Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Daklinza®		
Name of Active Ingredient: Daclatasvir		

SYNOPSIS

Final Clinical Study Report for Study AI444326

TITLE OF STUDY: Open-label, Randomized Study of Daclatasvir, Sofosbuvir, and Ribavirin for 12 vs 16 Weeks in Treatment-naïve and Treatment-experienced Patients with Genotype 3 Chronic Hepatitis C Infection with Compensated Advanced Fibrosis/Cirrhosis (F3/F4)

INVESTIGATORS/STUDY CENTERS: [redacted]

PUBLICATIONS:

Leroy V, Angus P, Bronowicki JP, et al. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: a randomized Phase III study (ALLY-3+). Hepatology 2016;63(5):1430-41.

STUDY PERIOD: Study Initiation Date: 16-Feb-2015 **CLINICAL PHASE:** 3B

Study Completion Date: 18-Dec-2015
(Last Patient, Last Visit)

OBJECTIVES: The primary objective of this study was to estimate the sustained virologic response (SVR) at follow-up Week 12 (SVR12) rate, defined as hepatitis C virus (HCV) ribonucleic acid (RNA) < lower limit of quantitation (LLOQ), target detected (TD) or target not detected (TND) at follow-up Week 12, in treatment-naïve and treatment-experienced subjects with advanced fibrosis or compensated cirrhosis (F3 or F4), treated with 12 or 16 weeks of daclatasvir (DCV) + sofosbuvir (SOF) + ribavirin (RBV) therapy.

The secondary objectives of this study were as follows:

- To assess safety as measured by the frequency of deaths, serious adverse events (SAEs), discontinuation due to adverse events (AEs), Grade 3/4 AEs, and Grade 3/4 laboratory abnormalities observed from clinical laboratory testing
- To assess antiviral activity as measured by the proportion of subjects who achieved HCV RNA < LLOQ, TD or TND at post-treatment Weeks 4 and 24

The exploratory objectives included the following:

- To describe genotypic substitutions associated with virologic failure for HCV
- To assess the relationship between efficacy and the rs12979860 single nucleotide polymorphisms (SNPs) in the interleukin 28B (IL28B) gene

This report includes data for the primary endpoint of this study (SVR12) and efficacy (SVR at follow-up Week 24 [SVR24]), safety, and resistance data through 24 weeks of follow-up.

METHODOLOGY: This was a Phase 3b, randomized, open-label, 2-arm study evaluating the combination therapy of DCV + SOF + RBV for 12- or 16-week duration in HCV genotype (GT)-3-treatment-naïve and HCV GT-3-treatment-experienced subjects with advanced fibrosis or compensated cirrhosis (F3 or F4). Subjects who have been previously treated with SOF were also permitted. Subjects were randomized 1:1 to receive

DCV + SOF + RBV therapy for 12 or 16 weeks and were followed off-treatment for 24 weeks. Randomization was stratified according to fibrosis stage stratum (F3 or F4) to achieve balance between the treatment arms within F3 or F4 stage. All subjects were planned to receive DCV (60 mg once daily [QD]) + SOF (400 mg QD) + weight-based RBV (1,000 and 1,200 mg per day for subjects weighing < 75 and ≥ 75 kg, respectively) for 12 or 16 weeks.

NUMBER OF SUBJECTS (Planned and Analyzed): A total of 50 (25 subjects in each treatment arm) HCV treatment-naïve or treatment-experienced subjects, chronically infected with HCV GT-3 with advanced fibrosis or compensated cirrhosis (F3 or F4), were planned to be included in this study. A total of 53 subjects were enrolled in this study. Of these, 50 subjects were randomized and treated with DCV + SOF + RBV for 12 weeks (24 subjects) and 16 weeks (26 subjects).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: The study population comprised adult men and women ≥ 18 years of age, who were chronically infected with HCV GT-3 (with a documented HCV RNA ≥ 10^4 IU/mL [10,000 IU/mL]) and had the following HCV treatment history:

- HCV treatment naïve: No previous exposure to any interferon formulation (ie, interferon alfa [IFNα] or peginterferon alfa), RBV, or any HCV direct-acting antivirals.
- HCV treatment experienced: Previous treatment with any of the following: 1) IFNα ± RBV, 2) SOF + RBV (except for subjects who discontinued SOF or RBV due to intolerance, including exacerbations of anemia), and 3) other anti-HCV agents (eg, cyclophilin inhibitors and inhibitors of microRNA). Previous exposure to non-structural protein 5A (NS5A) inhibitors was prohibited.

Subjects with advanced fibrosis or compensated cirrhosis were included.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, AND BATCH NUMBERS: All treated subjects received DCV (60 mg QD) + SOF (400 mg QD) + weight-based RBV (1,000 to 1,200 mg total daily dose) orally for 12 or 16 weeks. Subjects received either 400 mg (2 tablets for subjects < 75 kg) or 600 mg (3 tablets for subjects ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. Investigational product information is presented in Table 1.

Table 1: Investigational Product Identification

Drug Product	Formulation	Product Batch Number
DCV 60 mg	Film-coated tablet	4M57277
SOF 400 mg	Tablet	14SB022UD and 14SB025UD
RBV 200 mg	Film-coated tablet	4M58679

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, AND BATCH NUMBERS: Not applicable

CRITERIA FOR EVALUATION:

Efficacy: The primary efficacy endpoint was the proportion of subjects with SVR12. The secondary efficacy endpoint was the proportion of subjects who achieved HCV RNA < LLOQ, TD or TND at post-treatment Week 4 (SVR at follow-up Week 4 [SVR4]) and Week 24 (SVR24). The exploratory efficacy endpoints included the following:

- Frequency of genotypic substitutions associated with virologic failure for HCV
- The proportion of subjects with CC or non-CC GT at the IL28B rs12979860 SNPs who achieved SVR12

Safety: On-treatment safety, as measured by frequency of deaths, SAEs, discontinuations due to AEs, Grade 3/4 AEs, and Grade 3/4 laboratory abnormalities through the end of treatment plus 7 days, was considered a secondary endpoint for this study.

Other: Resistance testing was performed by next-generation sequencing ([redacted] using a 10% sensitivity cutoff) on samples from subjects with HCV RNA ≥ 1,000 IU/mL.

STATISTICAL CONSIDERATIONS: The analyses of study endpoints were performed on all randomized subjects. In this study, all randomized subjects were treated. The analyses of primary endpoint (the proportion of subjects with SVR12, defined as HCV RNA < LLOQ, TD or TND at follow-up Week 12) were performed for all treated subjects. Missing HCV RNA data at follow-up Week 12 were imputed using the next value carried backwards (NVCB) approach (ie, missing HCV RNA data in the follow-up Week 12 window were imputed using the next and closest available HCV RNA measurement after the follow-up Week 12 HCV RNA visit window). SVR12 rates and 2-sided 95% confidence intervals are presented by randomized treatment arm. For SVR12, sensitivity analyses were conducted using the modified intent-to-treat approach and observed values. All efficacy endpoints were summarized as randomized on all treated subjects. For SVR4, the imputation was based on the NVCB approach. For SVR24, the imputation was based on imputing missing data as non-responders. Analyses for the frequency of genotypic substitutions at baseline, on-treatment, and post-treatment associated with virologic failure for each treatment arm were also conducted. Safety data were summarized for treated subjects in each treatment arm.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: The subject disposition for this study is presented in Table 2.

Table 2: Subject Disposition

	DCV + SOF + RBV 12 Weeks	DCV + SOF + RBV 16 Weeks	Total
Subjects Treated	24	26	50
Subjects Who Completed the Treatment Period, n (%)	23 (95.8)	26 (100.0)	49 (98.0)
Subjects Who Did Not Complete the Treatment Period, n (%)	1 (4.2)	0	1 (2.0)
Death, n (%)	1 (4.2)	0	1 (2.0)
Subjects Who Entered the Follow-up Period, n (%)	23 (95.8)	26 (100.0)	49 (98.0)
Subjects Who Completed the Follow-up Period, n (%)	23 (100.0)	26 (100.0)	49 (100.0)
Subjects Who Did Not Complete the Follow-up Period, n (%)	0	0	0

Abbreviation: n = number of subjects.

Baseline demographics were comparable between subjects treated with DCV + SOF + RBV for 12 weeks and those treated for 16 weeks, except for gender. Overall, majority of the subjects were male, white (only 1 subject had a different race [ie, Asian]), and had a mean age of 54.1 years; only 1 subject (12-week treatment arm) was aged ≥ 65 years. The mean body mass index was 27.24 kg/m^2.

Baseline HCV disease characteristics were generally comparable between subjects treated with DCV + SOF + RBV for 12 weeks and those treated for 16 weeks. There were few differences in baseline disease characteristics observed in subjects between these 2 treatment arms and included the following: compared with subjects treated for 16 weeks, those treated for 12 weeks had a slightly higher proportion of subjects with an HCV RNA level ≥ 800,000 IU/mL (83.3% versus [vs] 80.8%, respectively), a higher proportion of subjects with cirrhosis (75.0% vs 69.2%, respectively), and a slightly higher proportion of subjects who failed to a previous HCV therapy (75.0% vs 73.1%, respectively). NS5A-A30 polymorphism was observed only in subjects treated for 12 weeks (25.0%). The key baseline characteristics of the subjects in this study are presented in Table 3.

Table 3: Key Baseline Demographic and Disease Characteristics (Treated Subjects)

Parameter	DCV + SOF + RBV 12 Weeks N = 24	DCV + SOF + RBV 16 Weeks N = 26	Total N = 50
Age (Years)			
Mean	53.0	55.0	54.1
< 65, n (%)	23 (95.8)	26 (100.0)	49 (98.0)
≥ 65, n (%)	1 (4.2)	0	1 (2.0)
Gender, n (%)			
Male	18 (75.0)	22 (84.6)	40 (80.0)
Female	6 (25.0)	4 (15.4)	10 (20.0)
Race			
White	23 (95.8)	26 (100.0)	49 (98.0)
Asian	1 (4.2)	0	1 (2.0)
HCV RNA			
Mean (log_{10} IU/mL)	6.66	6.70	6.68
≥ 800,000 IU/mL, n (%)	20 (83.3)	21 (80.8)	41 (82.0)
Prior Treatment Status, n (%)			
Naïve	6 (25.0)	7 (26.9)	13 (26.0)
Experienced	18 (75.0)	19 (73.1)	37 (74.0)
Cirrhosis, n (%)			
Present	18 (75.0)	18 (69.2)	36 (72.0)
Absent	6 (25.0)	8 (30.8)	14 (28.0)
Fibrosis Stage Stratum, n (%)			
F3	6 (25.0)	8 (30.8)	14 (28.0)
F4	18 (75.0)	18 (69.2)	36 (72.0)
IL28B rs12979860 GT, n (%)			
CC	11 (45.8)	11 (42.3)	22 (44.0)
CT	12 (50.0)	13 (50.0)	25 (50.0)
TT	1 (4.2)	2 (7.7)	3 (6.0)
NS5A Polymorphism, n (%)			
M28	0	1 (3.8)	1 (2.0)
A30	6 (25.0)	0	6 (12.0)
L31	0	0	0
Y93	1 (4.2)	1 (3.8)	2 (4.0)

Abbreviation: n = number of subjects.

Treatment Adherence: Adherence to the treatment regimen was high in this study; 84.0% of subjects were ≥ 95/95 adherent to treatment regimen (subjects had ≥ 95% adherence to planned treatment duration and ≥ 95% adherence to planned average daily dose of study drugs).

Efficacy Results: The definitions of key efficacy endpoints are provided in Table 4.

Table 4: Definitions of Key Efficacy Endpoints

Parameter	Definition
SVR4	Proportion of subjects with HCV RNA < LLOQ, TD or TND at follow-up Week 4
SVR12	Proportion of subjects with HCV RNA < LLOQ, TD or TND at follow-up Week 12
SVR24	Proportion of subjects with HCV RNA < LLOQ, TD or TND at follow-up Week 24
RVR	Proportion of subjects with HCV RNA < LLOQ, TND at Week 4 on treatment
eRVR	Proportion of subjects with HCV RNA < LLOQ, TND at both Weeks 4 and 12 on treatment
cEVR	Proportion of subjects with HCV RNA < LLOQ, TND at Week 12 on treatment
EOTR	Proportion of subjects with HCV RNA < LLOQ, TND at EOT
VBT	Confirmed ≥ 1 $\log_{10}$ IU/mL HCV RNA on-treatment increase from nadir or confirmed increase in HCV RNA ≥ LLOQ, if HCV RNA previously declined to < LLOQ, TD or TND
Relapse	HCV RNA < LLOQ, TND at EOT followed by confirmed detectable HCV RNA ≥ LLOQ in any follow-up visit window
Other Protocol-defined Failure	HCV RNA ≥ LLOQ at any time point not meeting the definition of VBT or relapse

Abbreviations: cEVR = complete early virologic response; EOTR = end-of-treatment response; eRVR = extended rapid virologic response; RVR = rapid virologic response; VBT = virologic breakthrough.

The following is a summary of the key efficacy results up to follow-up Week 24:

- Overall treatment with DCV + SOF + RBV for 12 or 16 weeks achieved high SVR12 rates (87.5% and 92.3% of subjects in the 12- and 16-week treatment arms, respectively).
  - SVR12 was numerically higher in subjects with advanced fibrosis (100.0% in both treatment arms) than in subjects with cirrhosis (83.3% and 88.9% in the 12- and 16-week treatment arms, respectively).
- In both treatment arms, mean HCV RNA levels declined rapidly from baseline, and on-treatment virologic response rates were fairly consistent between the 12- and 16-week treatment arms.
- The proportion of subjects who achieved SVR4 was 87.5% and 96.2% in the 12- and 16-week treatment arms, respectively, and the proportion of subjects who achieved SVR24 was 87.5% and 92.3% in the 12- and 16-week treatment arms, respectively.
- SVR12 rates with DCV + SOF + RBV were consistently high across most subgroups, including subjects with baseline HCV RNA ≥ 6,000,000 IU/mL (96.2% overall), those with IL28B rs1297860 non-CC GTs (85.7%), those who were treatment experienced (regardless of fibrosis stage; 89.2%), and those with cirrhosis who were treatment experienced (86.7%).
- All subjects with baseline NS5A-A30 polymorphism (100%; reported in the 12-week treatment arm only), and 1 of 2 (50%) subjects with baseline NS5A-Y93 polymorphism achieved SVR12.

- By follow-up Week 12, 5 (10.0%) subjects met the protocol-defined criteria for non-responders: 4 relapsers and 1 other on-treatment failure (death).
  - All but 1 relapser failed by follow-up Week 4; this subject relapsed between follow-up Weeks 4 and 12. No additional relapses were observed after follow-up Week 12 (100% concordance between SVR12 and SVR24).
  - All 4 relapsers had cirrhosis; 3 of them were treatment experienced; 2 received prior therapy with SOF + RBV; and 1 subject each had NS5A-Y93 and M28 polymorphisms at baseline.
- Results of analyses looking at predictors of response suggest the following:
  - A clear choice of time point for predictive use could not be selected.
  - No one-time range (for time to first undetectable HCV RNA) was clearly associated with SVR12 above the others due to the universally high rates of response and, in some cases, due to small sample sizes.
- An association of poor compliance with non-SVR12 was not apparent due to the small number of subjects who did not achieve SVR12 and the small number of subjects with poor compliance.

Safety Results: The following is a summary of key safety findings during the treatment and follow-up periods of this study. A summary of the safety results during the treatment period is presented in Table 5.

- One subject (in the 12-week treatment arm) died in this study during the treatment period; this death (congestive cardiomyopathy) was unrelated to study drug (by investigator assessment).
- SAEs were reported in 5 (10.0%) subjects and 2 (4.1%) subjects during the treatment and follow-up periods, respectively. None of these SAEs were considered by the investigator to be related to study drug.
- No AEs led to discontinuation or interruption of study drug in this study.
- The proportion of subjects with AEs during the treatment period was higher in subjects treated with study drugs for 12 weeks (95.8%) than those treated for 16 weeks (92.3%). The most commonly reported AEs (≥ 10% overall) were insomnia, fatigue, headache, asthenia, irritability, diarrhea, and dyspnea. During the follow-up period, the proportion of subjects with AEs was comparable between the subjects treated for 12 weeks (26.1%) and those treated for 16 weeks (26.9%). The most frequently reported AE was asthenia.
- Study drug-related AEs were reported in 42 subjects during the treatment period and in 3 subjects during the follow-up period. The most commonly reported (≥ 5% overall) study drug-related AEs during treatment were insomnia, fatigue, headache, asthenia, irritability, dyspnea, diarrhea, lethargy, and depression. The study drug-related AEs that occurred during follow-up were asthenia, headache, and decreased appetite.
- Grade 3 AEs were reported in 4 subjects during the treatment period and included gastrointestinal infection, somnolence, pneumonia, and anemia. One of these subjects also experienced a Grade 4 AE (congestive cardiomyopathy). During the follow-up period, no Grade 3 AEs were reported; a Grade 4 AE (hepatocellular carcinoma) occurred in 1 subject.
- No clinically relevant trends were apparent in the laboratory data from this study; none of the Grade 3/4 laboratory values led to discontinuation of study drug.
  - No subjects in this study met the laboratory criteria for potential drug-induced liver injury.
- The safety profile of DCV, SOF, and RBV in this study is consistent with the known safety profile of each individual agent and with the one observed with DCV + SOF without RBV in other clinical studies (ALLY program). There were no new or unexpected safety findings.

Table 5: On-treatment Safety with DCV + SOF + RBV Therapy (Treated Subjects)

	Number (%) of Subjects		
	DCV + SOF + RBV 12 Weeks (N = 24)	**DCV + SOF + RBV 16 Weeks (N = 26)**	**Total (N = 50)**
Death	1 (4.2)	0	1 (2.0)
SAEs	2 (8.3)	3 (11.5)	5 (10.0)
Grade 3 - 4 AEs	2 (8.3)	2 (7.7)	4 (8.0)
Most Common AEs (≥ 5% Overall)			
Insomnia	8 (33.3)	7 (26.9)	15 (30.0)
Fatigue	6 (25.0)	7 (26.9)	13 (26.0)
Headache	7 (29.2)	5 (19.2)	12 (24.0)
Asthenia	2 (8.3)	5 (19.2)	7 (14.0)
Irritability	5 (20.8)	2 (7.7)	7 (14.0)
Diarrhoea	1 (4.2)	4 (15.4)	5 (10.0)
Dyspnoea	2 (8.3)	3 (11.5)	5 (10.0)
Lethargy	2 (8.3)	2 (7.7)	4 (8.0)
Nausea	3 (12.5)	1 (3.8)	4 (8.0)
Back Pain	0	3 (11.5)	3 (6.0)
Depressed Mood	1 (4.2)	2 (7.7)	3 (6.0)
Depression	1 (4.2)	2 (7.7)	3 (6.0)
Hypertension	0	3 (11.5)	3 (6.0)
Pruritus	1 (4.2)	2 (7.7)	3 (6.0)
Most Common Study Drug-related AEs (≥ 5% Overall)			
Insomnia	7 (29.2)	6 (23.1)	13 (26.0)
Fatigue	4 (16.7)	7 (26.9)	11 (22.0)
Headache	5 (20.8)	4 (15.4)	9 (18.0)
Asthenia	2 (8.3)	5 (19.2)	7 (14.0)
Irritability	5 (20.8)	2 (7.7)	7 (14.0)
Dyspnoea	2 (8.3)	3 (11.5)	5 (10.0)
Diarrhoea	1 (4.2)	3 (11.5)	4 (8.0)
Lethargy	2 (8.3)	2 (7.7)	4 (8.0)
Depression	1 (4.2)	2 (7.7)	3 (6.0)
Grade 3/4 Laboratory Abnormalities			
ALT Increased	0	0	0
AST Increased	0	0	0

Table 5: On-treatment Safety with DCV + SOF + RBV Therapy (Treated Subjects)

	Number (%) of Subjects		
	DCV + SOF + RBV 12 Weeks (N = 24)	**DCV + SOF + RBV 16 Weeks (N = 26)**	**Total (N = 50)**
Hemoglobin Decreased	0	1 (3.8)	1 (2.0)
Total Bilirubin Increased	1 (4.2)	1 (3.8)	2 (4.0)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = number of subjects.

Other Results:

Resistance

The key conclusions on HCV drug resistance from this study are as follows:

Baseline NS5A Polymorphisms

- An association between baseline NS5A-Y93H and virologic outcome could not be determined.
  - All subjects advanced fibrosis achieved SVR12; however, none had Y93H at baseline.
  - Two of 3 subjects with cirrhosis and NS5A-Y93H at baseline (2 subjects with Y93H detected using a ≥ 10% cutoff and 1 subject with Y93H detected using a ≥ 1% cutoff) achieved SVR.
    - Of the 3 subjects with Y93H at baseline (≥ 1% cutoff), 1 subject with Y93H in the 12-week treatment arm did not achieve SVR12, while 2 subjects with Y93H in the 16-week treatment arm achieved SVR12.
  - In subjects who had cirrhosis without Y93H (≥ 10% cutoff), 90.9% (30/33) achieved SVR12.
- No subjects who previously failed SOF + RBV treatment had baseline NS5B polymorphisms associated with SOF resistance (≥ 1% cutoff).

NS5A and NS5B Resistance-associated Variants at Failure

- NS5A resistance-associated variants (RAVs) were detected in all 4 GT-3-infected subjects who relapsed.
  - NS5A-Y93H emerged in 3 subjects and preexisted at baseline in 1 subject.
    - Replacement of emergent Y93H was observed in 1 of the 3 subjects.
- NS5B RAVs were not detected at relapse (≥ 1% cutoff).

CONCLUSIONS:

The conclusions regarding the antiviral activity and safety up to follow-up Week 24 of the 12 or 16 weeks of treatment with DCV + SOF + RBV in subjects with HCV GT-3, with advanced fibrosis (F3) or compensated cirrhosis (F4), are as follows:

- High SVR12 rates were achieved in HCV GT-3-infected subjects with advanced fibrosis (F3) or compensated cirrhosis (F4) (SVR12 of 87.5% and 92.3% in the 12- and 16-week treatment arms, respectively).
  - High response rate was observed in subjects with advanced fibrosis (F3) in both treatment arms (100% SVR12 regardless of treatment arm).
  - High response rate was also observed among subjects with cirrhosis (86.1% [31/36] overall SVR12), mostly treatment experienced and with similar SVR12 rates in the 12-week treatment arm (83.3%) and 16-week treatment arm (88.9%).
  - On-treatment responses were comparable between both treatment arms. Relapse occurred in 4 subjects (2 in each treatment arm).

- Overall, high SVR24 rates were achieved in both 12- and 16-week treatment arms (87.5% and 92.3%, respectively).
- Based on the criteria HCV RNA < LLOQ, TD or TND, subjects who had HCV RNA values at follow-up Weeks 12 and 24 demonstrated 100% concordance between the 2 endpoints (SVR12 and SVR24). No relapses were observed after follow-up Week 12.
- Treatment with DCV + SOF + RBV for 12 or 16 weeks was safe and well tolerated, with no discontinuation of study drugs due to AEs and small number of treatment-emergent Grade 3/4 laboratory abnormalities. Overall, safety results were comparable between both treatment arms.
- An association between baseline NS5A-Y93H and virologic outcome could not be determined in GT-3-infected subjects with advanced fibrosis or cirrhosis.
- Only NS5A RAVs and no NS5B RAVs were detected in subjects at relapse.
- The all-oral combination of DCV + SOF + RBV, given for either 12 or 16 weeks at their standard doses and dosing schedules, demonstrated high and similar efficacy and good tolerability in HCV GT-3-infected subjects with compensated cirrhosis or advanced fibrosis, irrespective of past treatment experience or high baseline HCV RNA levels. DCV + SOF + RBV represents an important option for HCV GT-3-infected patients with advanced liver disease in urgent need of effective treatment.

DATE OF REPORT: 18-Aug-2016