5)
Asthenia	109 (27.1)	53 (26.5)
Pruritus	107 (26.6)	75 (37.5)
Anemia	96 (23.9)	99 (49.5)
Rash	93 (23.1)	69 (34.5)
Nausea	88 (21.9)	74 (37.0)
Neutropenia	87 (21.6)	27 (13.5)
Alopecia	86 (21.4)	32 (16.0)
Influenza Like Illness	85 (21.1)	38 (19.0)
Dry Skin	84 (20.9)	34 (17.0)
Pyrexia	80 (19.9)	42 (21.0)

Table 5: On-treatment Safety - Treated Subjects

	Number (%) of Subjects	
	DCV/P/R N = 402	**TVR/P/R N = 200**
Grade 3/4 Treatment Emergent Laboratory Abnormalities		
Hemoglobin	26 (6.5)	41 (20.7)
Absolute Neutrophil Count	104 (25.9)	41 (20.7)
Lymphocytes	67 (16.7)	44 (22.2)
Platelet Count	15 (3.7)	8 (4.0)
Alanine aminotransferase (ALT)	3 (0.7)	4 (2.0)
Aspartate aminotransferase (AST)	7 (1.7)	1 (0.5)
Total Bilirubin	4 (1.0)	6 (3.0)

Pharmacokinetic Results:

Steady-state concentrations of the three drugs were similar in both GT1a and GT1b HCV-infected subjects. DCV geometric mean Ctrough values ranged from 190 to 204 ng/mL through Week12, pegIFNα geometric mean Ctrough ranged from 10.9 to12.7 ng/mL, and RBV geometric mean Ctrough ranged from 1879 to 2146 ng/mL. DCV, pegIFNα, and RBV Ctrough data obtained from this study are consistent with the range of trough values observed in previous studies with HCV-infected subjects.

Other Results:

- In GT-1b subjects, NS5A polymorphisms at L28, R30, L31, and/or Y93 may be associated with virologic outcome in subjects treated with DCV/P/R. NS5A polymorphisms at L28, R30, L31, and/or Y93 were detected at baseline in 17.4% (43/247) of GT-1b subjects and accounted for 31.6% (12/38) of 38 non-SVR12 subjects with available baseline NS5A sequence. It is important to note that the presence of baseline NS5A polymorphisms at 28, 30, 31, and/or Y93 did not preclude subjects from achieving SVR as 72.1% (31/43) with these NS5A polymorphisms achieved SVR12.
- Although baseline resistance may be associated with a risk of GT-1b virologic failure, it was not an absolute predictor of failure.
- In GT-1a subjects, the non-CC IL28B genotype rather than baseline NS5A polymorphisms was associated with lower response rates in subjects treated with DCV/P/R.

CONCLUSIONS:

- High SVR12 rates were achieved in GT-1b subjects with DCV therapy: 85.1% with DCV/P/R and 81.3% with TVR/P/R. The SVR12 rate with DCV/P/R was non-inferior to TVR/P/R with a difference of 4.3% (95% CI: -3.3, 11.9).
- In GT-1a subjects, SVR12 (< LLOQ, TND or TD at follow-up Week 12) was achieved by 64.9% of DCV/P/R subjects and 69.7% of TVR/P/R subjects.
- Observed response rates among GT-1b subjects were consistently higher for the DCV/P/R arm across subgroups including age, gender, baseline viral load, cirrhosis status, and IL28B genotype compared with the TVR/P/R arm.
- DCV/P/R therapy demonstrated rapid and persistent antiviral activity as demonstrated by high rates of RVR, eRVR, cRVR, and EOTR. SVR24 was observed in 84.3% of evaluable GT-1b subjects treated with DCV/P/R compared to 80.6% of subjects treated with TVR/P/R.
- Concordance between SVR12 and SVR24 was above 99% in both treatment arms for GT-1b subjects.

- Higher SVR12 rates were observed both in GT-1b subjects in the DCV/P/R arm with and without baseline cirrhosis (86% vs 76.9%, respectively).
- DCV/P/R was highly efficacious in GT-1b subjects with either CC or non-CC alleles of the rs12979860 SNP in the IL28B gene, with SVR12 achieved in 96.2% of CC subjects, 82.0% of CT subjects, and 83.0% of TT subjects.
- Virologic failures were infrequent among GT-1b subjects.
- DCV/P/R treatment suppressed the majority of baseline polymorphisms observed at amino acid positions associated with drug resistance in subjects infected with GT-1b. Of the evaluated resistance-associated variants at baseline in treatment-naive subjects infected with GT-1b, there may be an association between NS5A polymorphisms at L28, R30, L31, and/or Y93 in combination with a non-CC IL28B genotype and virologic outcome.
- Achievement of SVR by DCV/P/R-treated subjects infected with GT-1a was not impacted by baseline resistance-associated variants; however, in those subjects with virologic escape, emergence of NS5A resistance-associated variants was observed.
- One on-treatment death was reported in the TVR/P/R arm, and one post-treatment death was reported in the DCV/P/R arm; both were considered not related to study drug by the investigator.
- Significantly lower proportions of DCV/P/R subjects than TVR/P/R subjects experienced hemoglobin < 10 g/dL.
- A numerically lower proportion of DCV/P/R subjects than TVR/P/R subjects had rash or rash-related events.
- Similar rates of Grade 3/4 neutrophil counts, lymphocyte counts, and platelet counts were seen between treatment arms.
- No differences were observed in the liver safety profile between the treatment arms.
- Overall, DCV/P/R therapy was well tolerated and safe with no unexpected findings. DCV/P/R therapy appears to have a better safety profile compared to that of TVR/P/R therapy with fewer SAEs and discontinuations due to AEs and significantly fewer Grade 3/4 anemia events reported for DCV/P/R treated subjects than TVR/P/R treated subjects.

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