BRISTOL-MYERS SQUIBB COMPANY

PEGINTERFERON LAMBDA-1a

Final Clinical Study Report for Study AI452033

SYNOPTIC REPORT

A DOUBLE-BLINDED, RANDOMIZED CONTROL STUDY EVALUATING THE EFFICACY AND SAFETY OF PEGINTERFERON LAMBDA-1a COMPARED TO PEGINTERFERON ALFA-2a, EACH IN COMBINATION WITH RIBAVARIN, IN THE TREATMENT OF NAIVE GENOTYPE 1 CHRONIC HEPATITIS C SUBJECTS

Indication:	Chronic Hepatitis C Virus Infection
Phase:	3
Study Initiation Date:	07-Jul-2010
Study Completion Date:	18-Sep-2014
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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 AI452033

TITLE OF STUDY: A Double-Blinded, Randomized Control Study Evaluating the Efficacy and Safety of Peginterferon Lambda-1a Compared to Peginterferon alfa-2a, Each in Combination with Ribavirin, in the Treatment of Naive Genotype 1 Chronic Hepatitis C Subjects.

PURPOSE: Study AI452033 was designed to evaluate the efficacy and safety of peginterferon lambda-1a (pegIFNλ, BMS-914143, hereafter referred to as Lambda), compared to peginterferon alfa-2a (Alfa-2a), each in combination with ribavirin (RBV) administered for 48 weeks, in treatment naïve subjects with genotype 1 (GT-1) chronic hepatitis C virus (HCV) infection. The study was conducted to be able to offer subjects who are infected with GT-1 chronic HCV infection and do not have access to an approved direct acting antiviral agent, an opportunity to be treated and cured with a potentially more tolerable interferon, Lambda, in combination with RBV.

A synoptic report format was chosen to report the results from this study, given 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 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.

The early closure of this study was implemented as follows: all treated subjects were to complete their full course of study therapy, allowing for conduct of the primary endpoint (safety) analysis. With the decision to terminate the study early, the formal post-dosing study period was eliminated. However, in order to fulfill the Sponsor's obligation to the subjects in this study, all study participants were provided the opportunity for 1 additional non-study, post-treatment visit (which included the provision of one off-treatment HCV RNA measure), in order for the Investigator and subject to understand whether a sustained virologic response (SVR) had or had not been achieved, and to guide subsequent HCV care. The specific timing of the post-treatment visit and decision to obtain a repeat HCV RNA assessment were at the investigator's discretion. These post-treatment assessments did not contribute to the study database, therefore off-treatment analyses are not provided in this report.

NUMBER OF SUBJECTS: Approximately 300 subjects were initially planned to be randomized in a 2:1 ratio of Lambda/RBV (N=200) or Alfa-2a/RBV therapy (N=100) for 48 weeks. A total of 76 subjects were enrolled and 40 subjects were randomized at 12 investigational sites in 2 countries – Korea and Mexico. Thirty nine (39) subjects received treatment with Lambda/RBV (N=26) and Alfa-2a/RBV (N=13) for 48 weeks.

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:

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

Table 1: Subject Disposition

	Lambda/RBV	Alfa-2a/RBV	Total
Subjects Enrolled	-	-	76
Subjects Randomized	-	-	40
Treated Subjects	26	13	39
Subject's completing the period (%)[a]	20 (76.9)	7 (53.8)	27 (69.2)
Subject's not completing the period (%)	6 (23.1)	6 (46.2)	12 (30.8)
Reason for non-completion (%)			
Adverse event	3 (11.5)	3 (23.1)	6 (15.4)
Lack of efficacy	3 (11.5)	3 (23.1)	6 (15.4)

Table 1: Subject Disposition

	Lambda/RBV	Alfa-2a/RBV	Total
Follow-up subjects	20	10	30
Subject's completing the study (%)	18 (90.0)	9 (90.0)	27 (90.0)
Subject's not completing the study (%)	2 (10.0)	1 (10.0)	3 (10.0)
Reason for non-completion (%)			
Subject withdrew consent	1 (5.0)	1 (10.0)	2 (6.7)
Other	1 (5.0)	0	1 (3.3)

[a] Completing the period = completing full planned treatment duration; Abbreviation: RBV=ribavirin

Table 2: Demographic and Baseline Disease Characteristics: All Treated Subjects

	Lambda/RBV N = 26	Alfa-2a/RBV N = 13	Total N = 39
Age (years)			
Mean	44.8	49.6	46.4
Median	44.5	46.0	46.0
Min, Max	20, 69	29, 73	20, 73
Age categorization (%)			
<21	1 (3.8)	0	1 (2.6)
21 - <65	24 (92.3)	11 (84.6)	35 (89.7)
≥65	1 (3.8)	2 (15.4)	3 (7.7)
Gender (%)			
Male	9 (34.6)	12 (92.3)	21 (53.8)
Female	17 (65.4)	1 (7.7)	18 (46.2)
Race (%)			
White	10 (38.5)	3 (23.1)	13 (33.3)
Korean	12 (46.2)	7 (53.8)	19 (48.7)
Other	4 (15.4)	3 (23.1)	7 (17.9)
Region (%)			
Asia	12 (46.2)	7 (53.8)	19 (48.7)
North America	14 (53.8)	6 (46.2)	20 (51.3)
HCV RNA (log10 IU/mL)			
Mean	6.56	6.52	6.54
HCV RNA Distribution (IU/mL) (%)			
<800,000	3 (11.5)	1 (7.7)	4 (10.3)
≥800,000	23 (88.5)	12 (92.3)	35 (89.7)

Abbreviations: HCV: hepatitis C virus, RBV: ribavirin, RNA: ribonucleic acid.

SUMMARY OF SAFETY RESULTS:

Extent of Exposure:

Study therapy:

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

The overall median treatment duration in both treatment groups was 48 weeks, consistent with the protocol-specified treatment period. The average doses of study drug in each treatment group were consistent with the protocol-specified doses for those agents.

Safety Results:

Primary Endpoint

- Overall, 1 (4%) subject in the Lambda/RBV group and 8 (61.5%) subjects in the Alfa-2a/RBV group reported on-treatment cytopenic abnormalities. Almost all cytopenic abnormalities on-treatment were either anemia or neutropenia. These results are consistent with the known risk of cytopenias associated with Alfa-2a treatment.

Secondary Endpoints

- There were no deaths in this study.
- Overall, 3 (11.5%) subjects reported on-treatment serious adverse events (SAEs) in the Lambda/RBV group, one of which (acute hepatitis) was considered by the Investigator to be related to study therapy. There were no SAEs reported in the Alfa-2a/RBV group.
- Overall, 6 subjects (3 [11.5%] subjects in the Lambda/RBV group and 3 [23.1%] subjects in the Alfa-2a/RBV group) discontinued study treatment due to adverse events (AEs). In the Lambda/RBV group, all events were hepatobiliary in nature, consistent with Lambda's known safety profile. In the Alfa-2a/RBV group, all events were also expected (cytopenias [n=2] or hepatitis [n=1]).
- Overall, 88.5% of subjects in the Lambda/RBV group and 84.6% of subjects in the Alfa-2a/RBV group reported at least 1 AE. Most AEs were mild to moderate (Grade 1/2) in intensity. Grade 3 to 4 AEs were reported in 7 (26.9%) subjects in the Lambda/RBV group and 5 (38.5%) subjects in the Alfa-2a/RBV group. The majority of reported Grade 3 to 4 events are reflective of the known safety profiles for Lambda (hepatobiliary [n=9]) and Alfa-2a (cytopenias [n=5], hepatitis [n=1]).
- Most laboratory abnormalities on-treatment were mild to moderate (Grade 1-2) in intensity. Liver-related laboratory abnormalities occurred in both groups, however events of Grade 3 to 4 hyperbilirubinemia were more frequently observed in the Lambda/RBV vs Alfa-2a/RBV group (3/26 [11.5%] vs 0/13 [0%], respectively). Hematological laboratory test abnormalities were more frequently observed in the Alfa-2a/RBV vs Lambda/RBV group (Grade 1 to 4 neutrophil abnormalities, 12/13 [92.3%] vs 4/26 [15.4%]; Grade 1 to 4 platelet abnormalities, 9/13 [69.2%] vs 2/26 [7.7%], respectively).

Dose Reductions During Study Therapy:

- Overall, 3 (11.5%) subjects in the Lambda/RBV group required a Lambda dose reduction, in each case due to elevated liver function tests.
- Overall, 6 (46.2%) subjects in the Alfa-2a/RBV group required an Alfa dose reduction. All 6 (46.2%) subjects had dose reductions due to hematologic toxicity and 1 of these subjects also had a dose reduction due to elevated liver function tests.
- A total of 5 (12.8%) subjects across the two treatment groups required a RBV dose reduction. Four (30.8%) subjects in the Alfa 2a/RBV group had dose reductions due to hematological toxicity and 1 of these subjects also had a dose reduction due to non-hematological toxicity. One (3.8%) subject in the Lambda/RBV group required a dose reduction due to elevated liver function tests.

Efficacy Results:

Due to early termination of the study, HCV RNA assessments were only performed during the on-treatment period of the study and through end-of-treatment. The key findings, based on the available data are:

- The RVR response was greater in the Lambda/RBV group as compared to the Alfa-2a/RBV group (23% vs 0%).

- All subjects in both groups achieved HCV RNA suppression at end-of-treatment.

CONCLUSIONS:

- Treatment with Lambda/RBV was overall safe and well tolerated, with lower on-treatment rates of cytopenia however higher rates of Grade 3 to 4 hyperbilirubinemia, as compared to Alfa-2a/RBV.
- More subjects achieved RVR in the Lambda/RBV group compared to the Alfa-2a/RBV group (23% vs 0%).
- All subjects in both groups achieved HCV RNA suppression at end-of-treatment.

DATE OF REPORT: 08-Oct-2015