BRISTOL-MYERS SQUIBB COMPANY

PEGINTERFERON LAMBDA-1A

Addendum to Clinical Study Report for Study AI452008

SYNOPTIC REPORT

A PHASE 2B, RANDOMIZED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF PEGYLATED INTERFERON LAMBDA (BMS-914143) ADMINISTERED WITH RIBAVIRIN PLUS A SINGLE DIRECT ANTIVIRAL AGENT (BMS-790052 OR BMS-650032) VERSUS PEGASYS ADMINISTERED WITH RIBAVIRIN (PART A) AND OF PEGYLATED INTERFERON LAMBDA (BMS-914143) ADMINISTERED WITH OR WITHOUT RIBAVIRIN PLUS 2 DIRECT ANTIVIRAL AGENTS (BMS-790052 AND BMS-650032) (PART B) IN CHRONIC HEPATITIS C GENOTYPE-1 TREATMENT NAÏVE SUBJECTS

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

Addendum to Clinical Study Report for Study AI452008

TITLE OF STUDY: A Phase 2b, Randomized Study to Evaluate the Safety and Efficacy of Pegylated Interferon Lambda (BMS-914143) Administered with Ribavirin Plus a Single Direct Antiviral Agent (BMS-790052 or BMS-650032) versus Pegasys Administered with Ribavirin (Part A) and of Pegylated Interferon Lambda (BMS-914143) Administered with or Without Ribavirin Plus 2 Direct Antiviral Agents (BMS-790052 and BMS-650032) (Part B) in Chronic Hepatitis C Genotype-1 Treatment Naïve Subjects.

PURPOSE: The results of the primary analysis of Part A have been presented separately in a final clinical study report (CSR). The results presented in this synoptic CSR include long-term maintenance of efficacy, immunogenicity, and resistance of Part A. In addition, efficacy and safety data are presented for the Substudy C.

A synoptic addendum report format was chosen to report the follow-up results of Part A and final results from Substudy C, since further development of Lambda was terminated due to the recent approvals of all-oral hepatitis C virus (HCV) treatment regimens that have reduced the unmet medical need and the potential role for interferon-based regimens in HCV. The decision to terminate the development of Lambda was not based on any new unexpected safety findings or efficacy observations.

Study AI452008 (D-LITE) was planned to be conducted in 2 parts, Parts A and B. However, Part B was not initiated due to observed potential drug-induced liver injury (pDILI) events and higher incidence of bilirubin and alanine aminotransferase (ALT) elevations when Lambda was combined with the 200 mg twice daily (BID) dose of BMS-650032 (Asunaprevir; ASV) in Part A. Hence further evaluation of Lambda in any treatment regimen with ASV 200 mg BID was stopped.

D-LITE Substudy C was subsequently initiated per protocol amendment (#7) after criteria for proceeding to Part B were not met. Substudy C was a 36-week single-arm study in 24 treatment-naïve non-cirrhotic subjects with GT-1b chronic HCV infection. Treatment duration was 12 weeks with Lambda/ribavirin (RBV)/daclatasvir (DCV). The study was designed to investigate if shorter treatment duration would lead to an efficacy response comparable to 24 weeks of treatment with Lambda/RBV/DCV. The rationale for the 12-week treatment duration was based on the PDR results from Part A of the study.

NUMBER OF SUBJECTS:

Part A: A total of 141 subjects (119 in the Global study and 22 subjects in the Japan substudy) were randomized and treated.

Substudy C: A total of 24 subjects were treated.

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:

Part A:

A total of 141 subjects (119 in the Global study and 22 subjects in the Japan substudy) were randomized and treated.

At the time of data cutoff for the primary analysis, 109 subjects were continuing in the follow-up (FU) period of the Global study. Of the 109 subjects that were continuing in the FU period, 98 subjects completed the FU period and 11 subjects did not complete the FU period for the following reasons: 5 were lost to FU, 4 withdrew consent, and 2 did not complete the FU for “other” reasons.

In the Japan Substudy, 20 subjects were continuing in the FU period of the study. All 20 subjects completed the FU period.

Complete details of subject disposition during the treatment period and baseline characteristics for Part A are presented in a separate final CSR.

Substudy C:

A total of 24 subjects were enrolled and treated in this study. All except one subject completed the study.

Subject disposition and baseline characteristics for Substudy C are presented in Table -1 and Table -2

Table -1: Subjects Disposition: Substudy C- Treated Subjects

	Number (%) subjects
	DCV/L/R
Subjects	24
Subjects completing the period	24 (100.0)
Subjects not completing the period	0
Subjects continuing in the study	23 (95.8)
Subjects not continuing in the study	1 (4.2)
Reason for not continuing in the study	
Lost to follow-up	1 (4.2)

Abbreviations: OL: open label, DCV: daclatasvir, L: lambda, R: ribavirin

Table -2: Demographic and Baseline Characteristics (Substudy C)

	DCV/L/R N=24
Age	
N	24
Mean	54.5
Median	55.0
Min, Max	28, 75
Q1, Q3	49.0, 59.5
Standard Deviation	9.979
Gender (%)	
Male	11 (45.8)
Female	13 (54.2)
Race (%)	
White	23 (95.8)
Black/African American	1 (4.2)
HCV RNA (log10 IU/mL)	
N	24
Mean	6.26
Median	6.26
Min, Max	5.1, 7.4
Q1, Q3	5.82, 6.71
Standard Deviation	0.602
HCV RNA Distribution (IU/mL) (%)	
< 800,000	7 (29.2)
>= 800,000	17 (70.8)
IL28B RS12979860 Genotype	
CC	8 (33.3)
Non CC	16 (66.7)

Abbreviations: OL: open label, DCV: daclatasvir, L: lambda, R: ribavirin

SUMMARY OF RESULTS

Exposure:

Part A:

Details about the extent of exposure in Part A is provided in the final CSR.

Substudy C:

- All 24 subjects received Lambda (180 μg weekly)/RBV (1000-1200 mg daily)/DCV (60 mg daily).
- The median duration of therapy with Lambda was 12 (12-13) weeks, RBV 84 (70-86) days, and DCV 84 (76-86) days respectively.
- There was no dose interruption or discontinuation of any of the drugs reported in the study.
- Ribavirin dose reduction was reported in 1 (4.2%) subject due to hematological toxicity (anemia).

Efficacy Results:

Part A - Virologic Response Results:

After final database lock of the study, there was an update in the number of subjects who had on-treatment virologic failures in the "Alfa group". Therefore while presenting FU efficacy results through FU Week 48, the updated on-treatment results were also included.

Global Study

- Virologic response was maintained from FU Week 24 through FU Week 48 in the Lambda/RBV+DAA groups, and declined in the alfa/RBV group.
- In the Lambda/RBV/ASV and Lambda/RBV/DCV groups, the mean change from baseline in HCV RNA log10 IU/mL was -3.91 and -3.86, respectively, at FU Week 24, and -3.91 and -4.14, respectively, at FU Week 48.
- In the alfa/RBV group, the mean change from baseline in HCV RNA log10 IU/mL was -2.42 and -1.45 at FU Weeks 24 and 48, respectively.
- The proportion of subjects with on-treatment failure (virologic breakthrough [VBT] and other on-treatment failure) in the Lambda/RBV+DAA groups were 7/38 (18.4%) in the Lambda/RBV/ASV group and 5/41 (12.2%) in the Lambda/RBV/DCV group vs. 22/40 (55.0%) in the alfa group.

Japan Substudy

- Virologic response was maintained from FU Week 24 through FU Week 48 in the Lambda/RBV+DAA groups and declined in the alfa group.
- In the Lambda/RBV/ASV and Lambda/RBV/DCV groups, the mean change from baseline in HCV RNA log10 IU/mL was -4.17 and -4.86 at FU Week 24 and -4.22 and -4.86, respectively, at FU Week 48.
- In the alfa/RBV group, the mean change from baseline was -1.82 at FU Week 24 and -0.10 at FU Week 48.
- One (1/6) subject in the Lambda/RBV/ASV group experienced virologic failure. This subject relapsed. There were no virologic failures in the Lambda/RBV/DCV group.
- Four (4/7) subjects experienced virologic failure in the alfa/RBV group, one experienced other on-treatment failure, and 3 subjects relapsed during FU.

Part A - Immunogenicity Results

Global Study

- In the Lambda/RBV/DCV group, 41 treated subjects were evaluated for ADA, and 3 (7.3%) had measurable ADA at baseline. Ten of the 41 subjects (24.3%) had positive ADA during treatment. Of the 38 subjects with evaluable data to assess neutralizing antibodies, 5 (13.2%) subjects had neutralizing ADA.
- In the Lambda/RBV/ASV group, 38 treated subjects were evaluated for ADA, and 2 (5.26%) had measurable ADA at baseline. Five of the 38 treated subjects (13.2%) had measurable ADA during treatment. Of the 36 subjects with evaluable data to assess neutralizing antibodies, 4 (11.1%) subjects had neutralizing ADA.

- In the alfa/RBV group, 40 treated subjects were evaluated for ADA, and no subjects had pre-existing ADA. Following administration of alfa/RBV, 12 of 40 subjects (30.0%) had an ADA response either on or off treatment.

The presence of ADA did not appear to have a major impact on the ability of subjects to achieve SVR12.

- Of the 31 subjects in the Lambda/RBV/DCV group who were ADA negative by end of treatment, 22 (71.0%) achieved SVR12 responses, while 9 (29%) did not. Of the 10 subjects who had a positive ADA response, 6 (60%) had SVR12 responses, while 4 (40%) did not.
- Of the 33 subjects in the Lambda/RBV/ASV group who were ADA negative by end of treatment, 21 (63.6%) achieved SVR12 response, while 12 (36.4%) did not. Of the 5 subjects with a positive ADA response, 4 (80%) had SVR12 responses, while 1 (20%) did not.
- Of the 32 subjects in the alfa/RBV group who were ADA negative by end of treatment, 11 (34.4%) had SVR12 responses, while 21 (66.6%) did not. Of the 8 subjects with detectable ADA positive samples, 4 (50%) achieved SVR12, while 4 (50%) did not.

Overall, no consistent trends were observed with respect to the presence of ADA and incidence of hypersensitivity reaction AEs, skin and subcutaneous tissue disorders, and gastrointestinal disorders, and therefore firm conclusions regarding the effects of ADA on safety in Lambda/RBV+DAA treated subjects cannot be made at this time.

Japan Substudy

- In the Lambda/RBV/ASV group, 6 treated subjects were evaluated for ADA, and 1 (16.7%) subject had measurable ADA at baseline. Of the 6 subjects, 1 (16.7%) subject had a positive ADA response with onset at Week 24.
- In the Lambda/RBV/DCV group, 8 treated subjects were evaluated for ADA and none had measurable ADA at baseline. Of the 8 subjects, 2 (25%) subjects had a positive ADA response and one subject (50%) had a neutralizing ADA response (of the 2 subjects who had positive ADA). The onset of ADA occurred at Week 8 for one of the subjects and at Week 24 for the second subject.
- In the alfa/RBV group, 7 treated subjects were evaluated for ADA and none had pre-existing ADA. Of the 7 subjects, 1 (14.3 %) subject had an ADA response with onset at Week 24.

Part A - Resistance Results:

Global and Japan Substudy

The persistence of NS5A resistance associated variants (RAVs) was monitored up to ≥ FU Week 48 in 6 (5 GT-1a and 1 GT-1b) virologic failures with available resistance data. A change in the detected NS5A RAVs was observed in all 6 virologic failures. Replacement of NS5A RAVs with wild-type sequence was not observed in the 5 GT-1a failures. However, changes in the detected NS5A RAVs were observed during the FU period in GT-1a subjects. Partial replacement of an NS5A RAV was observed in a GT-1b failure.

The persistence of NS3 RAVs was monitored up to ≥ FU Week 48 in 8 (6 GT-1a and 2 GT-1b) virologic failures with available resistance data. Replacement/partial replacement/no detection of NS3 RAVs was observed in 5 of the 8 failures.

Longer term FU studies would be required to fully understand the persistence of emergent DCV-resistant and ASV-resistant variants.

Substudy C -

Part C - Virologic Response Results:

- The proportion of subjects who achieved SVR12 (HCV RNA < LLOQ [TD or TND]) was 19/24 (79.2%) by mITT analysis. Observed rates were 19/23 (82.6%) at FU Week 12; one subject was lost to FU at on-treatment Week 8 and had undetectable HCV RNA at last visit.
- The proportion of subjects who achieved eRVR with HCV RNA < LLOQ target not detected at Week 4 and Week 12 was 19/24 (79.2%).
- The proportion of subjects who achieved SVR24 was 19/24 (79.2%).

- Four (4/24) subjects experienced virologic failure; all 4 subjects relapsed during FU.
- The proportion of subjects who achieved SVR12 in non-CC genotypes was 13/16 (81.3%) and in CC genotypes was 6/8 (75.0%).
- Most subjects achieved undetectable HCV RNA by Week 4. These rates were sustained through Week 12.
- The mean change from baseline in HCV RNA log10 IU/mL was -4.89 at on-treatment Week 12.

Part C - Resistance Results:

- There was no apparent association with baseline GT-1b NS5A RAVs and virologic response observed in this study.
- NS5A RAVs were detected in 3 of the 4 subjects.
- Emergent NS5A RAVs included L31V and Y93H.

Part C - Biomarkers:

- Serum protein biomarker (cytokines and chemokines) analyzed in this study were IP-10, MCP-1, MIP 1beta, IL-6, IL-8, IFN gamma, RANTES, B2M, and TNF alpha.
- There was no significant association between biomarker host immune response and clinical response to Lambda/RBV/DCV.

Safety:

Part A

Safety assessments were conducted through the end of treatment visit and therefore complete safety results of Part A are provided in the final CSR.

Substudy C

- There were no deaths, SAEs, or AEs leading to discontinuation reported during the study.
- Overall, 20 (83.3%) subjects experienced at least 1 AE during the treatment period.
- All AEs reported were mild to moderate in severity.
- The most frequently reported on-treatment AEs were asthenia, dry skin, pruritus, diarrhea, upper abdominal pain, arthralgia, myalgia, and insomnia.
- The most frequently reported on-treatment laboratory abnormalities were liver laboratory test abnormalities.
- No clinically relevant trends were observed in electrocardiogram (ECG) and physical measurements.

CONCLUSIONS:

Part A

- The efficacy results were consistent with the results presented in the final CSR.
- The presence of ADA among Lambda/RBV+DAA treated subjects did not appear to have a clinically relevant impact on the SVR12 responses or safety and the results were consistent in the Japan substudy.
- Across the Global study and the Japan substudy, emergent NS5A RAVs are more fit than NS3 RAVs when monitored to follow-up Week 48 and beyond.

Substudy C

- The Lambda/RBV/DCV regimen had a consistent SVR rates with other DAA regimens.
- Emergent NS5A RAVs included L31V and Y93H.
- No new safety findings were noted during the study. The regimen was generally well tolerated and had a safety profile consistent with that observed in previous Lambda studies.

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