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
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THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:

[redacted]

Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product:		
Name of Active Ingredient: peginterferon lambda-1a		

SYNOPSIS

Final Clinical Study Report for Study AI452005

TITLE OF STUDY: LIRA-B - Dose-ranging study to evaluate the safety, efficacy and pharmacokinetics of pegylated interferon Lambda monotherapy in interferon-naïve patients with chronic hepatitis B virus infection who are HBeAg-positive

INVESTIGATORS/STUDY CENTERS: Subjects were randomized at a total of 41 sites in North America (United States [9 sites], Canada [4 sites]), Europe (France [4 sites], Germany [3 sites], Italy [1 site], Netherlands [1 site]), and Asia-Pacific (Australia [6 sites], Hong Kong [3 sites], Korea [4 sites], Singapore [2 sites], Taiwan [4 sites]).

PUBLICATIONS: None.

STUDY PERIOD: Study Initiation Date: 15-Nov-2010 **CLINICAL PHASE:** 2
Database Lock: 13-Jun-2013

INTRODUCTION: Lambda (pegylated interferon [IFN] λ; BMS-914143) is an investigational product under development for the treatment of chronic hepatitis C virus infection. The present study (AI452005) was the first clinical study of Lambda in chronic hepatitis B virus (CHB) infection. This study (Part A: comparison of Lambda monotherapy to pegylated IFNα-2a [PEGASYS, hereafter referred to as alfa] monotherapy) failed to meet the prespecified non-inferiority criteria for the primary endpoint analysis and demonstrated comparably lower response rates for Lambda versus alfa for several of the key secondary endpoints. Based on these findings, a decision was made by the Sponsor in July 2013 to terminate the ongoing long-term follow-up phase (LTFU) and Part B substudy (Lambda + entecavir). Details concerning the design, analysis, and results for all efficacy, safety, pharmacokinetics (PK), and pharmacodynamic endpoints evaluated in Part A of this study through the Week 24 post-dosing timepoint are summarized in this clinical study report.

OBJECTIVES: The primary objectives were:

- To evaluate the safety and tolerability of Lambda as measured by the frequency of serious adverse events (SAEs) and discontinuations due to adverse events (AEs);
- To assess the hepatitis B e antigen (HBeAg) seroconversion rate at 24 weeks (Week 72) off treatment.

Secondary study objectives were:

- To evaluate antiviral activity, as determined by the proportion of subjects who achieve an hepatitis B virus (HBV) DNA < 50 IU/mL (approximately 300 copies/mL) using the Roche COBAS® TaqMan HBV Test for use with the High Pure System assay;
- To evaluate mean change from baseline in HBV DNA over time;
- To assess biochemical response rates;
- To evaluate the relationship between changes in serum HBV DNA and Lambda PK parameters;
- To evaluate HBeAg loss and seroconversion;
- To evaluate quantitative HBeAg (qHBeAg) levels over time;

- To characterize the PK of Lambda administered as a fixed dose;
- To evaluate for the presence of or change in titer of anti-drug antibodies (ADA) in treated subjects over time.

A list of the exploratory study objectives for this study is provided in the report body. Immunogenicity data for this study will be reported in an addendum to this report.

METHODOLOGY: Part A of Study AI452005 was a randomized, site- and subject-blinded, parallel, initially 3-arm, multicenter, Phase 2b study in IFN-naive subjects with CHB who had HBeAg-positive and compensated liver disease. Eligible subjects were initially randomized 1:1:1 to 1 of 3 treatment groups: Lambda 240 µg, Lambda 180 µg or conventional therapy with alfa at a standard dose of 180 µg. The Sponsor elected to discontinue further development of the Lambda 240 µg dose, and the protocol was amended to remove this dose. At this time, all subjects who had been initially randomized to the Lambda 240 µg dose were switched to the Lambda 180 µg dose, and all newly enrolled subjects were thereafter randomized 1:1 to either Lambda 180 µg or alfa. At the time of the dose adjustment, treatment assignments for subjects who were switched from the Lambda 240 µg to the Lambda 180 µg dose was no longer blinded at the site and subject level (median time on 240 ug dose was 4.0 weeks [range: 1.0 - 17.0]).

Subjects randomized to treatment received weekly subcutaneous (SC) injections of blinded therapy with their assigned drug for 48 weeks (on treatment period). All subjects who completed the treatment period, as well as subjects who discontinued study treatment prematurely (unless alternative HBV therapy was initiated), were followed for an initial 24 weeks off-treatment to assess for durability of response (24-week post-dosing period). All subjects who completed both 48 weeks of treatment and the initial 24-week post-dosing period, and for whom alternate HBV therapy had not been initiated, were to be followed for up to an additional 2.5 years (LTFU).

To characterize the PK profile of Lambda, intensive PK sampling was conducted on a subset of subjects (PK substudy) during the first week of dosing (Day 1 through 7) and at Week 12 (Days 85 through 91).

Available results from the LTFU, as well as from the Part B substudy aimed at providing preliminary data on the combination of Lambda plus entecavir (added in Protocol Amendment 7, April 2012); up through the time of study termination will be reported separately in an addendum to this report.

NUMBER OF SUBJECTS (Planned and Analyzed): Planned: 170 subjects randomized (85 to Lambda 180 µg and alfa groups). Enrolled (signed study-specific informed consent): 298; Randomized: 177 (81 Lambda 180 µg; 83 alfa; 13 Lambda 240 µg); Randomized and treated: 176 (80 Lambda 180 µg; 83 alfa; 13 Lambda 240 µg).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Men or women at least 18 years of age who had a history of CHB infection, defined as hepatitis B surface antigen (HBsAg)-positive serostatus at screening together with the presence of at least 1 other marker of HBV infection (e.g., detectable HBV DNA, HBeAg, and/or HBV genotype) on at least 1 other occasion ≥ 24 weeks prior to screening. The study targeted subjects with active viremia (HBV DNA > 10^5 copies/mL [(17,200 IU/mL]) and an elevated serum alanine aminotransferase (ALT) (> 47 U/L to < 10X upper limit of normal [ULN]). Subjects with compensated cirrhosis were allowed to participate, but enrollment was limited to 10% of the total study population. Subjects were IFN-naïve, and had not received prior HBV nucleos(t)ide therapy within 30 days prior to screening.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT: Lambda was supplied as 1-mL vials at a concentration of 0.2 mg/mL for administration by SC injection once weekly at a dose of 180 µg or 240 µg for 48 weeks. With implementation of Protocol Amendment 3 (19-Apr-2011), further treatment with the 240 µg dose was stopped, and all subjects assigned to this treatment dose were switched to treatment with Lambda 180 µg for the remainder of the treatment period. Container numbers for Lambda vials are listed by subject in an appendix.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Alfa was supplied as 1-mL vials at a concentration of 180 µg/mL for administration by SC injection once weekly at a dose of 180 µg for 48 weeks. Container numbers for alfa vials are listed by subject in an appendix.

CRITERIA FOR EVALUATION:

Efficacy: Serum samples were collected at baseline, and at scheduled timepoints during the 48-week treatment period and 24-week post-dosing follow-up, and tested for commonly used measures of the presence and intensity of HBV circulating in the blood: HBeAg, HBeAb, HBV DNA, HBsAg, and hepatitis B surface antibody (HBsAb), and qHBeAg and qHBsAg. ALT levels were also measured at baseline, on treatment, and during the post-dosing follow-up to assess the biochemical response.

Safety: Safety was evaluated by monitoring deaths, AEs, SAEs, AEs leading to discontinuation or dose modification (dose interruption or reduction), and by evaluating clinical laboratory abnormalities, and changes in clinical laboratory assessment, vital sign measurements, and 12-lead electrocardiogram (ECG) intervals. Investigators' terms for AEs were coded and grouped by system organ class using the Medical Dictionary for Regulatory Activities (MedDRA, version 16.0). AEs, SAEs, and clinical laboratory abnormalities occurring on treatment and during the follow-up period (for subjects who participated in follow-up period) were summarized separately.

Pharmacokinetics: Blood samples were collected prior to dosing from all subjects at Day 1 and at Weeks 2, 4, 12, 16, 24, 40, and 48 for determination of trough Lambda and alfa serum concentrations. In the subset of subjects who participated in the intensive PK substudy, sampling for Lambda serum concentrations was conducted during the first week of dosing and again at Week 12 to characterize the PK profile for Lambda and alfa. Lambda and alfa concentrations were measured using separate, validated electrochemiluminescent (ECL) immunoassays.

Pharmacodynamics: Blood samples were obtained at specified timepoints on treatment and at Week 24 post-dosing for determination of levels of host immune response markers (cytokines/chemokines, host gene expression markers [messenger RNA, mRNA], and cell surface markers from flow cytometry). Results for these exploratory endpoints are described in the report body.

Other: Blood samples for genetic analysis, collected on Day 1, were analyzed for single nucleotide polymorphisms (SNPs) in genes encoding proteins of the IFN-λ family (IL-28A, IL-28B, and IL-29) and 2 genes encoding subunits of IFN-λ and IFN-α receptors (IFN-AR2 and IL-10RB). Results of the exploratory pharmacogenetic analysis are provided in the report body.

STATISTICAL CONSIDERATIONS: Statistical analysis of efficacy endpoints was limited to the Lambda 180 µg and alfa groups. Safety data are analyzed for all 3 treatment groups separately (Lambda 240 µg, Lambda 180 µg, alfa). Efficacy and safety analyses were based on all treated subjects. For all analyses, on treatment was defined as the period from the first day of study treatment through 10 days after the last dose of study treatment; follow-up was defined as the period from the last dose of study therapy plus 11 days through the end of the follow-up period (i.e., through Week 72 for this report).

Response rates for all binary efficacy endpoints were assessed with using 2 different algorithms for treated subjects: (1) modified intent-to-treat (ITT) where subjects with missing data at the visit were counted as a failure and (2) observed values where subjects with missing data at the visit were excluded from the analysis at that visit.

The proportion of subjects meeting the primary endpoint of HBeAg seroconversion at Week 24 post-dosing in the Lambda 180 µg group versus the alfa group was analyzed using a 2-stage process, with the non-inferiority of Lambda to alfa tested initially. Non-inferiority of Lambda 180 µg to alfa was tested using the 80% confidence interval (CI) (based upon the normal approximation of the binomial distribution), for the difference in response rate between Lambda 180 µg and alfa. Non-inferiority was demonstrated if the lower limit of the 80% CI was greater than -15%. Treatment comparisons for the primary endpoint were stratified by region using Cochran Mantel Haenszel (CMH) weights.

With 85 subjects per group, there was approximately 80% power to demonstrate non-inferiority of Lambda 180 µg to alfa for the proportion of subjects with HBeAg seroconversion at Week 24 post-dosing assuming: (1) a response rate of 32% for Lambda 180 µg and alfa (Non-Completers = Failure), and (2) a -15% margin for comparison with the lower limit of the 80% 2-sided CI for the difference in response rates (Lambda minus alfa).

All binary efficacy response rates, including the proportion of subjects with HBV DNA < 50 IU/mL, HBeAg loss and seroconversion, HBsAg loss and seroconversion, and ALT normalization, were assessed by treatment using both the modified ITT and the observed values algorithms. In addition, continuous endpoints HBV DNA, qHBsAg and qHBeAg in $\log_{10}$ scale, and changes from baseline were summarized by treatment based on observed values.

Differences between Lambda 180 µg and alfa in the change from baseline log_{10} values for virologic and quantitative serologic measures were assessed at select timepoints using a linear regression model that included covariates of treatment regimen and baseline value. HBeAg seroconversion at Week 24 post-dosing was summarized by subgroups defined by baseline and on-treatment prognostic factors to examine the consistency of the treatment effect. In addition, logistic regression models were performed to identify baseline prognostic factors, early on-treatment responses, and end of treatment responses for predicting HBeAg seroconversion at Week 24 post-dosing. Odds ratios and associated p-values for the covariates were reported for both univariate and multivariate analyses.

Safety, serum Lambda and alfa concentrations, pharmacodynamic, immunogenicity, and pharmacogenomic data were descriptively summarized for each treatment group.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: A total of 177 subjects were randomized and 176 received at least 1 dose of study drug (Lambda 180 µg, 80; alfa, 83; Lambda 240 µg, 13). The majority (85.8%) of treated subjects completed the 48-week treatment period, and over 90% of subjects in the Lambda 180 µg and alfa groups entered the post-dosing follow-up period (Table 1). Baseline demographics and HBV disease characteristics were well balanced across the groups (Table 2). At baseline, few treated subjects were HBeAb positive (5 of 176) or had cirrhosis (8 of 176).

Table 1: Subject Disposition - Treated Subjects

	Lambda 240 µg N = 13	Lambda 180 µg N = 80	Alfa N = 83
Completing treatment period, n (%)	9 (69.2)	74 (92.5)	68 (81.9)
Reasons for not completing treatment, n (%)			
Adverse event	3 (23.1)	6 (7.5)	8 (9.6)
Withdrew consent	0	0	3 (3.6)
Lack of efficacy	0	0	2 (2.4)
Other	1 (7.7)	0	1 (1.2)
Continuing in follow-up period, n (%)	12 (92.3)	78 (97.5)	78 (94.0)
Completing 24-week follow-up, n (%)[a]	11 (91.7%)	70 (89.7%)	72 (92.3)

[a] Percentage based on number continuing in follow-up period.

Table 2: Baseline and Demographic Characteristics - Treated Subjects

	Lambda 240 µg N = 13	Lambda 180 µg N = 80	Alfa N = 83
Age years, mean (SD)	33.1 (7.17)	36.5 (10.19)	35.5 (9.42)
Male, n (%)	12 (92.3)	59 (73.8)	63 (75.9)
Race, n (%)			
Asian	9 (69.2)	72 (90.0)	75 (90.4)
White	4 (30.8)	3 (3.5)	4 (4.8)
Black-African American	0	4 (5.0)	2 (2.4)
Other	0	1 (1.3)	2 (2.4)
HBV DNA log_{10} IU/mL, mean (SD)	7.836 (1.2758)	7.625 (1.1677)	7.876 (0.9727)
qHBsAg log_{10} IU/mL,[a] mean (SD)	4.032 (1.0155)	3.968 (0.6855)	4.078 (0.7501)
qHBeAg log_{10} PEIU/mL,[a] mean (SD)	2.213 (0.8641)	2.208 (0.8493)	2.331 (0.6904)
ALT U/L, mean (SD)	126.2 (103.36)	149.6 (148.72)	131.1 (82.11)
HBV DNA Genotype, n (%)			
B	3 (23.1)	21 (26.3)	30 (36.1)
C	6 (46.2)	49 (61.3)	42 (50.6)
A or D or E	4 (30.8)	8 (10.0)	9 (10.8)
Missing/indeterminate	0	2 (2.6)	2 (2.4)

[a] Number with baseline values was 10, 75, and 81 for Lambda 240 µg, Lambda 180 µg, and alfa groups, respectively.
SD = standard deviation.

Efficacy Results:

While on-treatment results for HBeAg seroconversion were comparable across the 2 treatment groups through Week 48, the HBeAg seroconversion rate was lower in the Lambda 180 µg group compared with the alfa group during the post-dosing follow-up period. The results of the primary efficacy analysis were:

- At Week 24 post-dosing, rates of HBeAg seroconversion using the modified ITT algorithm were lower for Lambda 180 µg compared with alfa (11/80 [13.8%] vs. 25/83 [30.1%], respectively). The lower bound of the 80% CI between for Lambda 180 µg and alfa was -24%, and was less than the prespecified non-inferiority margin of -15%. Hence, non-inferiority for Lambda 180 µg compared to alfa was not demonstrated.
- Results of the primary analysis based on observed case data showed similar findings (Lambda 180 µg 11/55 [20.0%] vs alfa 25/61 [41.0%], respectively).
- The difference in treatment results for HBeAg seroconversion on treatment and during the post-dosing follow-up is primarily related to: (1) the greater loss of subjects who had been prior responders at Week 48 in the Lambda versus the alfa group (7 vs. 4 subjects, respectively) and (2) the smaller number of new events of HBeAg seroconversion during the post-dosing period in the Lambda versus the alfa group (4 vs. 15 subjects, respectively).
- For the majority of subgroup analyses related to baseline and on-treatment factors, the treatment difference in the HBeAg seroconversion rate at Week 24 post-dosing was consistent with the results of the primary efficacy analysis and favored the alfa group over the Lambda 180 µg group.

Results of end-of-treatment and Week 24 post-dosing timepoints of analyses for the primary and select key secondary and other serologic, virologic, and biochemical efficacy endpoints are summarized in Table 3.

Table 3: Summary of Results for Key Serologic, Virologic, and Biochemical Outcomes at Week 48 On Treatment and Week 24 Post-dosing - Treated Subjects in the Lambda 180 µg and Alfa Groups

Efficacy Endpoint	Week 48 On Treatment		Week 24 Post-dosing	
	Lambda 180 µg (N=80)	Alfa (N=83)	Lambda 180 µg (N=80)	Alfa (N=83)
Serologic				
HBeAg Seroconversion, n (%)[a]	14/80 (17.5)	15/83 (16.9)	11/80 (13.8)	25/83 (30.1)
HBeAg Loss, n (%)[a]	15/80 (18.8)	15/83 (18.1)	12/80 (15.0)	27/83 (32.5)
qHBeAg, change from baseline (log_{10} PEIU/mL), mean (SE) [n]	-1.191 (2.239) [68]	-1.347 (1.974) [62]	-0.869 (2.133) [51]	-1.496 (3.021) [58]
HBsAg Loss, n (%)[a]	2/80 (2.5)	0/83 (0.0)	2/80 (2.5)	0/83 (0.0)[b]
HBsAg Seroconversion, n (%)[a]	0/80 (0.0)	0/83 (0.0)	0/80 (0.0)	0/83 (0.0)[b]
qHBsAg, change from baseline (log_{10} IU/mL), mean (SE) [n]	-0.575 (0.954) [69]	-0.342 (0.945) [62]	-0.260 (0.804) [51]	-0.254 (0.665) [58]
Virologic				
HBV DNA, change from baseline (log_{10} IU/mL), mean (SE) [n]	-2.667 (3.402) [69]	-2.867 (3.469) [65]	-1.295 (3.856) [55]	-2.093 (4.173) [61]
HBV DNA < 50 IU/mL[a]	11/80 (13.8)	9/83 (10.8)	5/80 (6.3)	1/83 (1.2)
Biochemical				
ALT Normalization, n (%)	26/80 (32.5)	27/83 (32.5)	35/80 (43.8)	43/83 (51.8)

[a] Results shown for modified ITT algorithm.

[b] One subject had a response at Week 12 post-dosing but had missing data at Week 24 post-dosing.

Safety Results: Table 4 presents a summary of key safety findings for the on-treatment and follow-up (through Week 24 post-dosing) periods. Key safety findings were:

- Lambda was generally well tolerated. There were no deaths through Week 24 post-dosing.
- The primary safety endpoints of SAEs and discontinuations due to AEs were each balanced across the Lambda 180 µg and alfa groups, with frequencies in these 2 treatment groups for SAEs of 8.8% and 6.0%, respectively, and AEs leading to discontinuation of 7.5% and 9.6%, respectively.
- The spectrum of AEs with Lambda observed in this study was as expected, based on the underlying CHB disease and the cumulative safety data from the Lambda HCV development program.
- As expected, higher rates of flu-like symptoms and musculoskeletal symptoms were observed in the alfa group compared to the Lambda 180 µg group. Rates for other predetermined events of clinical interest (constitutional symptoms, neurologic events, and psychiatric events) were generally comparable in the 2 treatment groups.
- Treatment with alfa was associated with increased frequencies of cytopenias, in particular leukopenia, neutropenia, and thrombocytopenia (Grade 1 to 4), compared with the Lambda 180 µg group.
- The frequency of ALT flares during treatment was higher in the Lambda 180 µg group compared to the alfa group. The majority of events occurred early (within first 12 weeks of treatment) and correlated with a decline from baseline in HBV DNA. The frequency of post dosing flares was also higher in the Lambda 180 µg group; in this setting, all ALT flares were preceded by rebound viremia, similar to the pattern observed in the alfa group.
- There were no clinically meaningful changes in vital signs or ECG interval values on treatment in any treatment group.

Table 4: Summary of Safety On Treatment - Treated Subjects

	Number (%) Subjects		
	Lambda 240 µg (n=13)	**Lambda 180 µg (n=80)**	**Alfa (N=83)**
Deaths	0	0	0
SAEs	3 (23.1)	7 (8.8)	5 (6.0)
Discontinuation due to AEs	3 (23.1)	6 (7.5)	8 (9.6)
AE leading to dose reduction	3 (23.1)	10 (12.5)	23 (27.7)
AEs leading to dose interruption	5 (38.5)	12 (15.0)	6 (7.2)
AEs, Grade 1 to 4	13 (100.0)	76 (92.5)	77 (92.8)
AEs, Grade 3 or 4	7 (53.8)	22 (27.5)	23 (27.7)
Predetermined AEs, Grade 1 to 4[a]	12 (92.3)	40 (50.0)	60 (72.3)
Constitutional symptoms	5 (38.5)	28 (35.0)	26 (31.3)
Neurologic	4 (30.8)	18 (22.5)	30 (36.1)
Flu-like symptoms	3 (23.1)	13 (16.3)	45 (54.2)
Musculoskeletal symptoms	3 (23.1)	5 (6.3)	23 (27.7)
Psychiatric	3 (23.1)	11 (13.8)	15 (18.1)
Discontinuation due to TLT	2 (15.4)	5 (6.3)	1 (1.2)
Treatment-emergent lab abnormalities (Grade 3 or 4)[b]			
Leukocytes	0/13 (0)	0/80 (0)	1/82 (1.2)
Neutrophils + Bands (absolute)	0/13 (0)	2/80 (2.5)	17/82 (20.7)
Platelet count	0/13 (0)	0/80 (0)	1/82 (1.2)
ALT	7/13 (53.8)	33/80 (41.3)	19/82 (23.2)
AST	7/13 (53.8)	27/80 (33.8)	15/82 (18.3)
Total bilirubin	3/13 (23.1)	3/80 (3.8)	0/82 (0)

[a] Based on modified list. None of these events were Grade 3 or 4 in severity

[b] Number with abnormality/number evaluable (%). Data reflect worst toxicity grade (based on SI units).

Pharmacokinetic Results: Data from the intensive PK substudy were available for only 4 subjects in the Lambda 180 μg group and 4 in the alfa group. Comparison of PK parameters following administration of Lambda 180 μg at Days 1 and 85 showed modest drug accumulation, as demonstrated by the increase in Cmax and AUC(TAU) and the 1.52-fold increase in accumulation index. Geometric mean trough concentrations following administration of Lambda 180 μg (n =71) peaked at Week 4, and declined thereafter through Week 24, at which time they remained relatively consistent through Week 48 with little accumulation. From Week 24 to 48, geometric mean (SD) trough concentrations of Lambda in the 180 μg group ranged from 0.243 (86.5) ng/mL to 0.247 (82.7) ng/mL. Lambda serum composite trough concentrations were not correlated with HBeAg seroconversion in a logistic regression model, and correlation and regression analyses did not support a linear relationship between Lambda trough concentration and the change from baseline in HBV DNA and HBsAg at Weeks 12 or 24.

CONCLUSIONS:

Efficacy

Efficacy results varied by the study period, with key observations as follow:

- ***Post-Dosing***
  - The Lambda 180 μg group did not meet the criteria for non-inferiority to alfa for the primary endpoint of HBeAg seroconversion, based on the prespecified criteria for this analysis. At Week 24 post-dosing, the rates of HBeAg seroconversion were lower for Lambda compared with alfa.
  - This observation was primarily related to the comparatively greater number of new seroconversion events which occurred in the alfa as compared to Lambda group following discontinuation of study therapy
  - Secondary endpoint results at Week 24 post-dosing (qHBeAg, HBV DNA change from baseline, and ALT normalization) all numerically favored alfa, consistent with results for the primary endpoint analysis.
- ***On-Treatment***
  - Lambda 180 μg was associated with a more rapid and pronounced decline from baseline in both HBV DNA and qHBsAg through Week 24, as compared with alfa.
  - At Week 48 (EOT), Lambda 180 μg evidenced comparable efficacy to alfa based on serologic, virologic and biochemical response measures.
  - The Week 48 (EOT) rates of HBeAg seroconversion were approximately 17% for the Lambda 180 μg and alfa groups, and were lower than what has been historically observed for alfa in this study population.

Safety

- Rates of SAEs, AEs and discontinuations due to AE were comparable for the 2 treatment groups, with no unexpected safety signals identified.
- ALT Flares
  - On-treatment ALT flares were more frequent with Lambda 180 μg compared with alfa. Most ALT flares occurred within the first 12 weeks of treatment and were associated with an HBV DNA decline from baseline. The majority of events were asymptomatic and none were associated with any clinical or laboratory signs of hepatic decompensation.
  - Off-treatment ALT flares were also more frequent with Lambda 180 μg compared with alfa; in both groups these events were preceded by rebound viremia. Similar to on-treatment ALT flares, these events were well-tolerated, without any clinical or laboratory signs of hepatic compromise.

Pharmacokinetics

- Regression analyses did not support a linear relationship between Lambda Ctrough and change in serum HBV DNA.
- Following weekly SC dosing with Lambda, steady state appeared to be achieved within 4 weeks with modest accumulation.

DATE OF REPORT: 29-Jan-2014