# BRISTOL-MYERS SQUIBB COMPANY

## PEGINTERFERON LAMBDA-1a

**Final Clinical Study Report for Study AI452020**

**SYNOPTIC REPORT**

# A PHASE 3 BLINDED RANDOMIZED STUDY OF PEGINTERFERON LAMBDA-1a AND RIBAVIRIN COMPARED TO PEGINTERFERON ALFA-2a AND RIBAVIRIN, EACH ADMINISTERED WITH TELAPREVIR IN SUBJECTS WITH GENOTYPE-1 CHRONIC HEPATITIS C WHO ARE TREATMENT-NAÏVE OR RELAPSED ON TREATMENT WITH PEGINTERFERON ALFA AND RIBAVIRIN

| | |
|---|---|
| **Indication:** | Chronic Hepatitis C Virus Infection |
| **Phase:** | 3 |
| **Study Initiation Date:** | 19-Jun-2012 |
| **Study Completion Date:** | 04-Feb-2015 |
| **Report Date:** | 30-Jan-2016 |
| **Document Control Number:** | 930098249 |
| **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 AI452020

**TITLE OF STUDY:** A Phase 3 Blinded Randomized Study of Peginterferon Lambda-1a and Ribavirin Compared to Peginterferon Alfa-2a and Ribavirin, Each Administered with Telaprevir in Subjects with Genotype-1 Chronic Hepatitis C who are Treatment-naïve or Relapsed on Treatment with Peginterferon Alfa and Ribavirin.

**PURPOSE:** Study AI452020 was designed to evaluate the efficacy and safety of peginterferon lambda-1a (pegIFNλ-1a, BMS-914143, hereafter referred to as Lambda) compared to peginterferon alfa-2a (Alfa-2a) each in combination with ribavirin (RBV) administered for 24 or 48 weeks and with telaprevir (TVR) for the first 12 weeks of treatment, in treatment-naïve or treatment relapsed subjects with genotype 1 (GT-1) chronic hepatitis C virus (HCV) infection.

This study was conducted in two parts. Part A was a single arm, open label (OL) sentinel cohort which was completed prior to early termination of the Lambda program. The primary efficacy endpoint is the proportion of subjects who achieved extended rapid virologic response (eRVR). Part B was a randomized controlled, double-blind cohort study. Part B was initiated after the go criteria were achieved from Part A (an observed rate of ≤ 24% of drug-related adverse events leading to discontinuation). Part B of the study was stopped early due to program termination when all subjects had completed post treatment follow-up week 12 and were ongoing for follow-up week 24 assessment. The primary efficacy endpoint is the proportion of subjects who achieved sustained virologic response as post-treatment follow-up week 12 (SVR12). The results of both Part A and Part B are presented in this report.

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.

**NUMBER OF SUBJECTS:**

**Part A:** Approximately 25 subjects were planned for treatment and 27 subjects were treated with open label (OL) Lambda/RBV/TVR.

**Part B:** Approximately 609 subjects were planned to be randomized 2:1 to either Lambda/RBV/TVR (n=406) or Alfa-2a/RBV/TVR (n=203). A total of 621 subjects were randomized and 617 subjects were treated (411 with Lambda/RBV/TVR and 206 with Alfa-2a/RBV/TVR).

**SUMMARY OF RESULTS:**

Results are presented separately for Part A, followed by Part B.

**RESULTS FOR PART A:**

**Disposition, Demographics and Other Pertinent Baseline Characteristics - Part A:**

A total of 43 subjects were enrolled and 27 subjects were treated at 7 investigational sites in the United States of America. All subjects received treatment with Lambda/RBV/TVR.

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

**Table 1: Subject Disposition (Treatment Period and Follow-up Period) in All Treated Subjects - Part A**

| | Lambda/RBV/TVR N=27 |
|---|---|
| Subjects completing the treatment period (n, %) | 16 (59.3) |
| Subjects not completing the treatment period (n, %) | 11 (40.7) |

**Table 1: Subject Disposition (Treatment Period and Follow-up Period) in All Treated Subjects - Part A**

| | Lambda/RBV/TVR N=27 |
|---|---|
| Reason for not completing the treatment period (n, %) | |
| Lack of efficacy | 5 (18.5) |
| Adverse events | 2 (7.4) |
| Subject request to discontinue study treatment | 3 (11.1) |
| Lost to follow-up | 1 (3.7) |
| Subjects who entered follow-up (n) | 26 |
| Subjects completing the follow-up (n, %) | 21 (80.8)[a] |
| Subjects not completing the follow-up (n, %) | 5 (19.2) |
| Reason for not completing the follow-up (n, %) | |
| Lost to follow-up | 2 (7.7) |
| Follow-up no longer required per protocol | 1 (3.8) |
| Other | 2 (7.7) |

[a] Based on the final October 2015 locked database
Abbreviations: RBV=ribavirin, TVR=telaprevir

**Table 2: Demographic and Baseline Characteristics in All Treated Subjects - Part A**

| | Lambda/RBV/TVR N=27 |
|---|---|
| Age (years) | |
| Mean | 51.9 |
| Median | 54.0 |
| Min, Max | 23, 62 |
| Gender (n, %) | |
| Male | 18 (66.7) |
| Female | 9 (33.3) |
| Race (n, %) | |
| White | 17 (63.0) |
| Black/African American | 7 (25.9) |
| American Indian/Alaska native | 1 (3.7) |
| Other | 2 (7.4) |
| HCV RNA distribution (IU/mL) (n, %) | |
| < 800, 000 | 5 (18.5) |
| ≥ 800, 000 | 22 (81.5) |
| HCV genotype 1 subtype (n, %) | |

**Table 2: Demographic and Baseline Characteristics in All Treated Subjects - Part A**

| | Lambda/RBV/TVR N=27 |
|---|---|
| 1A | 19 (70.4) |
| 1B | 8 (29.6) |
| Prior relapse status to Alfa/RBV (n, %) | |
| Relapser | 6 (22.2) |
| Naive | 21 (77.8) |
| Cirrhosis status (n, %) | |
| Present | 5 (18.5) |
| Absent | 22 (81.5) |
| IL28B rs12979860 Genotype (n, %) | |
| CC | 6 (22.2) |
| CT | 16 (59.3) |
| TT | 5 (18.5) |

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

**Extent of Exposure - Part A:**

Time on therapy

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

The overall median treatment duration for Lambda/RBV was 168 days (24 weeks) and the median time on TVR was 83 days (12 weeks) which was consistent with the protocol-specified treatment period. The average doses of study therapy were also consistent with the protocol-specified doses for those agents.

Interruption of Study Therapy

Interruption of Lambda for more than 14 days was reported in 1 subject (3.7%) due to elevated liver function tests and interruption of RBV for more than 14 days was reported in 1 subject (3.7%) due to 'other' reason.

**Safety Results - Part A:**

- There were no deaths in Part A.
- Overall, 6 (22.2%) subjects experienced on-treatment SAEs, two events of which (both, jaundice) were considered by the Investigator to be related to study therapy. There were no SAEs reported during the follow-up period.
- Overall, 2 (7.4%) subjects with a total of 5 events discontinued study treatment due to AEs. All, 5 events were hepatobiliary in nature, consistent with Lambda's known safety profile. These results met the pre-specified criterion for initiation of Part B of the study (an observed rate of ≤ 24% of drug-related adverse events leading to discontinuation).
- Adverse events (all grades) of special interest (pre-specified) reported on-treatment with Lambda/RBV/TVR were as follows: occurrence of rash (17 subjects; 63.0%), constitutional symptoms (16 subjects; 59.3%), psychiatric symptoms (10 subjects; 37.0%), neurologic symptoms (8 subjects; 29.6%), musculoskeletal symptoms (5 subjects; 18.5%), and flu-like symptoms (4 subjects; 14.8%).
- Overall, 96.3% of subjects reported at least 1 AE during treatment. Most on-treatment AEs were mild to moderate (Grade 1 to 2) in intensity. Adverse events reported in > 20% of subjects in decreasing order of frequency were: fatigue (16 subjects; 59.3%), pruritus (13 subjects; 48.1%), diarrhea (13 subject; 48.1%), rash (12 subjects; 44.4%), nausea (11 subjects; 40.7%), headache (8 subjects; 29.6%), and insomnia (8 subjects; 29.6%).

- Overall, 8 (29.6%) subjects reported Grade 3 to 4 AEs during treatment. Events reported were hyperbilirubinemia (3 subjects; 11.1%), diarrhea (2 subjects; 7.4%), nausea, peptic ulcer hemorrhage, anemia, and hyperuricemia (each 1 subject; 3.7%). Hyperbilirubinemia is a known expected AE for Lambda when used in combination with RBV for treatment of chronic HCV infection. The other events (except peptic ulcer hemorrhage) are known to occur with HCV treatment with Alfa-2a, RBV or TVR.
- Overall, 12 (44.4%) subjects reported Grade 2 to 4 related AEs on-treatment. The AEs reported in > 5% of subjects were rash, generalized rash, hyperbilirubinemia (each 3 subjects; 11.1%), diarrhea, nausea, fatigue, insomnia, and anemia (each 2 subjects; 7.4%).
- During the follow-up period, AEs (all grades) were reported in 6 (23.1%) subjects. The AEs (n=8) reported during follow-up were nasopharyngitis, urinary tract infection, rash, generalized rash, chest pain, hyperbilirubinemia, increased alanine aminotransferase, and muscle spasm (each 1 subject; 3.8%).
- Most laboratory abnormalities on-treatment were mild to moderate (Grade 1 to 2) in intensity. The most frequently reported on-treatment (all grades) laboratory abnormalities were hepatobiliary in nature and included: increased alanine aminotransferase (13 subjects; 48.1%), increased aspartate aminotransferase (20 subjects; 74.1%), and increased total bilirubin (17 subjects; 63.0%). Other laboratory abnormalities which were reported in > 20% of subjects were decreased hemoglobin (10 subjects; 37.0%), increased amylase (9 subjects; 33.3%), and increased lipase (15 subjects; 55.6%). A similar trend was observed in Grade 3 to 4 laboratory abnormalities, with hepatobiliary events being the most commonly observed which included increased aspartate aminotransferase (6 subjects; 22.2%), increased total bilirubin (5 subjects; 18.5%), and increased alanine aminotransferase (3 subjects; 11.1%). The predominance of hepatobiliary-related laboratory abnormalities is consistent with the known safety profile of Lambda.
- Laboratory criteria for potential drug-induced liver injury (pDILI) was not met by any subject in Part A of this study.

Dose Reductions in Study Drug

- Overall, 3 (11.1%) subjects required a Lambda dose reduction, in each case due to elevated liver function tests.
- Of the 7 (25.9%) subjects who had RBV dose reductions, 3 (11.1%) had dose reductions due to elevated liver function tests, 3 (11.1%) for hematological toxicity, and 1 (3.7%) for non-hematological toxicity.

**Efficacy Results - Part A:**

Primary Efficacy Endpoint

The proportion of subjects who achieved eRVR (HCV RNA <LLOQ target not detected at Weeks 4 and 12) was 14/27 (51.9%) by modified ITT analysis. The observed eRVR rate was 14/25 (56.0%) (Table 3).

Secondary and Other Efficacy Endpoints

The results of secondary and other efficacy endpoints are summarized in Table 3.

**Table 3: Primary, Secondary, and Other Efficacy Endpoints in Treated Subjects - Part A**

| | Lambda/RBV/TVR |
|---|---|
| | **Responder/Evaluable (%)** |
| **Primary Endpoint** | |
| eRVR | |
| Modified ITT | 14/27 (51.9) |
| Observed values | 14/25 (56.0) |
| **Secondary and Other Endpoints** | |
| SVR12 | |
| Modified ITT | 13/27 (48.1) |
| Observed values | 13/24 (54.2) |

**Table 3: Primary, Secondary, and Other Efficacy Endpoints in Treated Subjects - Part A**

| | Lambda/RBV/TVR |
|---|---|
| | Responder/Evaluable (%) |
| SVR24 | |
| Modified ITT | 11/27 (40.7) |
| Observed values | 11/22 (50.0) |
| SVR12 in treatment naive | |
| Modified ITT | 10/21 (47.6) |
| Observed values | 10/19 (52.6) |

Abbreviations: eRVR= extended rapid virologic response, ITT=intent to treat, RBV=ribavirin, SVR12=sustained virologic response at post-treatment follow-up Week 12, SVR24= sustained virologic response at post-treatment follow-up Week 24, TVR=telaprevir

Virologic Failure

The overall rates of SVR12 failures for any reasons were 14/27 (51.9%) using modified ITT analysis.

**CONCLUSIONS - PART A**

Efficacy

- The proportion of subjects who achieved eRVR was 51.9% by modified ITT analysis.
- SVR12 and SVR24 rates by modified ITT analysis were 48.1% and 40.7%, respectively.

Safety

- There were no unexpected AEs; events observed were consistent with the known safety profile of Lambda.
  - Overall, Lambda/RBV/TVR was found to be relatively well tolerated with modest rates of grade 3 to 4 AEs (29.6%) and low rates of AEs leading to discontinuation of therapy (7.4%).
  - At least 1 AE was reported in 96% of subjects during the treatment period and most of these events were mild to moderate (Grade 1 to 2) in intensity. The most frequently reported Grade 3 to 4 AE was hyperbilirubinemia, which is consistent with the known safety profile of Lambda.
  - Most laboratory abnormalities on-treatment were mild to moderate (Grade 1 to 2) in intensity. The most frequently observed (all grades) laboratory abnormalities on-treatment were hepatobiliary in nature, again consistent with the known safety profile of Lambda.

**RESULTS OF PART B:**

**Disposition, Demographics, and Other Pertinent Baseline Characteristics - Part B:**

A total of 838 subjects were enrolled at 98 investigational sites in 15 countries (Austria, Belgium, Brazil, Canada, Czech Republic, France, Germany, Israel, Italy, Poland, Russia, Spain, Switzerland, the United Kingdom, and the United States of America); 621 of these subjects were randomized 2:1 to receive either Lambda/RBV/TVR or Alfa-2a/RBV/TVR. Of the 621 randomized subjects, 617 subjects (411 subjects in the Lambda/RBV/TVR group and 206 subjects in the Alfa-2a/RBV/TVR group) were treated.

Subject disposition and baseline characteristics for Part B are presented in Table 4 and Table 5.

**Table 4: Subject Disposition (Treatment Period and Follow-up Period) in All Treated Subjects - Part B**

| | Lambda/RBV/TVR N=411 | Alfa-2a/RBV/TVR N=206 | Total N=617 |
|---|---|---|---|
| Subjects completing the treatment period (n, %)[a] | 339 (82.5) | 171 (83.0) | 510 (82.7) |
| Subjects not completing the treatment period (n, %) | 72 (17.5) | 35 (17.0) | 107 (17.3) |
| Reason for not completing the treatment period (n, %) | | | |
| Lack of efficacy | 14 (3.4) | 6 (2.9) | 20 (3.2) |
| Adverse events | 33 (8.0) | 17 (8.3) | 50 (8.1) |
| Subject request to discontinue study treatment | 9 (2.2) | 7 (3.4) | 16 (2.6) |
| Subject withdrew consent | 4 (1.0) | 3 (1.5) | 7 (1.1) |
| Lost to follow-up | 5 (1.2) | 1 (0.5) | 6 (1.0) |
| Poor / non-compliance | 2 (0.5) | 0 | 2 (0.3) |
| Subject no longer meets study criteria | 1 (0.2) | 0 | 1 (0.2) |
| Other | 4 (1.0) | 1 (0.5) | 5 (0.8) |
| Subjects who entered follow-up (n) | 399 | 199 | 598 |
| Subjects completing the follow-up (n, %) | 364 (91.2) | 171 (85.9) | 535 (89.5) |
| Subjects not completing the follow-up (n, %) | 35 (8.8) | 28 (14.1) | 63 (10.5) |
| Reason for not completing the follow-up (n, %) | | | |
| Subject withdrew consent | 3 (0.8) | 2 (1.0) | 5 (0.8) |
| Death | 1 (0.3) | 0 | 1 (0.2) |
| Lost to follow-up | 10 (2.5) | 12 (6.0) | 22 (3.7) |
| Follow-up no longer required per protocol | 3 (0.8) | 2 (1.0) | 5 (0.8) |
| Other | 8 (2.0) | 8 (4.0) | 16 (2.7) |
| Not reported | 10 (2.5) | 4 (2.0) | 14 (2.3) |

Abbreviations: RBV=ribavirin, TVR=telaprevir
[a] completing the period = completing full planned treatment duration

**Table 5: Demographic and Baseline Characteristics in All Treated Subjects - Part B**

| | Lambda/RBV/TVR N=411 | Alfa-2a/RBV/TVR N=206 | Total N=617 |
|---|---|---|---|
| Age (years) | | | |
| Mean | 45.8 | 45.0 | 45.5 |
| Median | 48.0 | 46.0 | 47.0 |
| Min, Max | 19, 77 | 19, 71 | 19, 77 |
| Gender (n, %) | | | |
| Male | 259 (63.0) | 126 (61.2) | 385 (62.4) |

**Table 5: Demographic and Baseline Characteristics in All Treated Subjects - Part B**

| | Lambda/RBV/TVR N=411 | Alfa-2a/RBV/TVR N=206 | Total N=617 |
|---|---|---|---|
| Female | 152 (37.0) | 80 (38.8) | 232 (37.6) |
| Race (n, %) | | | |
| White | 362 (88.1) | 187 (90.8) | 549 (89.0) |
| Black/African American | 38 (9.2) | 14 (6.8) | 52 (8.4) |
| Asian | | | |
| Asian Indian | 2 (0.5) | 2 (1.0) | 4 (0.6) |
| Chinese | 1 (0.2) | 0 | 1 (0.2) |
| Asian Other | 4 (1.0) | 2 (1.0) | 6 (1.0) |
| American Indian/Alaska native | 4 (1.0) | 1 (0.5) | 5 (0.8) |
| HCV RNA distribution (IU/mL) (n, %) | | | |
| < 800, 000 | 57 (13.9) | 35 (17.0) | 92 (14.9) |
| ≥ 800, 000 | 354 (86.1) | 171 (83.0) | 525 (85.1) |
| HCV genotype 1 subtype (n, %) | | | |
| 1A | 171 (41.6) | 84 (40.8) | 255 (41.3) |
| 1B | 240 (58.4) | 122 (59.2) | 362 (58.7) |
| Prior relapse status to Alfa/RBV (n, %) | | | |
| Relapser | 101 (24.6) | 50 (24.3) | 151 (24.5) |
| Naive | 309 (75.2) | 156 (75.7) | 465 (75.4) |
| Not Reported | 1 (0.2) | 0 | 1 (0.2) |
| Cirrhosis status (n, %) | | | |
| Present | 31 (7.5) | 14 (6.8) | 45 (7.3) |
| Absent | 359 (87.3) | 185 (89.8) | 544 (88.2) |
| Not Reported | 21 (5.1) | 7 (3.4) | 28 (4.5) |
| IL28B rs12979860 Genotype (n, %) | | | |
| CC | 97 (23.6) | 48 (23.3) | 145 (23.5) |
| CT | 242 (58.9) | 125 (60.7) | 367 (59.5) |
| TT | 72 (17.5) | 33 (16.0) | 105 (17.0) |

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

**Extent of Exposure - Part B:**

Time on 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 the Lambda/RBV/TVR and Alfa-2a/RBV/TVR groups was 168 days (24 weeks) with a median time on TVR of 84 days (12 weeks) and was consistent with the protocol-specified treatment period. The average doses of study therapy in each treatment group were consistent with the protocol-specified doses for those agents.

**Safety Results - Part B:**

- Two subjects died in Part B of the study.
  - One subject in the Lambda/RBV/TVR group died on Day 169 (on-treatment Week 24) due to complications of pneumonia, which was considered by the Investigator to be not related to study therapy.
  - One subject in the Alfa-2a/RBV/TVR group died on Day 309 (on-treatment Week 40) due to hypoxia, which was considered by the Investigator to be related to study therapy, although the subject had a history of interstitial lung disease, and a long history of tobacco use.
- On-treatment SAEs were reported for 43 (10.5%) subjects in the Lambda/RBV/TVR group and 20 (9.7%) subjects in the Alfa-2a/RBV/TVR group. Overall, 37 (9.0%) subjects in the Lambda/RBV/TVR group and 17 (8.3%) subjects in the Alfa-2a/RBV/TVR group reported treatment-related SAEs. The majority of the reported SAEs are consistent with the known safety profiles of Lambda and Alfa-2a.
- Overall, 33 (8.0%) subjects in the Lambda/RBV/TVR group and 17 (8.3%) subjects in the Alfa-2a/RBV/TVR group discontinued study treatment due to AEs. In the Lambda/RBV/TVR group, most discontinuations were for hepatobiliary events, consistent with the known safety profile of Lambda. In the Alfa-2a/RBV/TVR group, most discontinuations were for anemia. More subjects in the Lambda/RBV/TVR group discontinued treatment during the first 4 weeks of treatment.
- The rates of pre-specified cytopenic abnormalities, flu like symptoms, and musculoskeletal symptoms were lower in the Lambda/RBV/TVR group than in the Alfa-2a/RBV/TVR group, respectively. The rates of rash related dermatologic events were consistent in the Lambda/RBV/TVR and Alfa-2a/RBV/TVR group.
- Overall, 91.7% of subjects in the Lambda/RBV/TVR group and 97.1% of subjects in the Alfa-2a/RBV/TVR group reported at least 1 AE. Most AEs were mild to moderate (Grade 1 to 2) in intensity. The majority of events are consistent with the known safety profiles of Lambda and Alfa-2a when used in combination with RBV and TVR.
- Grade 3-4 AEs were reported for 85 (20.7%) subjects and 60 (29.1%) subjects in the Lambda/RBV/TVR and Alfa-2a/RBV/TVR groups, respectively. The majority of these events are consistent with the known safety profiles for Lambda and Alfa-2a.
- Regarding AEs of special search categories: Grade 3 to 4 hepatobiliary disorders were reported more frequently in the Lambda/RBV/TVR group than in the Alfa-2a/RBV/TVR group (11.4% vs 1.5%), respectively. No clinically meaningful differences between the two groups were noted for any of the other events (ie, allergic/hypersensitivity reactions, autoimmune disorders, cardiomyopathy, or psychiatric disorders).
- Most laboratory abnormalities reported in either group were mild to moderate (Grade 1 to 2) in intensity.
- Grade 3 to 4 liver-related laboratory abnormalities were observed more frequently in the Lambda/RBV/TVR group, again consistent with the known safety profile of Lambda when used in combination with RBV. Conversely, Grade 3 to 4 hematological laboratory abnormalities were observed more frequently in the Alfa-2a/RBV/TVR group and are consistent with the known safety profiles of Alfa-2a when used in combination with RBV with or without TVR. Grade 3 to 4 increases in uric acid were observed in both treatment groups and is consistent with the known safety profile of Alfa-2a/RBV/TVR.
- Laboratory criteria for potential drug-induced liver injury as defined in the protocol (ALT ≥ 5x baseline or nadir value and ALT ≥ 10xULN, and total bilirubin ≥ 2xULN) were met by 7 (1.7%) subjects in the Lambda/RBV/TVR group and by none in the Alfa-2a/RBV/TVR group. None of these subjects died or had clinical hepatic decompensation.

Dose Reduction of Study Therapy

- Overall, 52 (12.7%) subjects in the Lambda/RBV/TVR group required a Lambda dose reduction: 42 (10.2%) subjects had dose reductions due to elevated liver function tests, 7 (1.7%) due to hematological toxicity, and 4 (1.0%) due to non-hematological toxicity.
- Overall, 29 (14.1%) subjects in the Alfa-2a/RBV/TVR group required an Alfa dose reductions: 25 (12.1%) subjects had dose reductions due to hematologic toxicity, 2 (1.0%) due to non-hematological toxicity, and 2 (1.0%) due to elevated liver function tests.
- Overall, 146 subjects across the two treatment groups required a RBV dose reduction due to one or more reasons: 61 (14.8%) subjects in the Lambda/RBV/TVR group and 85 (41.3%) subjects in the

Alfa-2a/RBV/TVR group. Most of the dose reductions (39 [9.5%] subjects in the Lambda/RBV/TVR group and 84 [40.8%] subjects in the Alfa-2a/RBV/TVR group) were due to hematological toxicity. There were 19 (4.6%) subjects in the Lambda/RBV/TVR group and 3 (1.5%) subjects in the Alfa-2a/RBV/TVR group who required dose reductions due to non-hematological toxicity. An additional 12 (2.9%) subjects in the Lambda/RBV/TVR group and 1 (0.5%) subject in the Alfa-2a/RBV/TVR group had dose reductions as a consequence of elevated liver function tests.

**Efficacy Results - Part B:**

Primary Efficacy Endpoint

The proportion of subjects who achieved SVR12 (by modified ITT; Table 6) were

- Lambda/RBV/TVR group: 313/411 (76.2%); 95% CI (72.0, 80.3).
- Alfa/RBV/TVR group: 169/206 (82.0%); 95% CI (76.8, 87.3).

The 95% confidence interval (CI) for the difference in proportions was -12.3%, 0.8%. Non-inferiority of Lambda/RBV/TVR to Alfa/RBV/TVR was not established because the lower limit of the 95% CI was less than the predefined non-inferiority margin of -12% (Table 6).

Secondary and Other Efficacy Endpoints

The results of virologic response for efficacy endpoints were summarized in Table 6. The rates of RVR and eRVR were lower with Lambda/RBV/TVR, even though the discontinuations due to AEs were consistent in both the treatment groups. More subjects in the Lambda/RBV/TVR group discontinued treatment during the first 4 weeks of treatment than in the Alfa-2a/RBV/TVR group, which contributed to lower RVR and eRVR rates and fewer subjects were eligible to complete 24 weeks of treatment.

**Table 6: Primary, Secondary, and Other Efficacy Endpoints in Treated Subjects - Part B**

| | Lambda/RBV/TVR | Alfa-2a/RBV/TVR |
|---|---|---|
| | Responder/Evaluable (%) | |
| **Primary Endpoints (by modified ITT)** | | |
| SVR12 | 313/411 (76.2) | 169/206 (82.0) |
| 95% CI | (72.0, 80.3) | (76.8, 87.3) |
| 95% CI for the difference in proportions | (-12.3, 0.8) | |
| p-value | 0.0855 | |
| **Secondary and Other Endpoints (by modified ITT)** | | |
| SVR12 in treatment naive only | 229/311 (73.6) | 127/155 (81.9) |
| RVR | 275/411 (66.9) | 157/206 (76.2) |
| eRVR | 263/411 (64.0) | 146/206 (70.9) |
| cEVR | 362/411 (88.1) | 176/206 (85.4) |
| EOTR | 368/411 (89.5) | 187/206 (90.8) |
| SVR24[a] | 185/223 (83.0) | 94/108 (87.0) |

[a] all subjects did not have SVR24 results due to early termination, hence observed values were reported

Abbreviations: cEVR=complete early virologic response, EOTR=end of treatment response, eRVR=extended rapid virologic response, RBV=ribavirin, RVR= rapid virologic response, SVR12=sustained virologic response at post-treatment follow-up Week 12, SVR24= sustained virologic response at post-treatment follow-up Week 24, TVR=telaprevir

Virologic Failure

The overall rate of virologic failure was higher in the Lambda/RBV/TVR group (98/411 [23.8%]) compared to the Alfa-2a/RBV/TVR group (37/206 [18.0%]), using modified ITT analysis. Also, a higher rate of relapse was observed in Lambda/RBV/TVR group than in the Alfa-2a/RBV/TVR group.

Virologic Response in Subgroups:

In general, SVR12 rates were lower in subjects who received Lambda/RBV/TVR compared with Alfa-2a/RBV/TVR in most of the subgroups except in relapsers to prior treatment for which the SVR12 (84.2% vs 82.0%) was consistent between the 2 groups. Higher rates of SVR12 response were achieved in GT 1b vs GT 1a, those with non-cirrhotic vs cirrhotic, baseline HCV RNA < 800,000 IU/mL vs ≥ 800,000 IU/mL, and those with eRVR status yes vs no, regardless of the treatment group. Responses in the Lambda treatment group were lower in treatment-naive subjects and subjects with moderate or severe fibrosis.

**CONCLUSIONS - PART B:**

Efficacy

- Non-inferiority of Lambda/RBV/TVR to Alfa 2a/RBV/TVR was not established for the primary endpoint of SVR12. Also, SVR12 rates were lower for Lambda/RBV/TVR than for Alfa-2a/RBV/TVR in treatment-naive subjects (73.6% vs 81.9%), but were consistent between treatment groups in relapsers to prior treatment (84.2% vs 82.0%).
- The rates of RVR and eRVR were lower with Lambda/RBV/TVR, even though the discontinuation due to AEs were consistent in both the treatment groups. More subjects in the Lambda/RBV/TVR group discontinued treatment during the first 4 weeks of treatment, which contributed to lower RVR and eRVR rates and fewer subjects were eligible to complete 24 weeks of treatment.

Safety

- Overall, Lambda/RBV/TVR was found to be relatively well tolerated, with no unexpected events and with an AE profile consistent with that expected for Lambda when used in combination with RBV for the treatment of chronic HCV infection.
- Grade 3 to 4 liver laboratory test abnormalities were observed more frequently in the Lambda/RBV/TVR 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 which were consistent with the known safety profiles of Lambda and Alfa-2a.

**DATE OF REPORT:** 30-Jan-2016