Poster 1103

Safety Profile of Peginterferon Lambda for Treatment of Chronic Hepatitis B (CHB) or Chronic Hepatitis C (CHC): Cross-Study Analysis of Patients Treated in Three Phase 2 Studies

Muir AJ,[1] Jurkowski C,[2] Cooney E,[2] Hillson J,[3] Lataillade M,[2] Mas Casullo V,[2] Gray T,[3] Xu D,[2] Yogendran L,[2] Srinivasan S[2]

[1]Duke Clinical Research Institute, Duke University, Durham, NC; [2]Bristol-Myers Squibb, Wallingford, CT; [3]Bristol-Myers Squibb/Zymogenetics, Seattle, WA

Corresponding author:
Andrew Muir (andrew.muir@duke.edu)

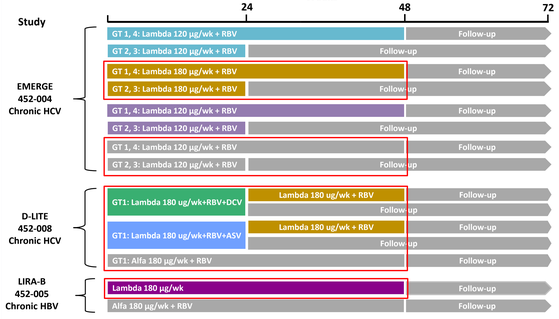
1. BACKGROUND

- Peginterferon Lambda-1a (Lambda) is a type III interferon with limited extra-hepatic receptor distribution, which may contribute to a favorable tolerability profile compared with alfa interferons
- Lambda has been evaluated in 3 phase 2 studies:
  - EMERGE: Lambda weekly plus ribavirin (RBV) vs peginterferon alfa (alfa) weekly plus RBV for chronic genotype 1–4 HCV infection[1]
  - D-LITE: Lambda weekly plus RBV with daclatasvir (DCV) or asunaprevir (ASV) versus alfa weekly plus RBV for chronic genotype 1 HCV infection[2]
  - LIRA-B: Lambda weekly versus alfa weekly for HBeAg-positive chronic HBV infection[3]
- Efficacy data from these trials showed that as compared with alfa-containing regimens, Lambda regimens were associated with a more rapid early viral decline and comparable SVR response rates in HCV (EMERGE)
- Safety data from these trials showed that
  - Lambda 180µg/RBV was associated with fewer hematologic abnormalities, musculoskeletal and flu-like symptoms, and dose reductions than alfa/RBV; grade 3-4 increases in total and direct bilirubin were more frequent with Lambda/RBV than alfa/RBV[1]
  - Lambda 180µg/RBV/DCV was well tolerated, with no serious adverse events (SAEs) related to study medication or discontinuations due to adverse events (AEs) among patients achieving a protocol-defined response[2]
  - Lambda 180µg monotherapy was associated with fewer adverse events of fever, myalgia, arthralgia, headache, dizziness, alopecia, pruritus, and rash, and with fewer hematologic abnormalities and higher rates of hepatic transaminase increases than alfa monotherapy[3]
- We present an integrated analysis of safety data for non-cirrhotic patients who received Lambda 180 µg weekly for 24-48 weeks from these 3 Lambda phase 2 studies

2. METHODS

- Available on-treatment safety data from non-cirrhotic patients were collected and grouped by regimen:
  - Lambda 180 µg/week plus RBV in chronic HCV GT1–4-infected patients (EMERGE)
  - Lambda, RBV, and DCV in chronic HCV GT1-infected patients (D-LITE)
  - Lambda, RBV, and asunaprevir (ASV) in chronic HCV GT1-infected patients (D-LITE)
  - Alfa 180 µg/week plus RBV in chronic HCV GT1–4 infected patients (EMERGE and D-LITE)
  - Lambda 180 µg/week in chronic CHB infection and HBeAg+ disease (LIRA-B)
- Frequencies of adverse events (AE)s, serious AEs (SAEs), discontinuations due to AEs, emergent grade 3–4 laboratory abnormalities (defined by DAIDS 2009), and AEs in special categories (defined by system organ class)—hematologic, hepatic, neuropsychiatric, autoimmune, and autoimmune-thyroid—were evaluated
- Differences > 2-fold between groups were identified and considered potentially clinically significant
- Data represent different durations of exposure (**Figure 1**)

Figure 1. Study Designs



GT, genotype; RBV, ribavirin; DCV, daclatasvir; ASV, asunaprevir

3. RESULTS

Table 1. Baseline Demographic and Disease Characteristics

Parameter	HBV-Lambda: Lambda 180 µg/week (N = 75)	HCV-Lambda: Lambda 180 µg/week + RBV (N = 131)	HCV-Lambda: Lambda 180 µg/week + RBV + ASV (N = 38)	HCV-Lambda: Lambda 180 µg/week + RBV + DCV (N = 45)	HCV-Alfa: Alfa 180 µg/week + RBV (N = 174)
Mean age, years	35.9	46.1	47.8	47.7	47.5
Male gender, n (%)	54 (72.0)	73 (55.7)	22 (57.9)	19 (42.2)	106 (60.9)
Race, n (%)					
White	3 (4.0)	110 (84.0)	31 (81.6)	34 (75.6)	146 (83.9)
Black/African American	4 (5.3)	12 (9.2)	0	3 (6.7)	10 (5.7)
Chinese	52 (69.3)	0	0	0	0
Japanese	0	0	6 (15.8)	8 (17.8)	7 (4.0)
Other	16 (21.3)	9 (6.9)	1 (2.6)	0	11 (6.3)
Viral load: HBV DNA *or* HCV RNA, mean $\log_{10}$ IU/mL (SD)	7.7 (1.1)	6.5 (0.6)	6.4 (0.6)	6.3 (0.7)	6.4 (0.6)
ALT, mean IU/mL (SD)	153.7 (152.5)	63.6 (37.7)	90.4 (81.7)	75.8 (69.3)	76.6 (54.7)

ALT, alanine aminotransferase

- HBV-infected patients were predominantly Asian; HCV-infected patients were predominantly white
- Mean baseline ALT was higher among HBV-infected patients than HCV-infected patients

3. RESULTS (cont)

Table 2. AEs, SAEs, Discontinuations due to AEs, and Deaths

Patients with event, n (%)	HBV-Lambda: Lambda 180 µg/week (N = 75)	HCV-Lambda: Lambda 180 µg/week + RBV (N = 131)	HCV-Lambda: Lambda 180 µg/week + RBV + ASV (N = 38)	HCV-Lambda: Lambda 180 µg/week + RBV + DCV (N = 45)	HCV-Alfa: Alfa 180 µg/week + RBV (N = 174)
AEs	71 (94.7)	118 (90.1)	38 (100.0)	43 (95.6)	170 (97.7)
SAEs	6 (8.0)	4 (3.1)	4 (10.5)	1 (2.2)	8 (4.6)
Discontinuations due to AEs	5 (6.7)	8 (6.1)	7 (18.4)	1 (2.2)	16 (9.2)
Grade 3 or 4 AEs	21 (28.0)	17 (13.0)	13 (34.2)	6 (13.3)	31 (17.8)
Deaths	0	0	0	0	1 (0.6)*

*The death occurred during follow-up and was due to cardiac arrest

- The highest incidence of grade 3–4 adverse events was noted when Lambda was studied as monotherapy for HBV and when Lambda/RBV was combined with ASV. These were events of increases in serum transaminases that necessitated discontinuation per protocol

Table 3. AEs Occurring in > 20% Patients in Any Group

Patients with event, n (%)	HBV-Lambda: Lambda 180 µg/week (N = 75)	HCV-Lambda: Lambda 180 µg/week + RBV (N = 131)	HCV-Lambda: Lambda 180 µg/week + RBV + ASV (N = 38)	HCV-Lambda: Lambda 180 µg/week + RBV + DCV (N = 45)	HCV-Alfa: Alfa 180 µg/week + RBV (N = 174)
AEs > 20% incidence	47 (62.7)	99 (75.6)	29 (76.3)	33 (73.3)	156 (89.7)
Fatigue	24 (32.0)	55 (42.0)	9 (23.7)	13 (28.9)	77 (44.3)
Headache	11 (14.7)	34 (26.0)	6 (15.8)	15 (33.3)	75 (43.1)
Pruritus	7 (9.3)	24 (18.3)	8 (21.1)	17 (37.8)	49 (28.2)
Myalgia	3 (4.0)	9 (6.9)	4 (10.5)	9 (20.0)	56 (32.2)
Nausea	12 (16.0)	30 (22.9)	10 (26.3)	13 (28.9)	50 (28.7)
Pyrexia	7 (9.3)	13 (9.9)	2 (5.3)	3 (6.7)	50 (28.7)
Arthralgia	0	10 (7.6)	5 (13.2)	5 (11.1)	45 (25.9)
Insomnia	7 (9.3)	26 (19.8)	6 (15.8)	11 (24.4)	44 (25.3)
ALT increased	14 (18.7)	0	8 (21.1)	1 (2.2)	0
AST increased	7 (9.3)	1 (0.8)	8 (21.1)	1 (2.2)	0
Rash	3 (4.0)	17 (13.0)	4 (10.5)	8 (17.8)	35 (20.1)

- Headache, myalgia, pyrexia, and arthralgia were more frequent with alfa- than with Lambda-containing regimens
- In addition, Lambda monotherapy in HBV was associated with fewer events of pruritus, insomnia and rash compared to alfa/RBV and Lambda/RBV for HCV
- Pruritus is a known adverse event of RBV[4]

Table 4. Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities

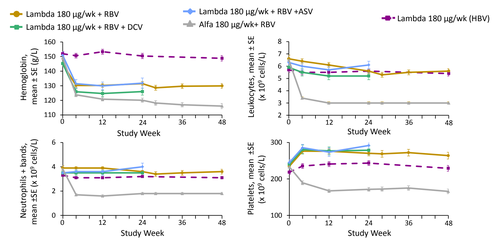
Patients with event, n (%)	HBV-Lambda: Lambda 180 µg/week (N = 75)	HCV-Lambda: Lambda 180 µg/week + RBV (N = 131)	HCV-Lambda: Lambda 180 µg/week + RBV + ASV (N = 38)	HCV-Lambda: Lambda 180 µg/week + RBV + DCV (N = 45)	HCV-Alfa: Alfa 180 µg/week + RBV (N = 174)
Hematologic					
Hgb	0	6 (4.6)	1 (2.6)	0	41 (23.7)
Leukocytes	0	1 (0.8)	0	1 (2.2)	13 (7.5)
Lymphocytes (absolute)	1 (1.3)	1 (0.8)	0	3 (6.7)	25 (14.5)
Neutrophils + bands (absolute)	1 (1.3)	1 (0.8)	0	0	38 (22.0)
Platelets	0	0	0	0	3 (1.7)
Hepatic					
ALT (ULN, 30–47 U/L)	32 (42.7)	3 (2.3)	6 (15.8)	1 (2.2)	9 (5.2)
AST (ULN, 30–45 U/L)	26 (34.7)	3 (2.3)	10 (26.3)	3 (6.7)	10 (5.8)
Total bilirubin (ULN, 19–21 µmol/L)	2 (2.7)	7 (5.4)	4 (10.5)	2 (4.4)	5 (2.9)

AST, aspartate aminotransferase

Criteria for grade 3–4 abnormalities per DAIDS 2009: Hgb: ≤ 7.4 g/dL; Leukocytes, ≤ 1499/mm³; Lymphocytes: ≤ 499/mm³; Neutrophils: grade ≤ 749/mm³; Platelets: ≤ 49,999/mm³; ALT and AST: ≥ 5.1 xULN; Tbili, ≥ 2.6 xULN.

- Grade 3–4 laboratory abnormalities in hematologic parameters were more frequent with alfa than with Lambda
- In Lambda-containing regimens, grade 3–4 ALT or AST elevations were more frequent in HBV than HCV
- Increases in total bilirubin were more common with Lambda/RBV regimens compared to alfa/RBV or Lambda alone

Figure 2. Hematologic Parameters Over Time

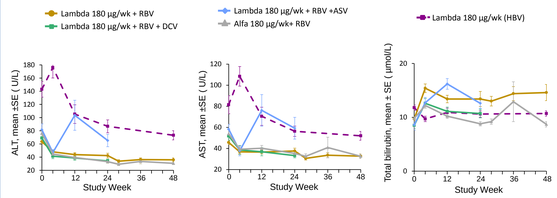


Most patients in the Lambda/RBV/DCV and Lambda/RBV/ASV groups were treated for 24 weeks; data for those groups is not available after week 24

- Reductions in mean hemoglobin, total leukocytes, neutrophils, and platelets were minimal to none for all Lambda-containing regimens, compared with reductions noted/identified in these parameters for alfa/RBV

3. RESULTS (cont)

Figure 3. Hepatic Parameters Over Time



ULN for these parameters varied by study: ALT, 30–47 U/L; AST, 30–45 U/L; Tbili, 19–21 µmol/L.
Most patients in the Lambda/RBV/DCV and Lambda/RBV/ASV groups were treated for 24 weeks, so data for those groups are not available after Week 24.

- In HBV infection, where baseline levels of transaminases are higher than in HCV infection, both the frequency and magnitude of transaminase elevations were higher than in HCV

Table 5. Neuropsychiatric AEs Occurring in > 5% Patients in Any Group

Patients with event, n (%)	HBV-Lambda: Lambda 180 µg/week (N = 75)	HCV-Lambda: Lambda 180 µg/week + RBV (N = 131)	HCV-Lambda: Lambda 180 µg/week + RBV + ASV (N = 38)	HCV-Lambda: Lambda 180 µg/week + RBV + DCV (N = 45)	HCV-Alfa: Alfa 180 µg/week + RBV (N = 174)
Headache	11 (14.7)	34 (26.0)	6 (15.8)	15 (33.3)	75 (43.1)
Insomnia	7 (9.3)	26 (19.8)	6 (15.8)	11 (24.4)	44 (25.3)
Irritability	0	24 (18.3)	6 (15.8)	9 (20.0)	26 (14.9)
Dizziness	4 (5.3)	11 (8.4)	6 (15.8)	1 (2.2)	19 (10.9)
Depression	3 (4.0)	13 (9.9)	1 (2.6)	4 (8.9)	18 (10.3)
Dysgeusia	0	1 (0.8)	2 (5.3)	4 (8.9)	17 (9.8)
Depressed mood	1 (1.3)	0	1 (2.6)	3 (6.7)	6 (3.4)
Sleep disorder	2 (2.7)	3 (2.3)	0	3 (6.7)	8 (4.6)
Anxiety	2 (2.7)	7 (5.3)	2 (5.3)	2 (4.4)	11 (6.3)
Disturbance in attention	0	2 (1.5)	1 (2.6)	1 (2.2)	10 (5.7)
Affect lability	0	1 (0.8)	2 (5.3)	2 (4.4)	8 (4.6)
Libido decreased	0	0	2 (5.3)	0	2 (1.1)

AEs from nervous system disorder and psychiatric disorder SOCs occurring in > 5% of patients are presented

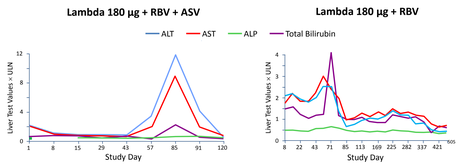
Table 6. Autoimmune- and Autoimmune Thyroid-Related Adverse Events

Patients with event, n (%)	HBV-Lambda: Lambda 180 µg/week (N = 75)	HCV-Lambda: Lambda 180 µg/week + RBV (N = 131)	HCV-Lambda: Lambda 180 µg/week + RBV + ASV (N = 38)	HCV-Lambda: Lambda 180 µg/week + RBV + DCV (N = 45)	HCV-Alfa: Alfa 180 µg/week + RBV (N = 174)
Dry eye	2 (2.7)	3 (2.3)	4 (10.5)	2 (4.4)	7 (4.0)
Psoriasis	0	0	0	1 (2.2)	1 (0.6)
Sarcoidosis	0	0	0	0	2 (1.1)
Crohn's disease	0	0	0	0	1 (0.6)
Erythema nodosum	0	0	0	0	1 (0.6)
Any thyroid abnormality	0	4 (3.1)	0	1 (2.2)	17 (9.8)
Hyperthyroidism	0	1 (0.8)	0	0	7 (4.0)
Hypothyroidism	0	1 (0.8)	0	0	8 (4.6)
Thyroiditis	0	0	0	0	4 (2.3)
Blood TSH decreased	0	0	0	1 (2.2)	1 (0.6)
Blood TSH increased	0	1 (0.8)	0	0	0
Goiter	0	1 (0.8)	0	0	0

Analysis based on standard MedDRA queries for hyperthyroidism, hypothyroidism and autoimmune

- Autoimmune thyroid events were less frequent with Lambda-containing regimens than with alfa/RBV

Figure 4. Sample Patients With Abnormalities in Hepatic Parameters

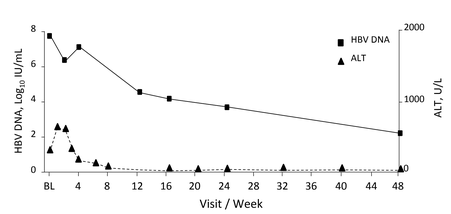


- 38 year-old white male, chronic HCV GT 1
- No concurrent medications
- Other AE reported: fatigue
- Associated lab abnormalities: increased GGT
- INR 1.1 (normal range, 0.8–1.4)
- Achieved SVR with Lambda 180 µg/RBV/ASV

- 50 year-old male, chronic HCV GT 1
- No concurrent medications
- Symptoms reported: fatigue
- Associated lab abnormalities: increased GGT
- INR 1.0
- Achieved SVR after 48 weeks of treatment

3. RESULTS (cont)

Figure 5. Sample HBV-Infected Patient With On-Treatment ALT Flares: Kinetics of ALT, HBV DNA, HBeAg, and HBsAg in a Lambda-Treated Patient



HBeAg	+	+	+	+
HBeAb	-	-	-	-
HBsAg	+		+	+
HBsAb	-		-	-

- This patient's flare was managed with dose interruption followed by dose reduction of Lambda

4. CONCLUSIONS

- Phase 2 data for Lambda 180 µg/week + RBV ± direct-acting antiviral (DAA) in patients with chronic HCV demonstrate:
  - Markedly fewer hematologic abnormalities observed with Lambda/RBV regimens than with alfa/RBV
  - Grade 3–4 hyperbilirubinemia occurs more commonly with Lambda/RBV regimens than with alfa/RBV
  - Grade 3–4 ALT or AST elevations occurred more frequently in patients receiving Lambda/RBV/ASV; this combination regimen is no longer in development
- Phase 2 data for Lambda 180 µg/week in patients with chronic HBV demonstrate:
  - Use of Lambda in HBV was associated with more frequent Grade 3–4 ALT or AST elevations than use in HCV
- In these phase 2 studies, hepatic abnormalities were reversible and manageable with dose withholding and dose adjustment of Lambda
- Clinical adverse events:
  - Rates of myalgia, pyrexia, and arthralgia with Lambda monotherapy (for HBV) or with RBV ± DAA (for HCV) appear to be lower than for alfa/RBV
  - Autoimmune thyroid events were observed less frequently with Lambda-containing regimens than with alfa/RBV
- In phase 2 studies, Lambda demonstrates improved tolerability and a differentiated safety profile relative to alfa. These observations should be confirmed in larger phase 3 studies, which are on-going

5. REFERENCES

1. Muir AJ, et al. *63rd AASLD*; November 9-13, 2012; Boston, MA. Abstract 214.
2. Vierling JM, *et al.* 63rd AASLD; November 9-13, 2012; Boston, MA. Abstract LB-9.
3. Chan HL, *et al. 63rd AASLD*; November 9-13, 2012; Boston, MA. Abstract LB-14.
4. COPEGUS prescribing information; accessed at FDA.gov website, 25/10/2013.

6. DISCLOSURES

- Dr. Muir has received grant funding from Abbvie, Achillion, BMS, Gilead, GSK, Merck, Novartis, Roche, and Vertex; and has served as a consultant for Abbvie, Achillion, BMS, Gilead, GSK, Merck, Salix, and Vertex
- Study sponsored by Bristol-Myers Squibb
- Presentation includes discussion of investigational drugs not approved for use in humans
- Editorial assistance was provided by Jennifer Tobin of Articulate Science and funded by Bristol-Myers Squibb
- CJ, EC, JH, ML, VMC, TG, DX, LY, and SS are employees or former employees of Bristol-Myers Squibb and may also be stockholders of Bristol-Myers Squibb