BRISTOL-MYERS SQUIBB COMPANY

PEGINTERFERON LAMBDA-1A

Final Clinical Study Report for Study AI452021

SYNOPTIC REPORT

A PHASE 3 EVALUATION OF DACLATASVIR IN COMBINATION WITH PEGINTERFERON LAMBDA-1A AND RIBAVIRIN (RBV) OR TELAPREVIR IN COMBINATION WITH PEGINTERFERON ALFA-2A AND RBV IN PATIENTS WITH CHRONIC HEPATITIS C GENOTYPE 1B WHO ARE TREATMENT NAÏVE OR PRIOR RELAPSERS TO ALFA/RBV THERAPY (THE STRUCTURE STUDY)

Indication:	Chronic Hepatitis C Virus Infection
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THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:

[redacted]

SYNOPSIS

Final Clinical Study Report for Study AI452021

TITLE OF STUDY: A Phase 3 Evaluation of Daclatasvir in Combination with Peginterferon Lambda-1a and Ribavirin (RBV) or Telaprevir in Combination with Peginterferon alfa-2a and RBV in Patients with Chronic Hepatitis C Genotype 1b who are Treatment Naïve or Prior Relapsers to Alfa-2a/RBV Therapy (The Structure Study).

PURPOSE:

Study AI452021 was designed to determine the efficacy and safety of daclatasvir (DCV) in combination with peginterferon lambda-1a (IFNλ, BMS-914143, hereafter referred to as Lambda), and ribavirin (RBV) relative to telaprevir (TVR) in combination with peginterferon alfa-2a (Alfa-2a) and RBV in subjects with chronic hepatitis C virus (HCV) infection with genotype (GT) 1b who were treatment naïve or prior relapsers to Alfa-2a/RBV therapy. In this study, Lambda/RBV/DCV-treated subjects would receive triple therapy for 12 weeks followed by an additional 12 weeks of Lambda/RBV therapy. Alfa-2a/RBV/TVR-treated subjects who achieved extended rapid virologic response (eRVR) would receive triple therapy for 12 weeks followed by an additional 12 weeks of Alfa-2a/RBV. Alfa-2a/RBV/TVR-treated subjects who did not achieve eRVR but continued to demonstrate benefit from ongoing therapy would receive triple therapy for 12 weeks followed by an additional 36 weeks of Alfa-2a/RBV for a total duration of 48 weeks treatment.

A synoptic report format was chosen to report the results from this study since further development of Lambda was terminated due to the recent approvals of all-oral HCV treatment regimens that have reduced the unmet medical need and the potential role for interferon-based regimens for the treatment of chronic HCV infection. The decision to terminate the development of Lambda was not based on any new unexpected safety findings or efficacy observations. Study AI452021 was terminated after all subjects completed the Week 12 follow-up visit.

NUMBER OF SUBJECTS: A total of 641 subjects were enrolled at 85 investigational sites in 13 countries (Argentina, France, Germany, Israel, Italy, Japan, Korea, Poland, Russia, Spain, Taiwan, the United Kingdom, and the United States of America); 444 of these subjects were randomized 2:1 to the Lambda/RBV/DCV and Alfa-2a/RBV/TVR groups, respectively.

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:

Subject disposition and baseline characteristics are presented in Table 1 and Table 2.

Table 1: Subject Disposition (Treatment Period and Follow-up Period) in all treated subjects

	Lambda/RBV/DCV	Alfa-2a/RBV/TVR	Total
Subjects Enrolled (n)	-	-	641
Subjects Randomized, n (%)	-	-	444 (69.3)
Subjects Not Randomized, n (%)	-	-	197 (30.7)
Subjects Treated (n)	294	146	440
Subjects completing the period[a], n (%)	271 (92.2)	99 (67.8)	370 (84.1)
Subjects not completing the period, n (%)	23 (7.8)	47 (32.2)	70 (15.9)
Reason for not completing the period, n (%)			
Lack of efficacy	4 (1.4)	3 (2.1)	7 (1.6)
Adverse event	16 (5.4)	28 (19.2)	44 (10.0)
Subjects request to discontinue study therapy	2 (0.7)	7 (4.8)	9 (2.0)
Subject withdrew consent	1 (0.3)	3 (2.1)	4 (0.9)

Table 1: Subject Disposition (Treatment Period and Follow-up Period) in all treated subjects

	Lambda/RBV/DCV	Alfa-2a/RBV/TVR	Total
Lost to follow-up	0	2 (1.4)	2 (0.5)
Subject no longer meets study criteria	0	3 (2.1)	3 (0.7)
Other	0	1 (0.7)	1 (0.2)
Subjects who entered follow-up[b] (n)	291	138	429
Subjects completing the study, n (%)	284 (97.6)	130 (94.2)	414 (96.5)
Subjects not completing the study, n (%)	7 (2.4)	8 (5.8)	15 (3.5)
Reason for not completing the study, n (%)			
Subject withdrew consent	0	3 (2.2)	3 (0.7)
Death	0	1 (0.7)	1 (0.2)
Lost to follow-up	3 (1.0)	1 (0.7)	4 (0.9)
Follow-up no longer required per protocol	3 (1.0)	1 (0.7)	4 (0.9)
Other	1 (0.3)	2 (1.4)	3 (0.7)

[a] completing the period = completing full planned treatment duration

[b] continuing in the study = entering follow-up period.

Abbreviations: DCV=daclatasvir, RBV=ribavirin, TVR=telaprevir

Table 2: Demographic and Baseline Characteristics - All Treated Subjects

	Lambda/RBV/DCV	Alfa-2a/RBV/TVR	Total
	N=294	N=146	N=440
Age (Years)			
Mean	50	48	49
Min, Max	19, 74	19, 72	19, 74
Gender, n (%)			
Male	157 (53.4)	70 (47.9)	227 (51.6)
Female	137 (46.6)	76 (52.1)	213 (48.4)
Race, n (%)			
White	178 (60.5)	88 (60.3)	266 (60.5)
Black or African American	4 (1.4)	2 (1.4)	6 (1.4)
Asian	110 (37.4)	55 (37.7)	165 (37.5)
Other	2 (0.7)	1 (0.7)	3 (0.7)
HCV RNA distribution (IU/mL), n (%)			
< 800, 000	43 (14.6)	25 (17.1)	68 (15.5)
≥ 800, 000	251 (85.4)	121 (82.9)	372 (84.5)
Prior relapse status to Alfa/RBV, n (%)			
Relapsers	56 (19.0)	30 (20.5)	86 (19.5)

Table 2: Demographic and Baseline Characteristics - All Treated Subjects

	Lambda/RBV/DCV	Alfa-2a/RBV/TVR	Total
	N=294	N=146	N=440
Naive	235 (79.9)	115 (78.8)	350 (79.5)
Other	3 (1.0)	1 (0.7)	4 (0.9)
IL28B rs12979860 Genotype, n (%)			
CC	115 (39.1)	55 (37.7)	170 (38.6)
CT	134 (45.6)	65 (44.5)	199 (45.2)
TT	25 (8.5)	20 (13.7)	45 (10.2)
Not reported	20 (6.8)	6 (4.1)	26 (5.9)
Stage of Fibrosis, n (%)			
None or mild fibrosis	171 (58.2)	83 (56.8)	254 (57.7)
Moderate or severe fibrosis	90 (30.6)	41 (28.1)	131 (29.8)
Cirrhosis	20 (6.8)	14 (9.6)	34 (7.7)
Not reported	13 (4.4)	8 (5.5)	21 (4.8)

Abbreviations: DCV=daclatasvir, RBV=ribavirin, TVR=telaprevir, HCV=hepatitis C virus, RNA=ribonucleic acid

SUMMARY OF SAFETY RESULTS:

Extent of Exposure:

Time on therapy

The time on therapy in the two groups was consistent with the protocol-specified treatment period for each agent.

The median time on study therapy for Lambda/RBV/DCV and Alfa-2a/RBV/TVR groups was 24 weeks and the median time on DCV and TVR was 12 weeks. The average doses in each treatment group were consistent with the protocol-specified doses.

Safety Results:

- One (1) subject (Alfa-2a/RBV/TVR group) was reported to have died in the study. The cause of death was reported to be myocardial infarction and was considered by the investigator to be not related to the study drug.
- Serious adverse events (SAE) were reported in 11 (3.7%) subjects in the Lambda/RBV/DCV group and 16 (11.0%) subjects in the Alfa-2a/RBV/TVR group. Most SAEs occurred in one subject in one or both treatment groups with the exception of rash (5 [3.4%] subjects in the Alfa-2a/RBV/TVR group), jaundice (3 [1.0%] subjects in the Lambda/RBV/DCV group), malaise and acute renal failure (2 [1.4%] subjects in the Lambda/RBV/DCV group).
- The number of subjects discontinuing treatment due to an adverse event (AE) was 16 (5.4%) in the Lambda/RBV/DCV group and 41 (28.1%) in the Alfa-2a/RBV/TVR group. Liver laboratory test abnormalities were the most common event that led to treatment discontinuation in the Lambda/RBV/DCV group and hematological laboratory test abnormalities and skin related AEs were the most common events resulting in treatment discontinuation in the Alfa-2a/RBV/TVR group.
- Overall, 86.4% subjects in the Lambda/RBV/DCV group and 94.5% subjects in the Alfa-2a/RBV/TVR group reported at least 1 adverse event (AE). Most AEs were mild to moderate (Grade 1-2) in intensity.
- Grade 3-4 AEs were reported for 37 (12.6%) subjects and 59 (40.4%) subjects in the Lambda/RBV/DCV and Alfa-2a/RBV/TVR groups, respectively.

- Regarding AEs of special search category; Grade 3 to 4 hepatobiliary disorders were reported more frequently in the Lambda/RBV/DCV group than in the Alfa 2a/RBV/TVR group (9.2% vs 3.4%) while Grade 3 to 4 allergic/hypersensitivity reactions were reported more frequently in the Alfa 2a/RBV/TVR group than in the Lambda/RBV/DCV group (8.9% vs 2.0%). No major differences were noted in autoimmune disorders, cardiomyopathy, and psychiatric disorders.
- Grade 3 to 4 liver laboratory test abnormalities were reported more frequently in the Lambda/RBV/DCV group than in the Alfa-2a/RBV/TVR group which included increased alanine aminotransferase (4.4% vs 1.4%), increased aspartate aminotransferase (8.8% vs 2.7%), and increased total bilirubin (9.5% vs 2.1%), respectively.
- Grade 3 to 4 hematological laboratory test abnormalities were reported more frequently in the Alfa-2a/RBV/TVR group than in the Lambda/RBV/DCV group which included decreased hemoglobin (20.5% vs 2.0%), decreased leukocytes (13.0% vs 0.7%), decreased absolute lymphocytes (20.5% vs 3.4%), and decreased absolute neutrophils (24.7% vs 1.0), respectively.
- Laboratory criteria for potential drug-induced liver injury (ALT ≥ 5x baseline or nadir value and ALT ≥ 10xULN, and total bilirubin ≥2xULN) as defined in the protocol was met by 1 subject in the Alfa-2a/RBV/TVR group.

Dose Reduction of Study Therapy

- Of the 26 (8.8%) subjects who had Lambda dose reductions: 19 (6.5%) underwent dose reduction due to elevated liver function tests, 4 (1.4%) due to non-hematological toxicity and 3 (1.0%) due to hematological toxicity.
- Of the 33 (22.6%) subjects who had Alfa-2a dose reductions: 28 (19.2%) were dose reduced due to hematological toxicity, 5 (3.4%) due to non-hematological toxicity, and 1 (0.7%) subject due to elevated liver function tests.
- Overall, 118 subjects had RBV dose reductions: 40 (13.6%) subjects in the Lambda/RBV/DCV group and 78 (53.4%) subjects in the Alfa-2a/RBV/TVR group. Most of the dose reductions (26 [8.8%] subjects in the Lambda/RBV/DCV group and 71 [48.6%] subjects in the Alfa-2a/RBV/TVR group) were due to hematological toxicity; 9 (3.1%) subjects in the Lambda/RBV/DCV group and 12 (8.2%) subjects in the Alfa-2a/RBV/TVR group had dose reduction due to non-hematological toxicity. An additional 9 (3.1%) subjects in the Lambda/RBV/DCV group had dose reduction as a consequence of elevated liver function tests.

Efficacy Results:

- Lambda/RBV/DCV demonstrated superior efficacy relative to Alfa 2a/RBV/TVR in this study, as assessed by the primary endpoint SVR12, which was achieved in 261/294 (88.8%) subjects in the Lambda/RBV/DCV group versus 103/146 (70.5%) subjects in the Alfa 2a/RBV/TVR group based on modified intent to treat (ITT) analysis (95% CI = [9.9, 25.7] for the difference in proportions; P value < 0.0001). Observed SVR12 rates in the Lambda/RBV/DCV and Alfa-2a/RBV/TVR groups were 261/286 (91.3%) and 103/131 (78.6%), respectively.
- Lambda/RBV/DCV also demonstrated superior efficacy relative to Alfa-2a/RBV/TVR, as assessed by the key secondary endpoint of SVR12 in treatment naive subjects, which was achieved in 211/235 (89.8%) subjects in the Lambda/RBV/DCV group versus 83/115 (72.2%) subjects in the Alfa 2a/RBV/TVR group based on modified ITT analysis (95% CI = [8.8, 26.3] for the difference in proportions; P value < 0.0001). Observed rates in the Lambda/RBV/DCV and Alfa 2a/RBV/TVR groups were 211/228 (92.5%) and 83/105 (79.0%), respectively.
- The modified ITT analysis was not possible for the key secondary endpoint of SVR24 due to early termination of the study. The observed rates for SVR24 in the Lambda/RBV/DCV and Alfa-2a/RBV/TVR groups were 243/268 (90.7%) and 88/112 (78.6%), respectively.
- The overall rates of SVR12 virologic failure for any reason were 33/294 (11.2%) in the Lambda/RBV/DCV group and 43/146 (29.5%) in the Alfa-2a/RBV/TVR group using modified ITT analysis.
- Regarding non-virologic efficacy results; the rates of rash related dermatologic events (26.5% vs 37.0%; 95% CI = [-20.1, -1.9] for the difference in proportions; P value < 0.0177), cytopenic abnormalities (10.2% vs 56.2%; 95% CI = [-54.4, -37.5] for the difference in proportions; P value < 0.0001), and flu like symptoms

(9.9% vs 27.4%; 95% CI = [-24.9, -9.2] for the difference in proportions; P value < 0.0001) were lower in the Lambda/RBV/DCV group than in the Alfa-2a/RBV/TVR group, respectively. The rates of musculoskeletal symptoms were similar in the Lambda/RBV/DCV and Alfa-2a/RBV/TVR group (17.7% vs 19.9%; 95% CI = [-9.8, 5.5] for the difference in proportions; P value < 0.5840).

CONCLUSIONS:

- In this trial, Lambda/RBV/DCV demonstrated superior efficacy relative to Alfa-2a/RBV/TVR, as assessed by both the primary (SVR12) and key secondary endpoint (SVR12 in treatment naive subjects).
- The non-virologic endpoints of rash-related dermatologic events, cytopenic abnormalities, flu-like symptoms were less frequent in the Lambda/RBV/DCV group when compared to Alfa-2a/RBV/TVR group.
- Overall, 24 weeks of lambda/RBV/DCV was found to be well-tolerated compared with Alfa-2a/RBV/TVR based on response guided therapy, with lower rates of SAEs, AEs leading to treatment discontinuation, and Grade 3-4 AEs.
- Grade 3 to 4 liver laboratory test abnormalities were observed more frequently in the Lambda/RBV/DCV group than in the Alfa 2a/RBV/TVR group, while Grade 3 to 4 hematologic laboratory abnormalities were observed more frequently in the Alfa-2a/RBV/TVR group.

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