BRISTOL-MYERS SQUIBB COMPANY

PEGINTERFERON LAMBDA-1a

Final Clinical Study Report for Study AI452016

SYNOPTIC REPORT

A LONG-TERM FOLLOW-UP STUDY OF SUBJECTS WHO PARTICIPATED IN A CLINICAL TRIAL IN WHICH PEGINTERFERON LAMBDA-1a (BMS-914143) WAS ADMINISTERED FOR THE TREATMENT OF CHRONIC HEPATITIS C

Indication:	Chronic Hepatitis C Virus Infection
Phase:	3
Study Initiation Date:	08-Mar-2012
Study Completion Date:	11-Nov-2014
Report Date:	16-Oct-2015
Document Control Number:	930094919
Previous Version(s) of this Report:	None

THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:

[redacted]

SYNOPSIS

Final Clinical Study Report for Study AI452016

TITLE OF STUDY: A Long-Term Follow-Up Study of Subjects Who Participated in a Clinical Trial in which Peginterferon lambda-1a (BMS-914143) was administered for the Treatment of Chronic Hepatitis C.

PURPOSE: BMS-914143 (Lambda; Peginterferon lambda-1a; PEG-rIL-29) was under development as an alternative to peginterferon alfa (either -2a or -2B) (Alfa) for treatment of chronic hepatitis C (CHC) in combination with ribavirin (RBV) and/or other direct acting antiviral agents (DAAs). Previous studies demonstrated long-term durability of virologic response in most patients who achieved sustained virologic response at follow-up week 24 (SVR24) with peginterferon alfa based therapies for chronic hepatitis C virus (HCV) infection. Comparable information on long-term durability of virologic response was not yet available for Lambda or for regimens combining Lambda, RBV and/or DAAs.

Study AI452016 was a long-term non-interventional (observational) follow-up study designed to determine the durability of virologic response in subjects who participated in a previous clinical study in which Lambda was administered and who achieved SVR in the previous (parent) study. Subjects were to be followed for up to approximately 3 years after enrollment.

This study (AI452016) was stopped early due to the decision to terminate the Lambda clinical development program, therefore a very limited data set was available for analysis. A synoptic report format was chosen to report the efficacy (durability of SVR), safety (limited to long-term progression of liver disease), and the duration of persistence of anti-lambda antibodies results.

NUMBER OF SUBJECTS: A total of 1000 subjects were planned to be enrolled in this study. At the time of early study termination, 235 eligible subjects (200 Lambda-treated subjects and 35 Alfa-treated subjects) were enrolled from 5 different studies which included AI452004 (526H04), AI452008, AI452017, AI452020, and AI452021. The analysis is focused on the 200 subjects who received Lambda in the parent study.

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:

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

Enrollment was ongoing at the time of early study termination. Of the 235 enrolled subjects, none completed the planned 3-year follow-up in this study.

Table 1: Subjects Disposition - Eligible Subjects

	Lambda N=200	Alfa N=35
	Number of subjects (%)	
Subjects completing the study	0	0
Subjects not completing the study	200 (100.0)	35 (100.0)
Reason for not completing the study		
Subject withdrew consent	5 (2.5)	1 (2.9)
Lost to follow-up	8 (4.0)	0
Administrative reason by sponsor	183 (91.5)	32 (91.4)
Other	4 (2.0)	2 (5.7)

Table 2: Baseline Demographic and Disease Characteristics - Eligible Subjects

	Lambda N=200
Parent Study (N, %)	
AI452004 (526H04)	78 (39.0)
AI452008	32 (16.0)
AI452017	82 (41.0)
AI452020	1 (0.5)
AI452021	7 (3.5)
Age (years)	
Mean	46.1
Min, Max	20, 75
Age categorization (N, %)	
< 21	1 (0.5)
21 - < 65	190 (95.0)
≥ 65	9 (4.5)
Gender (N, %)	
Male	111 (55.5)
Female	89 (44.5)
Race	
White	173 (86.5)
Black/African American	9 (4.5)
Asian	17 (8.5)
Other	1 (0.5)
HCV Genotype/Subtype (N, %)	
1	111 (55.5)
1A	31 (15.5)
1B	69 (34.5)
Subtype not reported	11 (5.5)
2	34 (17.0)
3	48 (24.0)
4	7 (3.5)
4A	1 (0.5)
4C	4 (2.0)
4I	1 (0.5)
Subtype not reported	1 (0.5)

Table 2: Baseline Demographic and Disease Characteristics - Eligible Subjects

	Lambda N=200
Cirrhosis status (N, %)	
Present	7 (3.5)
Absent	191 (95.5)
Not reported	2 (1.0)
IL28B_RS12979860 Genotype (N. %)	
CC	56 (28.0)
CT	36 (18.0)
TT	13 (6.5)
Non-CC	19 (9.5)
Not reported	76 (38.0)

SUMMARY OF RESULTS:

Duration of Study Participation:

At the time of early study termination, subjects in the Lambda treatment arm had participated in this long-term follow up study (LTFU) for a median of 434.5 days (62.1 weeks) with an interquartile range from 92 to 808.5 days (13.1 to 115.5 weeks).

Efficacy Results:

Primary Efficacy Endpoint

- Among the 200 subjects previously treated with Lambda who achieved protocol defined SVR, only 1 subject (infected with HCV genotype-1b) had loss of previously demonstrated SVR in this study (AI452016). Genotypic sequence analysis of virus in this case was not performed due to early termination of the study and a decision to discard all stored blood samples; and therefore it was not possible to assess if this subject experienced re-infection or true virologic relapse.

Secondary Efficacy Endpoint

- Seventy two (72/200; 36%) subjects who entered the study (AI452016) with anti-drug antibody (ADA) positive at end of treatment (EOT) in the parent study. At the end of 96 weeks of follow-up in study AI452016, 32/72 (44.4%) subjects became ADA-negative and 24/72 (33.3%) subjects remained ADA-positive.
- The ADA titers declined in the majority of subjects over time despite the fact that ADA remained positive in a subset of subjects.
- Seventeen (17/200; 8.5%) subjects who entered the study (AI452016) were positive for the neutralizing antibody (NAB) at EOT in the parent study. Three (3/17; 17.6%) of them became NAB-negative before 96 weeks of follow-up in study AI452016. The other 14/17 (82.4%) subjects were NAB positive at end of follow-up and there were no SAEs observed for these subjects.

Safety Results:

- Overall, no deaths, no events of hepatic disease progression, and no treatment-related serious adverse events (SAE) were reported during the study (AI452016).
- Most laboratory abnormalities reported on-study were Grade 1 or 2 in severity.
- Grade 3 to 4 laboratory test abnormalities were reported in 2 subjects

- One subject in the /Lambda/RBV/asunaprevir (ASV) group from the parent study had a Grade 3 increased alanine aminotransferase (ALT) in the last available sample at long-term follow-up Week 72 of the study (AI452016), which was not associated with viral breakthrough or hepatic decompensation.
- One subject in the Lambda/RBV group from the parent study had an isolated Grade 4 increase in serum international normalized ratio (INR) level at long-term follow-up Week 48 of the study (AI452016), which was not associated with any reported SAEs or other laboratory changes indicative of hepatic decompensation. The previous and subsequent serum INR values for this subject were within normal range

CONCLUSIONS:

- The available data from this small study of relatively limited long-term follow-up duration suggests the treatment response (SVR12) to a Lambda-based HCV regimen is durable.
- The limited available immunogenicity data from this study suggest a progressive loss over time in ADA and NAB, as measured by reversion to seronegative status and/or decline in titer, among those subjects who were positive to one or both antibodies at EOT in the parent study.

Safety

- No treatment-related SAEs were reported during the follow-up period.
- There were no reported clinical events or measured laboratory changes indicative of hepatic disease progression over time.

DATE OF REPORT: 16-Oct-2015