# BRISTOL-MYERS SQUIBB COMPANY

## Daclatasvir (BMS-790052)

### Final Clinical Study Report for Study AI444043

# A PHASE 3, OPEN LABEL STUDY OF SAFETY AND EFFICACY WITH BMS-790052 (DACLATASVIR) PLUS PEG-INTERFERON ALFA 2A AND RIBAVIRIN IN PREVIOUSLY UNTREATED HCV PATIENTS COINFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS (HIV) AND HEPATITIS C VIRUS (HCV)

| | |
|---|---|
| **Indication:** | HCV |
| **Phase:** | 3 |
| **Study Initiation Date:** | 13-Dec-2011 |
| **Study Completion Date:** | 10-Sep-2014 |
| **Report Date:** | 17-Mar-2015 |
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**THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE**

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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 AI444043

**TITLE OF STUDY:** A Phase 3, Open Label Study Of Safety And Efficacy With BMS-790052 (Daclatasvir) Plus Peg-Interferon Alfa-2a And Ribavirin In Previously Untreated HCV Patients Coinfected With Human Immunodeficiency Virus (HIV) And Hepatitis C Virus (HCV)

**INVESTIGATORS/STUDY CENTERS:** 84 sites in 13 countries (Spain, Russia, Italy, Canada, France, Argentina, Brazil, Germany, Puerto Rico, Australia, Belgium, the United Kingdom, and the United States) enrolled 549 subjects.

**PUBLICATIONS:** None

**STUDY PERIOD:** Study Initiation Date: 13-Dec-2011 **CLINICAL PHASE:** 3
Study Completion Date: 10-Sep-2014

**RESEARCH HYPOTHESIS:** In chronically-infected HCV genotype 1 (GT-1) subjects coinfected with HIV (receiving or not receiving highly active antiretroviral therapy [HAART]), response-guided treatment with daclatasvir (DCV) for 24 weeks in combination with peg-interferon α-2a (pegIFNα) and ribavirin (RBV) for 24 to 48 weeks (determined by protocol-defined virologic response [VR 4&12 = HCV RNA < lower limit of quantitation [LLOQ], target not detected [TND] at Week 4 and Week 12] is well tolerated and demonstrates a rate of sustained virologic response at 12 weeks (SVR12) greater than the historical rate of 29% seen in the APRICOT study in HIV/HCV (GT-1) coinfected subjects receiving pegIFNα/RBV.

**OBJECTIVES:**

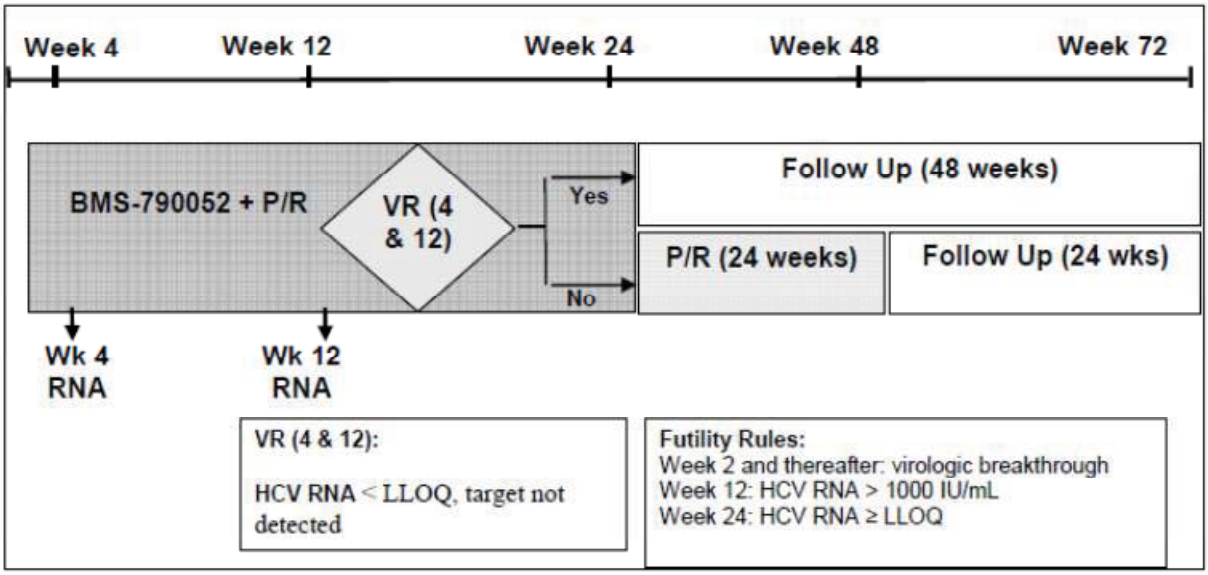
**Primary:** To assess efficacy, as determined by the proportion of subjects with SVR12, defined as HCV RNA < LLOQ target detected or not detected at post-treatment Week 12.

**Secondary:**

- To assess the proportion of subjects with GT-1 infection who achieved HCV RNA < LLOQ TD or TND at Weeks: 1, 2, 4, 6, 8, and 12; both Weeks 4 and 12; EOT; post-treatment Week 24 (SVR24); and post-treatment Week 48 (SVR48) for subjects who achieved VR 4&12
- To assess the proportion of subjects with GT-1 infection who achieved HCV RNA < LLOQ, TND at Weeks: 1, 2, 4, 6, 8 and 12; both Weeks 4 and 12; EOT; post-treatment Week 12; post-treatment Week 24; and post-treatment Week 48 for subjects who achieved VR 4&12
- To assess safety, as measured by the frequency of serious adverse events (SAEs) and discontinuations due to adverse events (AEs)
- To assess the proportion of subjects who received HAART and who maintained their HIV RNA < 40 copies/mL and the proportion of subjects who received HAART and experienced confirmed HIV RNA ≥ 400 copies/mL at end of treatment
- To assess the relationship between efficacy and the rs12979860 single nucleotide polymorphisms (SNP) in the IL-28B gene

**METHODOLOGY:** This was a Phase 3 open-label, multicenter study conducted in subjects coinfected with HIV-1 and HCV GT-1. The study design schema is depicted in Figure 1.

**Figure 1: AI444043 Study Design Schema**




Approximately 300 subjects were planned to begin treatment with DCV plus pegIFNα/RBV for 24 weeks. Of these 300 subjects, approximately 250 subjects were to be on highly active antiretroviral therapy (HAART) and up to 50 subjects may not be on HAART. These 300 subjects were to be at least 40% each of HCV GT-1a or GT-1b.

The total duration of the study was 72 weeks (on-treatment phase plus follow-up). The dose of DCV was 60 mg once daily (QD), unless otherwise dictated by concomitant HAART therapy (30 mg QD with ritonavir-boosted protease inhibitors (PIs) and 90 mg QD with non-nucleoside reverse transcriptase inhibitors [NNRTIs] except rilpivirine; DCV dosed at 60 mg QD.

Subjects were evaluated for Virologic Response (VR), defined as HCV RNA < LLOQ, target not detected at both Weeks 4 and 12 (VR 4&12). Treatment was assigned as follows:

- Subjects who achieved VR 4&12 completed 24 weeks of triple therapy
- Subject not achieving VR 4&12 completed 24 weeks of triple therapy and an additional 24 weeks of pegIFNα/RBV (total of 48 weeks of pegIFNα/RBV).

The primary analysis was conducted after all subjects completed 12 weeks of follow-up. This final analysis was conducted after all subjects completed the study. Both analyses are presented in this CSR.

The last visit was defined as the follow-up Week 48 visit for subjects who achieved virologic response VR 4&12 and completed 24 weeks of triple therapy, or the follow-up Week 24 visit for subjects who did not achieve VR 4&12 and completed 24 weeks of triple therapy plus 24 additional weeks of pegIFNα/RBV. The end of study was defined as the date that the last subject completed the follow up Week 24 or 48 visit, was lost to follow up, or discontinued from the study.

**NUMBER OF SUBJECTS (Planned and Analyzed):** Planned: Approximately 300 subjects were planned to receive treatment with DCV for 24 weeks plus pegIFNα/RBV for 24 to 48 weeks. Analyzed: 549 subjects were enrolled and 301 subjects entered the treatment period and received treatment. A total of 277 subjects were on HAART (132 in the 30 mg DCV group, 39 in the 60 mg DCV group, and 106 in the 90 mg DCV group) and 24 subjects were not on HAART.

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:** The study population was to consist of adult men and women ≥18 to 70 years of age chronically infected with HCV GT-1a or -1b who had an HCV RNA viral load of $\geq 10^4$ IU/mL (10,000 IU/mL); were HCV-treatment naive; had no previous exposure to any interferon formulation

(i.e., IFNα, pegIFNα) or RBV; were HIV-1 infected; and were seronegative for hepatitis B surface antigen (HBsAg). Subjects receiving HAART had to have HIV RNA < 40 copies/mL at screening and be < 400 copies/mL for at least 6 months prior to screening, and CD4 ≥ 100 cells/μL at screening. For subjects not on HAART, CD4 had to be ≥ 350 cells/μL at screening. Subjects with compensated cirrhosis were permitted in the study.

**TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:** DCV was administered as one 60 mg tablet taken orally once daily (QD) unless otherwise dictated by concomitant HAART therapy: 30 mg QD with ritonavir-boosted PIs and 90 mg QD with NNRTIs, with the exception of rilpivirine (NNRTI) which was to be administered with 60 mg DCV QD) with or without a meal. PegIFNα was given once weekly (QW) as a subcutaneous injection at a dose of 180 μg, and RBV was given twice daily (BID), in the morning and evening with food. For subjects weighting < 75 kg, the total RBV dose was 1000 mg/day, and for subjects weighting ≥ 75 kg, the total RBV dose was 1200 mg/day. 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 | 1M49091, 2D72563, 1G66277, 2G72986 |
| BMS-790052 -05 30 mg (as the free base) | Film-coated tablet | 1K68499 |
| 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 | 0D60446, 0L58093, 1D68247, 1C69521, 0J64930, 1C69525, 1G66275, 1G66271, 1J68674, 2A74450, 1J68676, 2F69998, 2J72328, 2J72929 |

**REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:** None

**CRITERIA FOR EVALUATION:**

**Efficacy:** The primary efficacy endpoint was antiviral activity, as determined by the proportion of treated subjects with SVR12, defined as HCV RNA < LLOQ TD or TND at post-treatment Week 12; missing HCV RNA data at follow-up Week 12 were imputed using the Next Value Carried Backwards (NVCB) analysis method.

Secondary efficacy assessments included the following:

- HCV RNA < LLOQ, TD or TND, at each of the following timepoints: Weeks 1, 2, 4, 6, 8, and 12; at both Weeks 4 and 12; EOT; post-treatment Week 24 (SVR24); and post-treatment Week 48 (SVR48) for subjects who achieve VR 4&12.
- HCV RNA < LLOQ, TND, at each of the following timepoints: Weeks 1, 2, 4, 6, 8, and 12; at both Weeks 4 and 12; EOT; post-treatment Week 12, post-treatment Week 24; and post-treatment Week 48 for subjects who achieve VR 4&12.
- The proportion of subjects who were receiving HAART and who maintained their HIV RNA < 40 copies/mL and the proportion of subjects who were receiving HAART and who experienced confirmed HIV RNA ≥ 400 copies/mL at end of treatment.
- The relationship between efficacy and the rs12979860 SNP in the IL-28B gene.

**Safety:** Safety endpoints included deaths, SAEs, AEs leading to discontinuation, Grade 3 or 4 AEs, Grade 3 or 4 laboratory abnormalities, and HIV-related opportunistic infections.

**Pharmacokinetics:** PK parameters were derived from plasma concentration versus time data. Daclatasvir Ctrough was assessed for all subjects with available data. The PK parameters assessed for the intensive PK sub-study

included: Cmax, Tmax, C0, C24, AUC(0-6), and AUC(0-24) for DCV and Cmax, Tmax, C0, C12, and AUC(0-12) for darunavir (DRV) and lopinavir (LPV).

**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 with pegIFNα and RBV by population sequencing on all baseline samples and in all subjects with HCV RNA ≥ 1000 IU/mL who had HCV virologic failure or relapse. HIV resistance testing was done at HIV viral breakthrough (confirmed HIV RNA ≥ 400 copies/mL).

**STATISTICAL CONSIDERATIONS:**

The primary hypothesis to be tested was that response-guided treatment with DCV for 24 weeks in combination with pegIFNα and RBV for 24 or 48 weeks is well tolerated and demonstrates an SVR12 rate greater than the historical rate (29%) for pegIFNα/RBV used in chronically-infected HCV GT-1 subjects who were HCV-treatment naive and coinfected with HIV (receiving or not receiving HAART).

The primary endpoint, sustained virologic response at follow-up week 12 (SVR12) was defined as HCV RNA < LLOQ (target detected or target not detected) at post-treatment Week 12.

The proportion of subjects with SVR12 at post-treatment Week 12 was summarized using point estimates and 2-sided 95% confidence intervals (CIs). In primary analysis, response rate and 2-sided 95% CI were based on all treated subjects. The primary analysis for the primary endpoint will use all treated subjects and include the imputation of missing HCV RNA data at post-treatment Week 12. The imputation algorithm will be based on the NVCB approach.

The following sensitivity analyses on the primary endpoint were also conducted: SVR12 rates and confidence intervals used all treated subjects. The SVR12 status for subjects with missing follow-up Week 12 HCV RNA was counted as non-responders [mITT: Non-Completer (NC)= Failure (F)]. SVR12 rates and confidence intervals were also computed using observed values. This sensitivity analysis was based on subjects who had a post-treatment Week 12 HCV RNA measurement [NC = Missing (M) analysis].

Pharmacokinetics: All available trough concentration data from subjects who received study drug were reported. Any concentration data either out of collection time window or with prior dose time missing or non standard dose amounts were excluded from the summary but included in a listing. For the intensive PK sub-study, historical data from AI444032 was used to provide the parallel reference to compare PK parameters of DCV when given alone to DCV when co-administered with DRV and LPV. A formal statistical comparison was not performed.

Intensive PK Sub-Study: Pharmacokinetic parameters were listed and summary statistics were calculated for each PK parameter for DCV, DRV and LPV by study day for all evaluable subjects. To assess the effect on DRV/RTV or LPV/RTV before and after co-administration with DCV, a general linear mixed effect model with treatment and subject as fixed effects and measurements within each subject as repeated measures was fitted to the log-transformed PK parameters (Cmax, Tmax, AUC(0-12), and C12) of DRV/RTV or LPV/RTV for use in the estimation of effects and construction of CIs. Point estimates and 90% CIs for treatment differences on the log scale were exponentiated to obtain estimates for ratios of geometric mean ratios (GMRs) on the original scale. In the comparison, DRV/RTV or LPV/RTV administered alone were the reference treatments.

**SUMMARY OF RESULTS:**

**Disposition and Baseline Demographic and Disease Characteristics:** Of the 549 subjects enrolled, 301 subjects entered the treatment period and received treatment. A total of 248 subjects were enrolled but did not enter the treatment period. The most common reason for not entering the treatment period was that the subject no longer met the study criteria (204/248 [82.3%]). Per protocol, at least 40% of the treated population had to be HCV GT-1a and at least 40% had to be HCV GT- 1b. The GT-1a group was enrolled much quicker than the GT-1b group. Subsequently, a large number of enrolled subjects were not eligible for treatment because of having GT-1a.

Of the 301 subjects treated, 277 subjects were on HAART (132 in the 30 mg DCV group, 39 in the 60 mg DCV group, and 106 in the 90 mg DCV group) and 24 subjects were not on HAART (Table 2). Among those receiving HAART, the proportion of subjects that completed the treatment period were comparable across the 3 DCV doses (30 mg, 60 mg, and 90 mg QD). A higher proportion of treated subjects in the smaller non-HAART cohort (87.5%) completed the treatment period compared with those in the HAART cohort (76.5%).

Overall, the mean age of treated subjects was 46.1 years and included 76.1% males. The population was predominantly White (83%); 15% self-identified as Black/African-American and 2% Asian. Enrollment in the study was globally distributed with the majority of treated subjects from Europe (54%); 36% were from North America, 7% from South America, and 4% from Australia.

The mean HCV RNA for the overall treated population was 6.24 log10 IU/mL, and 73% had a high (≥ 800,000 IU/mL) baseline HCV viral load. Ten percent (n= 30) were cirrhotic as determined by biopsy or Fibroscan (where approved). By design, there was an even distribution of GT-1a and GT-1b subjects treated (52% and 48%, respectively). A minority of subjects (32%) had the favorable IL-28B haplotype (CC).

The baseline characteristics were comparable between the DCV dosing groups (30, 60, 90 mg/day) within the cohort of subjects receiving HAART (Table 3). Some notable differences between the HAART and Non-HAART cohorts were, higher values in the HAART cohort for: mean age (47 vs. 36 years), proportion of subjects of Black race (16% vs. 4%) and non-Europeans (48% vs. 21%), and cirrhosis (11% vs. 4%). A greater proportion of HCV GT-1a subjects in the non-HAART cohort had notable baseline Resistance Associated Variants (RAVs) compared to GT-1a subjects in the HAART cohort (31% vs. 8%, respectively). Baseline disease characteristics were generally well balanced across the 3 DCV dose groups with the following notable exception: there was a higher proportion of GT-1a subjects in the DCV 60 mg group (80%) compared to the 30 mg and 90 mg groups (48% and 47%, respectively).

**Table 2: Subject Disposition**

| | HAART | | | | | |
|---|---|---|---|---|---|---|
| | **DCV 30 mg** | **DCV 60 mg** | **DCV 90 mg** | **HAART Total** | **Non-HAART** | **Total** |
| No. of Subjects Enrolled | | | | | | 549 |
| No. of Subjects Treated | 132 | 39 | 106 | 277 | 24 | 301 |
| No of Subjects completing treatment | 101 (76.5) | 29 (74.4) | 82 (77.4) | 212 (76.5) | 21 (87.5) | 233 (77.4) |
| No. of Subjects Discontinued[a] | 31 (23.5) | 10 (25.6) | 24 (22.6) | 65 (23.5) | 3 (12.5) | 68 (22.6) |
| Lack of efficacy | 12 (9.1) | 4 (10.3) | 14 (13.2) | 30 (10.8) | 1 (4.2) | 31 (10.3) |
| Adverse event | 7 (5.3) | 3 (7.7) | 6 (5.7) | 16 (5.8) | 1 (4.2) | 17 (5.6) |
| Subject request | 4 (3.0) | 0 | 1 (0.9) | 5 (1.8) | 1 (4.2) | 6 (2.0) |
| Withdrew consent | 5 (3.8) | 1 (2.6) | 1 (0.9) | 7 (2.5) | 0 | 7 (2.3) |
| Lost to follow-up | 1 (0.8) | 2 (5.1) | 2 (1.9) | 5 (1.8) | 0 | 5 (1.7) |
| No longer meets criteria | 1 (0.8) | 0 | 0 | 1 (0.4) | 0 | 1 (0.3) |
| Other | 1 (0.8) | 0 | 0 | 1 (0.4) | 0 | 1 (0.3) |
| Follow-up subjects | 121 | 34 | 102 | 257 | 24 | 281 |
| No of Subjects completing follow-up | 114 (94.2) | 32 (94.1) | 95 (93.1) | 241 (93.8) | 21 (87.5) | 262 (93.2) |
| No of Subjects not completing follow-up | 7 (5.8) | 2 (5.9) | 7 (6.9) | 16 (6.2) | 3 (12.5) | 19 (6.8) |

a. One subject, AI444043-49-0035 in the DCV 60 mg group died during the treatment phase.
Abbreviations: DCV=daclatasvir; HAART=highly active antiretroviral therapy

**Table 3: Baseline Demographic and Disease Characteristics**

| | HAART | | | | | |
|---|---|---|---|---|---|---|
| | **DCV 30 mg** | **DCV 60 mg** | **DCV 90 mg** | **HAART Total** | **Non-HAART** | **Total** |
| Age, yrs, median (range) | 47.0 (22, 69) | 50.0 (28, 61) | 47.0 (27, 65) | 47.0 (22, 69) | 34.5 (24, 55) | 47.0 (22, 69) |
| Male, n (%) | 105 (79.5) | 32 (82.1) | 79 (74.5) | 216 (78.0) | 13 (54.2) | 229 (76.1) |
| Race, n (%) | | | | | | |
| White | 110 (83.3) | 34 (87.2) | 83 (78.3) | 227 (81.9) | 22 (91.7) | 249 (82.7) |
| Black/African American | 19 (14.4) | 5 (12.8) | 20 (18.9) | 44 (15.9) | 1 (4.2) | 45 (15.0) |
| Native Hawaiian/Other | 1 (0.8) | 0 | 0 | 1 (0.4) | 0 | 1 (0.3) |
| Asian Other | 1 (0.8) | 0 | 3 (2.8) | 4 (1.4) | 1 (4.2) | 5 (1.7) |
| Other | 1 (0.8) | 0 | 0 | 1 (0.4) | 0 | 1 (0.3) |
| Region | | | | | | |
| Europe | 79 (59.8) | 20 (51.3) | 44 (41.5) | 143 (51.6) | 19 (79.2) | 162 (53.8) |
| North America | 44 (33.3) | 14 (35.9) | 45 (42.5) | 103 (37.2) | 4 (16.7) | 107 (35.5) |
| South America | 4 (3.0) | 3 ( 7.7) | 13 (13.2) | 21 (7.6) | 0 | 21 ( 7.0) |
| Australia | 5 (3.8) | 2 (5.1) | 3 (2.8) | 10 (3.6) | 1 (4.2) | 11 ( 3.7) |
| HCV RNA, $\log_{10}$ IU/mL, mean (SD) | 6.36 (0.763) | 6.13 (0.839) | 6.11 (0.928) | 6.23 (0.846) | 6.33 (0.805) | 6.24 (0.842) |
| HCV RNA, n (%) | | | | | | |
| < 800,000 IU/mL | 27 (20.5) | 14 (35.9) | 31 (29.2) | 72 (26.0) | 8 (33.3) | 80 (26.6) |
| ≥ 800,000 IU/mL | 105 (79.5) | 25 (64.1) | 75 (70.8) | 205 (74.0) | 16 (66.7) | 221 (73.4) |
| HCV Genotype, n (%) | | | | | | |
| Subtype 1a | 63 (47.7) | 31 (79.5) | 50 (47.2) | 144 (52.0) | 13 (54.2) | 157 (52.2) |
| Subtype 1b | 69 (52.3) | 8 (20.5) | 56 (52.8) | 133 (48.0) | 11 (45.8) | 144 (47.8) |
| IL-28B RS12979860, n (%) | | | | | | |
| CC | 36 (27.3) | 14 (35.9) | 39 (36.8) | 89 (32.1) | 6 (25.0) | 95 (31.6) |
| CT | 72 (54.5) | 22 (56.4) | 50 (47.2) | 144 (52.0) | 15 (62.5) | 159 (52.8) |
| TT | 22 (16.7) | 3 (7.7) | 12 (11.3) | 37 (13.4) | 2 (8.3) | 39 (13.0) |
| Not reported | 2 (1.5) | 0 | 5 (4.7) | 7 (2.5) | 1 (4.2) | 8 (2.7) |
| Cirrhosis, n (%) | | | | | | |
| Present | 16 (12.1) | 5 (12.8) | 8 (7.5) | 29 (10.5) | 1 (4.2) | 30 (10.0) |
| Absent | 111 (84.1) | 33 (84.6) | 94 (88.7) | 238 (85.9) | 23 (95.8) | 261 (86.7) |
| Not reported | 5 (3.8) | 1 (2.6) | 4 (3.8) | 10 (3.6) | 0 | 10 (3.3) |
| CD4 count, cells/$mm^3$, mean (SD) | 570.8 (245.73) | 568.2 (249.18) | 559.2 (245.19) | 565.9 (245.17 | 615.1 (216.88) | 569.9 (243.05) |
| CD4 count, cells/$mm^3$, < 200 | 4 (3.0) | 2 (5.1) | 4 (3.8) | 10 (.6) | 0 | 10 (3.3) |
| PI-based HAART, n (%) | | | | | | |
| Overall | 132 (100) | 11 (28.2) | 10 (9.4) | 153 (55.2) | - | 153 (50.8) |
| Atazanavir/ritonavir | 104 (78.8) | 3 (7.7) | 3 (2.8) | 110 (39.7) | - | 110 (36.5) |
| Darunavir/ ritonavir | 19 (14.4) | 4 (10.3) | 2 (1.9) | 25 (9.0) | - | 25 (8.3) |
| Lopinavir/ritonavir | 9 (6.8) | 4 (10.3) | 5 (4.7) | 18 (6.5) | - | 18 (6.0) |

**Table 3: Baseline Demographic and Disease Characteristics**

| | HAART | | | | | |
|---|---|---|---|---|---|---|
| | DCV 30 mg | DCV 60 mg | DCV 90 mg | HAART Total | Non-HAART | Total |
| NNRTI-based HAART, n (%) | | | | | | |
| Overall | 0 | 4 (10.3) | 95 (89.6) | 99 (35.7) | - | 99 (32.9) |
| Efavirenz | 0 | 2 (5.1) | 82 (77.4) | 84 (30.3) | - | 84 (27.9) |
| Nevirapine | 0 | 1 (2.6) | 13 (12.3) | 14 (5.1) | - | 14 (4.7) |
| Etravirine | 0 | 1 (2.6) | 0 | 1 (0.4) | - | 1 (0.3) |
| Other HAART Regimen, n (%) | | | | | | |
| Overall | 0 | 24 (61.5) | 1 (0.9) | 25 (9.0) | - | 25 (8.3) |
| HIV RNA < 40 copies/mL | 87/130 (66.9) | 28/39 (71.8) | 92/106 (86.8) | 207/275 (75.3) | NA | NA |
| IP-10 (pg/mL), n (%) | | | | | | |
| < 150 | 9 (6.8) | 6 (15.4) | 6 (5.7) | 21 (7.6) | 0 | 21 (7.0) |
| 150-600 | 94 (71.2) | 25 (64.1) | 82 (77.4) | 201 (72.6) | 13 (54.2) | 214 (71.1) |
| >600 | 28 (21.2) | 8 (20.5) | 13 (12.3) | 49 (17.7) | 10 (41.7) | 59 (19.6) |
| Not reported | 1 (0.8) | 0 | 5 (4.7) | 6 (2.2) | 1 (4.2) | 7 (2.3) |

Abbreviations: DCV=daclatasvir, EOT=end-of-treatment, HAART=highly active antiretroviral therapy, HCV=hepatitis C virus, HIV=human immunodeficiency virus, IP-10=interferon-gamma inducible protein-10, LLOQ=lower limit of detection, N=number, NA=not applicable, RNA=ribonucleic acid, SD=standard deviation, TD=target detected, TND=target not detected, VR=virologic response

**Efficacy Results:**

Efficacy results are presented in Table 4.

- **Primary Endpoint:** The overall SVR12 rate (HCV RNA < LLOQ, TD or TND at post-treatment Week 12) was 74.4% (224/301 subjects; 95% CI [69.5, 79.3]) and the lower bound of its 95% CI was higher than the estimated historical rate (69.5% vs. 29%).
  - Sensitivity analyses: Results by modified intent-to-treat (mITT) analysis were consistent with the primary analysis: SVR12 of 72.4% (218/301 subjects); 95% CI (67.4, 77.5). The analysis based on observed values was 82.0%, (218/266 subjects); 95% CI (77.3, 86.6), including SVR12 rates > 75% across both cohorts and all 3 DCV dosing groups.
- **Secondary Endpoints:**
  - Treatment with DCV/pegIFNα/RBV resulted in a rapid and persistent virologic response. Among all treated subjects, the on-treatment virologic response rates were 83.7% (HCV RNA < LLOQ, TD or TND) and 66.4% (TND) at Week 4, and 85.7% (TD or TND) and 82.1% (TND) at Week 12.
  - Overall, 10.5% (26/247) of treated subjects with HCV RNA < LLOQ, TND at EOT did not achieve SVR12. The majority of subjects had post-treatment failure due to confirmed HCV relapse (6.9%; 17/247); 3.6% (9/247) subjects had missing HCV RNA at post-treatment Week 12 and on subsequent time points. Rates of post-treatment HCV failure were comparable between the HAART and non-HAART cohorts.
  - There was high concordance (209/213; 98.1%) between SVR12 and SVR24.
  - Among all treated subjects, 16.9% (51/301) met the protocol defined criteria for on treatment virologic failure. The most common reason for on-treatment virologic failure was virologic breakthrough (VBT), occurring at an overall rate of 8.0% (24/301). The second most common reason for on-treatment virologic failure was due to "other on-treatment failure" (detectable HCV RNA at EOT) in 7.6% (23/301) subjects.
  - The majority of subjects that achieved SVR12 first obtained HCV RNA < LLOQ, TND between Week 4 and Week 8.

- The highest Positive Predictive Value (PPV) for SVR12 was observed for those who had VR 4&12 (also referred to as eRVR; HCV RNA <LLOQ, TND at both Weeks 4 and 12); 92.1% of subjects who achieved VR 4&12 also achieved SVR12. The highest Negative Predictive Value (NPV), other than end-of-treatment response (ETVR) was observed for complete early virologic response (cEVR; HCV RNA <LLOQ, TND at Week 12) which showed that 90.7% of subjects who did not achieve cEVR also did not achieve SVR12.
- Key subgroup analysis results were as follows:
  - SVR12 rates were higher among subjects whose baseline HCV RNA was < 800,000 IU/mL (85.0% [68/80]) than in subjects whose baseline HCV RNA was ≥ 800,000 IU/mL (70.6% [156/221]).
  - SVR12 rates were higher among subjects who had the IL-28B rs12979860 CC genotype (88.4% [84/95]) than in subjects with the non-CC genotypes: IL-28B CT (69.8% [111/159]) and IL-28B-TT (61.5% [24/39]).
  - SVR12 was higher in HCV subtype GT-1b (79.2% [114/144]) vs. HCV subtype GT-1a (70.1% [110/157]).

**Table 4: Primary and Key Secondary Endpoints and Comparisons**

| | HAART | | | | | |
|---|---|---|---|---|---|---|
| | DCV 30 mg | DCV 60 mg | DCV 90 mg | HAART Total | Non-HAART | Total |
| **Primary endpoint** | | | | | | |
| Responder/evaluable[a] | 99/132 (75.0) | 28/39 (71.8) | 76/106 (71.7) | 203/277 (73.3) | 21/24 (87.5) | 224/301 (74.4) |
| 95% CI | (67.6, 82.4) | (57.7, 85.9) | (63.1, 80.3) | (68.1, 78.5) | (74.3, 100.0) | (69.5, 79.3) |
| HCV RNA (<LLOQ, TD or TND) | | | | | | |
| Week 1 | | | | 110/277 (39.7) | 10/24 (41.7) | 120/301 (39.9) |
| Week 4 | | | | 229/277 (82.7) | 23/24 (95.8) | 252/301 (83.7) |
| Week 12 | | | | 236/277 (85.2) | 22/24 (91.7) | 258/301 (85.7) |
| VR 4&12 | | | | 218/277 (78.7) | 22/24 (91.7) | 240/301 (79.7) |
| EOT | | | | 235/277 (84.8) | 23/24 (95.8) | 258/301 (85.7) |
| PT Wk 12 | | | | 203/277 (73.3) | 21/24 (87.5) | 224/301 (74.4) |
| PT Wk 24 | | | | 195/277 (70.4) | 20/24 (83.3) | 215/301 (71.4) |
| Non-responder | 33/132 (25.0) | 11/39 (28.2) | 30/106 (28.3) | 74/277 (26.7) | 3/24 (12.5) | 77/301 (25.6) |
| HCV RNA >LLOQ TND at EOT | 9/132 (6.8) | 4/39 (10.3) | 11/106 (10.4) | 24/277 (8.7) | 2/24 (8.3) | 26/301 (8.6) |
| Confirmed relapser | 6/107 (5.6) | 2/32 (6.3) | 8/86 (9.3) | 16/225 (7.1) | 1/22 (4.5) | 17/247 (6.9) |
| Other non-respond | 3/107 (2.8) | 2/32 (6.3) | 3/86 (3.5) | 8/225 (3.6) | 1/22 (4.5) | 9/247 (3.6) |
| On-treatment failure | 24/132 (18.2) | 7/39 (17.9) | 19/106 (17.9) | 50/277 (18.1) | 1/24 (4.2) | 51/301 (16.9) |
| VBT | 14/132 (10.6) | 2/39 (5.1) | 8/106 (7.5) | 24/277 (8.7) | 0/24 (0.0) | 24/301 (8.0) |
| HCV RNA >1000 IU/mL at Wk 12 | 0/132 (0.0) | 0/39 (0.0) | 2/106 (1.9) | 2/277 (0.7) | 0/24 (0.0) | 2/301 (0.7) |
| HCV RNA ≥ LLOQ at Wk 24 | 1/132 (0.8) | 0/39 (0.0) | 1/106 (0.9) | 2/277 (0.7) | 0/24 (0.0) | 2/301 (0.7) |
| Other on-trt failure | 9/132 (6.8) | 5/39 (12.8) | 8/106 (7.5) | 22/277 (7.9) | 1/24 (4.2) | 23/301 (7.6) |
| **SVR12 by On-Treatment Response Status** | | | | | | |
| Week 4 (RVR) | 71/81 (87.7) | 24/27 (88.9) | 64/70 (91.4) | 159/178 (89.3) | 20/22 (90.9) | 179/200 (89.5) |
| Week 12 (cEVR) | 97/111 (87.4) | 28/31 (90.3) | 74/83 (89.2) | 199/225 (88.4) | 20/22 (90.9) | 219/247 (88.7) |
| Week 4&12 (eRVR) | 69/76 (90.8) | 24/26 (92.3) | 64/68 (94.1) | 157/170 (92.4) | 19/21 (90.5) | 176/191 (92.1) |
| EOT (ETVR) | 98/107 (91.6) | 28/32 (87.5) | 75/86 (87.2) | 201/225 (89.3) | 20/22 (90.9) | 221/247 (89.5) |

a. NVCB imputation

Abbreviations: cEVR=complete early virologic response (HCV RNA < LLOQ, TND at Week 12 of treatment); CI=confidence interval; DCV=daclatasvir; EOT=end of treatment eRVR=extended rapid virologic response (HCV RNA < LLOQ, TND at both Weeks 4 and 12 of treatment); ETVR=end-of-treatment response (also known as EOTR); F/U=follow-up; GT=genotype; HAART=highly active antiretroviral therapy, HCV=hepatitis C virus; LLOQ=lower limit of quantitation; on-trt=on-treatment; NVCB= Next Value Carried Backwards; RVR=rapid virologic response (HCV RNA < LLOQ, 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; VR 4&12= virologic response at Weeks 4 and 12; Wk=Week.

**Safety Results:**

Safety results are summarized in Table 5. Results were consistent with those previously reported in the APRICOT study in HIV/HCV GT-1 coinfected subjects treated with pegIFNα/RBV for 48 weeks.

- Two deaths were reported (cause of death: biventricular cardiac failure in 1 subject during the treatment phase and cardiac arrest in 1 subject during the post-treatment follow-up). Both subjects were in the HAART cohort. The subject who died during the treatment phase experienced concurrent SAEs of congestive cardiac failure

(biventricular cardiac failure) and pancytopenia that were considered by the investigator as not related to treatment with DCV but related to treatment with pegIFNα/RBV. The post-treatment death due to cardiac arrest was not considered by the investigator to be related to study therapy.

- On-treatment SAEs were reported for 24 (8.0%) subjects overall (all 24 were in the HAART cohort). The most commonly reported SAEs were associated with infections/infestations (7 subjects with 9 events). Four subjects had hematology-related SAEs (3 with anemia and 1 additional subject with pancytopenia), and 2 subjects had SAEs of psychiatric disorders (1 each, depression and mental status change). Nine (3.0%) subjects had SAEs that were considered by the investigator to be related to study therapy.
- Adverse events leading to discontinuation of study therapy were reported for 18 (6.0%) subjects: 17 (6.1%) in the HAART cohort and 1 (4.2%) in the non-HAART cohort. All 18 AEs leading to discontinuation were considered by the investigator to be related to study treatment. The most common AEs leading to discontinuation were related to psychiatric disorders and the blood/lymphatic system (6 and 7 subjects, respectively). Most of the subjects who discontinued due to psychiatric AEs were receiving concomitant NNRTIs.
- The most frequent (> 20% overall) AEs (all grades) reported included: fatigue (37.9%), neutropenia (29.2%), anemia (26.9%), asthenia (25.9%), headache (25.6%), decreased appetite (24.3%), insomnia (21.9%), and pyrexia (21.6%). These AEs are commonly associated with pegIFNα/RBV therapy. No unique AEs were identified for DCV in this study.
- On-treatment Grade 3 to 4 AEs, regardless of relationship to study drug, were reported for 32.2% of subjects; the majority of these events were related to hematologic abnormalities.
- The most frequent (> 5% overall) Grade 3 to 4 laboratory abnormalities included: neutropenia (35.0%), leukopenia (21.5%), hyperbilirubinemia (20.9%; primarily indirect bilirubin), and hypophosphatemia (12.1%). Most subjects with Grade 3 to 4 TBILI elevations were also receiving concomitant ATV/RTV.
- No pDILI cases were observed in the study.
- No clinically relevant differences were observed in the safety profile of subjects with baseline cirrhosis compared with those without cirrhosis.

**Table 5: Safety summary**

| | HAART | | | | | |
|---|---|---|---|---|---|---|
| | DCV 30 mg (N=132) | DCV 60 mg (N=39) | DCV 90 mg (N=106) | HAART Total (N=277) | Non-HAART Total (N=24) | Total (N=301) |
| **Adverse Events** | | | | | | |
| Deaths | 0 | 1 (2.6) | 1 (0.9) | 2 (0.7) | 0 | 2 (0.7) |
| SAEs | 12 (9.1) | 6 (15.4) | 6 (5.7) | 24 (8.7) | 0 | 24 (8.0) |
| AEs Leading to Discontinuation of Study Therapy | 7 (5.3) | 4 (10.3) | 6 (5.7) | 17 (6.1) | 1 (4.2) | 18 (6.0) |
| Grade 3 to 4 AEs | 46 (34.8) | 12 (30.8) | 35 (33.0) | 93 (33.6) | 4 (16.7) | 97 (32.2) |
| Most frequent AEs (>20% overall) | | | | | | |
| Fatigue | 45 (34.1) | 16 (41.0) | 47 (44.3) | 108 (39.0) | 6 (25.0) | 114 (37.9) |
| Neutropenia | 42 (13.8) | 7 (17.9) | 35 (33.0) | 84 (30.3) | 4 (16.7) | 88 (29.2) |
| Anemia | 33 (25.0) | 10 (25.6) | 34 (32.1) | 77 (27.8) | 4 (16.7) | 81 (26.9) |
| Asthenia | (40 (30.3) | 7 (17.9) | 19 (17.9) | 66 (23.8) | 12 (50.0) | 78 (25.9) |
| Headache | 29 (22.0) | 13 (33.3) | 28 (26.4) | 70 (25.3) | 7 (29.2) | 77 (25.6) |
| Decreased appetite | 32 (24.2) | 9 (23.1) | 27 (25.5) | 68 (24.5) | 5 (20.8) | 73 (24.3) |
| Insomnia | 36 (27.3) | 10 (25.6) | 17 (16.0) | 63 (22.7) | 3 (12.5) | 66 (21.9) |
| Pyrexia | 28 (21.2) | 6 (15.4) | 19 (17.9) | 53 (19.1) | 12 (50.0) | 65 (21.6) |
| **Grade 3 to 4 Treatment Emergent Laboratory Abnormalities** | | | | | | |
| Hemoglobin | 2 (1.5) | 2 (5.4) | 0 | 4 (1.5) | 0 | 4 (1.3) |
| Platelet count | 5 (3.8) | 2 (5.4) | 6 (5.7) | 13 (4.8) | 0 | 13 (4.4) |
| INR | 1 (0.8) | 0 | 1 (1.0) | 2 (0.7) | 0 | 2 (0.7) |
| Leukocytes (WBC) | 26 (19.8) | 6 (16.2) | 30 (28.6) | 62 (22.7) | 2 (8.3) | 64 (21.5) |
| Neutrophils+Bands | 54 (41.2) | 8 (21.6) | 39 (7.1) | 101 (37.0) | 3 (12.5) | 104 (35.0) |
| ALT | 2 (1.5) | 0 | 1 (1.0) | 3 (1.1) | 0 | 3 (1.0) |
| AST | 4 (3.1) | 1 (2.7) | 0 | 5 (1.8) | 0 | 5 (1.7) |
| Total bilirubin | 59 (45.0) | 0 | 3 (2.9) | 62 (22.7) | 0 | 62 (20.9) |
| Total lipase | 2 (1.5) | 1 (2.7) | 3 (2.9) | 6 (2.2) | 2 (8.3) | 8 (2.7) |
| Inorganic phosphorus | 14 (10.7) | 10 (27.0) | 12 (11.4) | 36 (13.2) | 0 | 36 (12.1) |
| Potassium - low | 1 (0.8) | 0 | 0 | 1 (0.4) | 0 | 1 (0.3) |
| Sodium - low | 1 (0.8) | 0 | 1 (1.0) | 2 (0.7) | 0 | 2 (0.7) |

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; DCV=daclatasvir; HAART=highly active antiretroviral therapy; INR=International Normalized Ratio; SAE=serious adverse event; WBC=white blood cell

Note: Per DAIDS and FDA guidelines, grading is not applied to lymphocytes in HIV-positive subjects.

**Pharmacokinetic Results:**

The range of DCV Ctrough values was similar between subjects on HAART therapy that received 30, 60, or 90 mg QD DCV and those subjects not on HAART therapy (non-HAART) that received 60 mg QD DCV The majority of subjects receiving 30 mg QD DCV with ritonavir-boosted protease inhibitors received ATV/RTV which is known to decrease DCV exposure Median Ctrough values of subjects receiving 90 mg QD in the presence of an inducer trended lower than the other groups.

Intensive Sub-Study: The adjusted geometric mean ratios of DRV PK before and after co-administration with DCV and 90% CI for DRV Cmax, AUC(TAU), and C12 were 0.972 (0.80,1.17), 0.900 (0.73, 1.11) and 0.983 (0.67,1.44), respectively. These data suggest that there is no, or minimal effect, of DCV on DRV PK in HIV coinfected subjects.

The adjusted geometric mean ratios of LPV PK before and after co-administration with DCV and 90% CI for LPV Cmax, AUC(TAU), and C12 were 1.128 (1.06, 1.41), 1.150 (0.77, 1.72), and 1.535 (0.46, 5.07), respectively. The results indicate that although LPV PK parameters appear to be modestly higher, daclatasvir co-administration has no clinically meaningful effect on the pharmacokinetics of LPV especially considering the small sample (N=5) size and high variability. These results indicate that DCV does not have a large effect on LPV/RTV PK despite the uncertainty in the interaction due to the small sample size and large variability.

**Other Results:**

The following are the key conclusions on HCV drug resistance from this study:

- SVR12 rates were lower in subjects with baseline NS5A polymorphisms compared to those without baseline NS5A polymorphisms.
  - The proportion of GT-1a subjects with baseline NS5A polymorphisms at Q30 and/or Y93 was 5.9% (9/153). SVR12 was achieved in 44.4% (4/9) of the 9 subjects compared with 72.2% (104/144) without these NS5A polymorphisms. These SVR12 rates compared with 70.6% (108/153) for all GT-1a subjects with an NS5A sequence at baseline.
  - The proportion of GT-1b subjects with baseline NS5A polymorphisms at L31 and/or Y93 was 11.6% (16/138). SVR12 was achieved in 50.0% (8/16) of these GT-1b subjects compared with 82.0% (100/122) of subjects without these NS5A polymorphisms. These SVR12 rates compared with 78.3% (108/138) for all GT-1b subjects with an NS5A sequence at baseline.
- NS5A RAVs were generally detected at failure in subjects with analyzable NS5A sequence.
  - GT-1a substitutions at Q30 most frequently emerged (60.5% [23/38]), and frequently emerged together with substitutions at M28 or L31 or Y93 (50% [19/38]).
  - GT-1b substitutions at L31 and Y93 most frequently emerged (63.2% [12/19]) and 63.2% [12/19], respectively); 52.6% [10/19]) of virologic failures had both L31 and Y93 RAVs emerge together.
- NS5A RAVs at failure for subjects treated with DCV/pegIFNa/RBV: NS5A RAVs were generally detected at failure in subjects with analyzable NS5A sequence.
  - GT-1a substitutions at Q30 most frequently emerged (60.5% [23/38]), and frequently emerged together with substitutions at M28 or L31 or Y93 (50% [19/38]).
  - GT-1b substitutions at L31 and Y93 most frequently emerged (63.2% [12/19]) and 63.2% [12/19], respectively); 52.6% [10/19]) of virologic failures had both L31 and Y93 RAVs emerge together.

**CONCLUSIONS:**

- The study met the primary efficacy endpoint; the SVR12 rate was 74% with DCV plus pegIFN/RBV and the lower bound of its 95% CI (69.5, 79.3) is higher than the estimated historical rate of 29% with pegIFNα/RBV
  - SVR 12 rate was similar to those reported with this regimen in HCV monoinfected subjects
  - Comparable SVR 12 rates with DCV doses of 30, 60, 90 mg/day
- SVR12 rates were higher in GT-1 subjects without baseline NS5A polymorphisms at amino acid positions 28, 30, 31, or 93 vs with these polymorphisms; however, the overall SVR12 rates were only slightly reduced (GT-1a: < 2%; GT-1b: < 4%) due to the low prevalence of these NS5A polymorphisms.
- DCV plus pegIFNα/RBV was well tolerated
  - No unique safety signal was observed with DCV; AEs were typical of pegIFNα/RBV treatment
  - Low rates of SAEs (overall: 8.0%)
  - Low rates of AEs leading to discontinuation (overall: 6.0%)
  - Safety profile was similar between DCV doses (30, 60, 90 mg/day)
- HCV study therapy did not compromise HIV-control
- DCV Ctrough was similar across the 30, 60, and 90 mg DCV dose groups in subjects on HAART
- Exposure of DCV (dose-normalized to 60 mg) when co-administered with DRV/RTV or LPV/RTV was comparable to the historical control

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