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:		

SYNOPSIS

Clinical Study Report for Study 526H04 (AI452004) - Phase 2a and Phase 2b

TITLE OF STUDY: Randomized, Controlled Phase 2a/b Study of the Efficacy and Safety of PEG-rIL-29 Administered in Combination with Ribavirin to Treatment-Naive Subjects with Chronic Hepatitis C Virus Infection

INVESTIGATORS/STUDY CENTERS:

Phase 2a: Investigators at 8 study sites in the United States, Puerto Rico, and Canada; Phase 2b: Investigators at 78 study sites in 9 countries (United States/Puerto Rico, Canada, Australia, Austria, Germany, Spain, France, Poland, and Romania)

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date:

14 October 2009 (Phase 2a)

17 May 2010 (Phase 2b)

Study Completion Date:

20 July 2011 (Phase 2a)

20 January 2012 (Phase 2b)

CLINICAL PHASE: Phase 2

OBJECTIVES:

Phase 2a

Phase 2a was conducted in 2 parts. The primary objective of Part 1 was to characterize the pharmacokinetics (PK) of a single dose of PEG-rIL-29 (Lambda) administered as a single agent at 4 fixed dose levels (i.e., not weight-based) in treatment-naive subjects with chronic hepatitis C virus (HCV) infection.

The primary objective of Part 2 was to evaluate the safety and tolerability of Lambda (using the same 4 dose levels investigated in Phase 2a Part 1) administered in combination with ribavirin (RBV) for up to 24 weeks (in genotype [GT]-2, -3 subjects) or 48 weeks (in GT-1, -4 subjects). Secondary objectives were to characterize the PK and immunogenicity and evaluate the efficacy of Lambda (based on changes in HCV RNA levels over time) with repeated dosing.

Phase 2b

The primary objective of Phase 2b was to evaluate the efficacy and safety of Lambda through Week 12 of up to 4 dose levels selected from Phase 2a, administered in combination with RBV, compared to pegylated interferon alfa-2a (i.e., alfa-2a) administered in combination with RBV, in treatment-naive subjects with chronic HCV infection.

Secondary objectives of Phase 2b were to evaluate the efficacy and safety of Lambda/RBV vs. alfa-2a/RBV for up to 48 weeks, assess the population PK of Lambda and the relationship between Lambda exposure and antiviral effect, and evaluate the immunogenicity of Lambda.

METHODOLOGY:

This was a Phase 2a/b randomized, controlled, multicenter study of Lambda administered subcutaneously (SC) weekly in combination with daily oral RBV in treatment-naive subjects with chronic GT-1, -2, -3, or -4 HCV infection. This study also included 2 distinct substudies to evaluate shortened treatment durations in patients with potentially more favorable host genotype and HCV genotypes (Substudy C and Substudy D, respectively; reported separately).

Phase 2a

Phase 2a was an open-label study conducted in 2 parts. In Part 1, subjects received a single fixed dose of 80, 120, 180, or 240 µg Lambda or 180 µg alfa-2a administered SC as a single agent. In Part 2, subjects enrolled in Part 1 received repeated weekly dosing with Lambda or alfa-2a, administered SC at the same dose level that they received in Part 1, in combination with daily oral RBV for 24 weeks (for GT-2, -3 subjects) or 48 weeks (for GT-1, -4 subjects). For each subject, treatment in Part 2 was initiated 2 weeks after the dose administered in Part 1.

Phase 2b

Phase 2b was a double-blind study. Subjects were randomized in an equal ratio to 1 of 3 dose levels of Lambda selected from Phase 2a or to 180 µg alfa-2a. Enrollment in Phase 2b began after all subjects in Phase 2a completed a minimum of 4 weeks of combination treatment with Lambda/RBV or alfa-2a/RBV, and after dose levels for Phase 2b had been selected.

Approximately 150 subjects were to be randomized per group in Phase 2b. Each arm was to include approximately 102 subjects with GT-1, 28 subjects with GT-2 or -3, 10 subjects with GT-4, and 10 subjects with cirrhosis and no history or evidence of decompensated liver disease. As in Phase 2a, subjects received Lambda/RBV or alfa-2a/RBV for 24 weeks (for GT-2, -3 subjects) or 48 weeks (for GT-1, -4 subjects). All subjects were followed for 24 weeks after completion of treatment to assess sustained response.

The primary analysis of efficacy and safety was performed after all subjects completed 12 weeks of treatment. The final analysis was performed after all subjects had completed 24 weeks of follow-up.

NUMBER OF SUBJECTS (Planned and Analyzed):

Phase 2a

Planned: Approximately 55 subjects were planned, including a minimum of 6 GT-1 subjects per arm.

Analyzed: A total of 57 subjects were randomized. All 57 randomized subjects received a single dose of Lambda or alfa-2a in Part 1; 55 of these 57 subjects received combination treatment with Lambda/RBV or alfa-2a/RBV in Part 2.

Phase 2b

Planned: A total of 600 subjects were planned.

Analyzed: Randomized: 570 subjects; treated: 567 subjects (240 µg Lambda, n=144; 180 µg Lambda, n=141; 120 µg Lambda, n=140; alfa-2a, n=142).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Eligible subjects were males or females between the ages of 18 and 70 years who had chronic HCV infection of GT-1, -2, -3, or -4 and a minimum HCV RNA level of 100,000 IU/mL. Subjects with mixed genotype HCV infection were not allowed. Subjects could have received no prior therapy for chronic HCV, other than up to 2 weeks of single-agent therapy with a direct-acting antiviral agent such as an HCV protease or polymerase inhibitor. With the exception of the exploratory group of approximately 10 subjects per treatment group in Phase 2b, subjects must have had documented absence of cirrhosis.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

Subjects randomized to Lambda treatment groups received Lambda administered weekly by SC injection at a dose level of 80 µg (Phase 2a only), 120 µg, 180 µg, or 240 µg for up to 24 or 48 weeks.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

Subjects randomized to the alfa-2a treatment group received Pegasys® (peginterferon alfa-2a) administered weekly by SC injection at a dose level of 180 µg for up to 48 weeks. .

All subjects self-administered RBV orally twice daily. Subjects with HCV GT-1 or -4 started at a total daily dose of 1000 mg (subjects weighing less than 75 kg) or 1200 mg (subjects weighing 75 kg or more). Subjects with HCV GT-2 or -3 of any weight started at a total daily dose of 800 mg.

Batch numbers for drug products used during the study are provided in Table 1.

Table 1: Batch Numbers

Drug Product	Phase 2a	Phase 2b
Lambda, 0.5 mg/mL	ZDF0801C	ZDF0801A, ZDF0801E, ZDF0801F, ZDF0801G, ZDF0801D
Lambda, 0.2 mg/mL	ZDF0901B, ZD0901C	ZDF0901C, ZDF0901D, ZDF0901E, ZDF1001C
Ribasphere® (ribavirin)	A39109Z, A47521Z	A47521Z, A53008Z
Pegasys® (peginterferon alfa-2a)	B1134	B1031B01, B1025B01, B1040B01

CRITERIA FOR EVALUATION:

Efficacy: Antiviral activity was assessed by measuring serum HCV RNA at scheduled time points. HCV RNA was evaluated using the COBAS TaqMan HCV Test v2.0 (lower limit of quantification [LOQ] = 25 IU/mL).

In Phase 2a, virologic response was defined as HCV RNA < LOQ. In Phase 2b, virologic response was defined as the HCV RNA target not detected in the assay (hereafter referred to as "undetectable"). This more stringent definition was adopted in Phase 2b to be consistent with response definitions used in studies of direct acting antiviral agents. For both Phase 2a and Phase 2b, efficacy results are presented using both definitions (< LOQ and undetectable) to permit comparison of results between both phases of the study.

The following definitions of response endpoints were used to evaluate efficacy:

- Rapid virologic response (RVR) rate, defined as the proportion of subjects with virologic response at Week 4
- Complete early virologic response (cEVR) rate, defined as the proportion of subjects with virologic response at Week 12
- Early virologic response (EVR) rate, defined as the proportion of subjects with ≥ 2-log10 decrease from baseline in HCV RNA at Week 12
- Extended RVR (eRVR) rate, defined as the proportion of subjects with virologic response at Week 4 and at Week 12
- End of treatment virologic response (ETVR) rate, defined as the proportion of subjects with virologic response at the end of treatment
- Sustained virologic response (SVR) rate, defined as the proportion of subjects with virologic response at 4 weeks (SVR4), 12 weeks (SVR12), and 24 weeks (SVR24) of post-treatment follow-up
- Proportion of subjects with viral relapse, defined as follows:

  - Phase 2a: subjects who completed the treatment period, achieved virologic response at the end of treatment, and subsequently developed HCV RNA levels ≥ LOQ during the post-treatment follow-up period.
  - Phase 2b: subjects with undetectable HCV RNA at the end of treatment who developed HCV RNA levels ≥ LOQ in the post-treatment follow-up period. A second analysis of relapse included only subjects who were evaluable for relapse (defined as subjects who had completed the full treatment period, were undetectable at the end of treatment (EOT), and had at least one post-treatment follow-up HCV RNA result).
- Proportion of subjects with viral breakthrough, defined as follows:
  - Phase 2a: subjects who achieved virologic response for at least 2 consecutive assessments at least 7 days apart and:
    - Completed the full treatment period but did not achieve ETVR, or
    - Had HCV RNA ≥ LOQ on their last HCV RNA assessment on or prior to premature discontinuation of treatment
  - Phase 2b: subjects who had a confirmed >1-log increase in HCV RNA above nadir or confirmed HCV RNA ≥ LOQ after confirmed virologic response during the treatment period.
- Time to viral clearance, defined as the time from initiation of treatment to the first occurrence of virologic response.

Safety: Safety was assessed by deaths, serious adverse events (SAEs), adverse events (AEs), AEs leading to discontinuation, laboratory abnormalities, electrocardiogram (ECG) results, and vital signs.

Pharmacokinetics: PK was assessed by measuring serum concentrations of Lambda and alfa-2a at specified time points using validated immunoassays.**Immunogenicity:** Serum samples to evaluate antibody responses directed against Lambda were collected from all subjects at specified timepoints during the study. Analysis of immunogenicity was restricted to subjects who were treated with Lambda. Serum samples from these subjects were first screened for reactivity to Lambda in vitro. Samples that were considered reactive were further tested for specificity and titer. Samples that were considered positive for specific antibodies to Lambda were further tested for neutralization capacity in vitro.

STATISTICAL CONSIDERATIONS:

In Phase 2a, analyses were descriptive. Select safety information from Part 1 was summarized separately from Part 2.

In Phase 2b, the primary efficacy endpoint was the proportion of subjects achieving cEVR. The primary efficacy analysis compared this endpoint between each Lambda dose level and alfa-2a using a Cochran-Mantel-Haenszel chi-square test controlling for genotype (i.e., GT-1 vs. GT-2 or -3). This analysis was performed after all randomized subjects completed 12 weeks of treatment and is summarized in the Week 12 Interim CSR ([redacted]). Results presented in this report are based on the final database after all subjects had completed 24 weeks of follow-up.

The following secondary efficacy parameters were summarized by treatment group in each phase of the study: change from baseline in HCV RNA and the proportion of subjects with RVR, cEVR (Phase 2a), ETVR, SVR12, and SVR24.

PK parameters were estimated using noncompartmental analysis and summarized using descriptive statistics for Phase 2a. For Phase 2a/2b, population PK analyses were performed using nonlinear mixed effects modeling to describe the PK of Lambda including the investigation of covariate effects on PK parameters.

SUMMARY OF RESULTS:

Results for subjects with HCV GT-1 and -4 and subjects with HCV GT-2 and -3 were summarized separately in both Phase 2a and Phase 2b.

<u>Phase 2a</u>

Disposition (Phase 2a):

A total of 57 subjects were randomized in Phase 2a; all 57 randomized subjects received single-agent treatment with Lambda or alfa-2a in Part 1 of Phase 2a. Two subjects who received monotherapy in Part 1 did not continue in Part 2: 1 in the Lambda group who chose to withdraw and 1 in the alfa-2a group who was lost to follow-up. Most discontinuations in Part 2 were among GT-1, -4 subjects (18/28 [64.3%]), whose prescribed duration of treatment was 48 weeks. Two of 18 (11.1%) GT-2, -3 subjects, whose prescribed duration of treatment was 24 weeks, discontinued prematurely. Among GT-1, -4 subjects in the Lambda group, lack of efficacy was the most common reason for discontinuation (7/28 [25.0%] subjects), with 3/7 (42.9%) subjects discontinuing in the Lambda 80-µg group. The proportion of GT-1, -4 subjects discontinuing due to AEs was numerically lower in the Lambda group (2/28 [7.1%]) compared with the alfa-2a group (2/6 [33.3%]). None of the GT-2, -3 subjects discontinued due to AEs.

Demographics (Phase 2a):

Most subjects in Phase 2a were male and most were white. The median age ranged from 39 to 55 across treatment groups.

Efficacy Results (Phase 2a): Virologic response rates in Phase 2a Part 2 were similar between Lambda/RBV and alfa-2a/RBV groups among both genotype cohorts, with the exception of numerically lower RVR and cEVR rates among GT-1, -4 subjects who received 80 µg Lambda and numerically lower SVR24 rates among GT-2, -3 subjects who received 80 µg Lambda (Table 2).

Table 2: Phase 2a — Summary of Virologic Response (mITT Analysis Set [Imputed])

Virologic Response[a]	Alfa-2a + RBV	Lambda + RBV				
		240 µg	180 µg	120 µg	80 µg	Total
GT-1, -4	**N=5**	**N=7**	**N=6**	**N=7**	**N=7**	**N=27**
RVR, n (%)	1/5 (20.0)	1/7 (14.3)	2/6 (33.3)	1/7 (14.3)	0/7 (0.0)	4/27 (14.8)
cEVR, n (%)	1/5 (20.0)	2/7 (28.6)	2/6 (33.3)	5/7 (71.4)	0/7 (0.0)	9/27 (33.3)
SVR24, n (%)	1/5 (20.0)	1/7 (14.3)	1/6 (16.7)	2/7 (28.6)	1/7 (14.3)	5/27 (18.5)
GT-2, -3	**N=5**	**N=4**	**N=5**	**N=4**	**N=5**	**N=18**
RVR, n (%)	5/5 (100)	4/4 (100)	2/5 (40.0)	4/4 (100)	3/5 (60.0)	13/18 (72.2)
cEVR, n (%)	5/5 (100)	4/4 (100)	4/5 (80.0)	4/4 (100)	3/5 (60.0)	15/18 (83.3)
SVR24, n (%)	4/5 (80.0)	2/4 (50.0)	4/5 (80.0)	4/4 (100)	1/5 (20.0)	11/18 (61.1)

a HCV RNA not detected in the assay

Safety Results (Phase 2a):

Overall, Lambda was well tolerated. There were no deaths. Among the 57 subjects who received at least a single dose of Lambda or alfa-2a, 6 subjects had SAEs (Lambda, 5; alfa-2a, 1). SAEs considered related to study drug were as follows: Grade 4 [redacted] Grade 3 pneumonitis, and Grade 3 overdose in 1 Lambda-treated subject each and Grade 4 [redacted] in 1 alfa-2a–treated subject. Other AEs were generally low-grade and self-limited, and occurred with similar frequency across dose and treatment groups. No subject experienced an AE meeting criteria for dose-limiting toxicity.

Hematologic laboratory abnormalities were less common on Lambda compared to alfa-2a. Transient elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were more common on Lambda and were generally observed with greater incidence in the Lambda 240-µg group compared to other Lambda dose groups.

Pharmacokinetic Results (Phase 2a):

Following a single SC injection of Lambda in Phase 2a Part 1, median time to maximum concentration (Tmax) values ranged from 12.0 to 25.1 hours postdose (overall individual Tmax range = 4.0 to 73.1 h). The mean elimination half-life (t1/2,λz) ranged from 37 to 52 hours. Estimated mean clearance (CL/F) and volume (VZ/F) values were relatively consistent across the 120-, 180-, and 240-µg dose groups (1.82 to 2.07 L/h and 113 to 135 L, respectively; CL/F and VZ/F were lower in the 80-µg dose group at 1.04 L/h and 46 L, respectively). Estimates of exposure, mean area under the curve (AUC)0-168h and peak concentration (Cmax), appeared to increase in approximate proportion to dose. However, results from the power model analysis were inconclusive with regard to dose, potentially due to the small sample size and observed variability in the PK data. Using this power model, there was no apparent effect of body weight on Lambda exposure following single-dose administration. Other covariates, such as HCV genotype, host interleukin 28B (IL28B) genotype, and other subject characteristics (age, race, sex, and body mass index) did not appear to affect Lambda exposure.

At Weeks 3 and 11 of Phase 2a Part 2, following repeat SC dosing of Lambda in combination with RBV, median Tmax values ranged from 12.0 to 24.6 hours postdose (overall Tmax range = 3.4 to 96.4 h). The range of mean t1/2,λz was 36 to 61 hours. In general, exposure based on mean Cmax and AUC0-168h increased in a dose-dependent manner. Mean accumulation indices based on trough values obtained following the Week 3 and Week 11 doses ranged from 0.86 to 1.97.

Pharmacodynamic Results (Phase 2a):

Following a single dose of alfa-2a, interferon (IFN) gamma levels were higher, while Lambda did not induce IFN gamma. Higher levels of IL-6 and the pro-inflammatory CCR5 chemokines MCP-1 and MIP-1beta were observed following single dose of alfa-2a compared to Lambda. Subjects in all study arms showed higher levels of the CXCR3 chemokines IP-10 and iTAC following a single dose of alfa-2a or Lambda. IP-10 and iTAC increases following alfa-2a dosing were transient and rapid, while increases following Lambda dosing were transient, but less rapid.

Several changes in cell populations were observed, most notably in CD4+ and CD8+ T cell subsets. While mean CD4+ and CD8+ T cells decreased over time in subjects who received alfa-2a, no dose-dependent decrease in mean CD4+ or CD8+ T cells was observed in subjects receiving Lambda, likely reflecting the lack of expression of the interferon lambda receptor subunit IL28RA on peripheral cells as compared to the expression of the interferon alpha receptor subunits.

Phase 2b

Because the 80-µg Lambda dose was associated with less antiviral activity compared to other dose groups in Phase 2a, only the 240-, 180-, and 120-µg dose levels were selected for evaluation in Phase 2b.

Results for noncirrhotic subjects with HCV GT-1 and -4 and with HCV GT-2 and -3 and for cirrhotic subjects with HCV GT-1 and -4 and with HCV GT-2 and -3 were summarized separately.

Disposition (Phase 2b):

The disposition of subjects in Phase 2b is summarized in Table 3.. Among noncirrhotic GT-1, -4 subjects, lack of efficacy, including meeting protocol-defined futility criteria, was the most common reason for premature treatment discontinuation in the Lambda and alfa-2a groups (23.7% and 24.3%, respectively). Discontinuation due to lack of efficacy was rare among noncirrhotic GT-2, -3 subjects, with only 1 subject in the Lambda 120-µg group discontinuing for this reason. GT-2, -3 subjects in the Lambda groups discontinued most frequently due to AEs or withdrawal of consent (4.5% and 5.7%, respectively). In the alfa-2a group, equal numbers of GT-2, -3 subjects (6.7%) discontinued due to AEs, lost to follow-up, or other reason.

Among cirrhotic GT-1, -4 subjects, lack of efficacy was the most common reason for premature discontinuation in the Lambda (29.2%) and alfa-2a (42.9%) groups, followed by AEs (20.8% on Lambda and 14.3% on alfa-2a). Only 2 GT-2, -3 subjects, both in the Lambda 180-µg group, discontinued prematurely, 1 due to AEs and 1 due to lack of efficacy.

Table 3: Phase 2b — Subject Disposition

Subject Disposition	Alfa-2a + RBV	Lambda + RBV 240 µg	Lambda + RBV 180 µg	Lambda + RBV 120 µg	Lambda + RBV Total
Noncirrhotics					
GT-1, -4					
Randomized, n	103	104	103	99	306
Received Study Drug, n/N (%)	103/103 (100)	104/104 (100)	102/103 (99.0)	98/99 (99.0)	304/306 (99.3)
Premature Disc. Treatment, n/N (%)	44/103 (42.7)	39/104 (37.5)	39/102 (38.2)	39/98 (39.8)	117/304 (38.5)
GT-2, -3					
Randomized, n	30	30	29	29	88
Received Study Drug, n/N (%)	30/30 (100)	30/30 (100)	29/29 (100)	29/29 (100)	88/88 (100)
Premature Disc. Treatment, n/N (%)	6/30 (20.0)	7/30 (23.3)	2/29 (6.9)	3/29 (10.3)	12/88 (13.6)
Cirrhotics					
GT-1, -4					
Randomized, n	7	7	8	10	25
Received Study Drug, n/N (%)	7/7 (100)	7/7 (100)	7/8 (87.5)	10/10 (100)	24/25 (96.0)
Premature Disc. Treatment, n/N (%)	4/7 (57.1)	6/7 (85.7)	4/7 (57.1)	4/10 (40.0)	14/24 (58.3)
GT-2, -3					
Randomized, n	2	3	3	3	9
Received Study Drug, n/N (%)	2/2 (100)	3/3 (100)	3/3 (100)	3/3 (100)	9/9 (100)
Premature Disc. Treatment, n/N (%)	0/2 (0.0)	0/3 (0.0)	2/3 (66.7)	0/3 (0.0)	2/9 (22.2)

Demographics (Phase 2b):

Demographics were generally balanced between treatment groups. Most subjects, regardless of cirrhosis status or genotype, were White (> 80%). The median age ranged from 48 to 57 years. Among noncirrhotic subjects, approximately 60% were males; among cirrhotic subjects, approximately 70% were males.

Efficacy Results (Phase 2b): A more rapid early virologic response was observed in the Lambda vs. alfa-2a groups regardless of genotype. Virologic response at post-dosing Week 24 (SVR24) was similar between Lambda and alfa-2a treatments.

Noncirrhotic GT-1, -4: The proportion of subjects with undetectable HCV RNA at Week 4 (RVR) was significantly higher ($p < 0.05$) in the Lambda 240- and 180-µg groups compared with the alfa-2a group. The proportion with undetectable HCV RNA at Week 12 (cEVR) was significantly higher ($p < 0.05$) in all Lambda dose groups compared with the alfa-2a group. The rates of SVR24 and relapse were similar across Lambda doses and treatment groups (Table 4 and Table 5, respectively).

Noncirrhotic GT-2, -3; The proportion of subjects with undetectable HCV RNA at Week 4 (RVR) was significantly higher ($p < 0.05$) in the Lambda 240- and 180-µg groups compared with the alfa-2a group. The rates of cEVR, SVR24, and relapse were similar across Lambda doses and treatment groups (Table 4 and Table 5).

Table 4: Phase 2b — Summary of Virologic Response (Noncirrhotic Subjects – mITT Analysis Set [Imputed])

		Lambda + RBV			
Virologic Response[a]	**Alfa-2a + RBV**	**240 µg**	**180 µg**	**120 µg**	**Total**
GT-1, -4	**N=103**	**N=104**	**N=102**	**N=98**	**N=304**
RVR, n (%)	6 (5.8)	17 (16.3)*	15 (14.7)*	6 (6.1)	38 (12.5)
cEVR, n (%)	38 (36.9)	59 (56.7)*	57 (55.9)*	54 (55.1)*	170 (55.9)
SVR24, n (%)	38 (36.9)	41 (39.4)	38 (37.3)	45 (45.9)	124 (40.8)
GT-2, -3	**N=30**	**N=30**	**N=29**	**N=29**	**N=88**
RVR, n (%)	9 (30.0)	20 (66.7)*	22 (75.9)*	13 (44.8)	55 (62.5)
cEVR, n (%)	26 (86.7)	26 (86.7)	28 (96.6)	26 (89.7)	80 (90.9)
SVR24, n (%)	16 (53.3)	18 (60.0)	22 (75.9)	19 (65.5)	59 (67.0)

*p < 0.05 compared to alfa-2a
a HCV RNA not detected in the assay

Table 5: Phase 2b — Proportion of Subjects with Viral Breakthrough or Relapse (Noncirrhotic Subjects – mITT Analysis Set [Imputed])

			Lambda + RBV			
Variable	**Statistic[c]**	**Alfa-2a + RBV**	**240 µg**	**180 µg**	**120 µg**	**Total**
GT-1, -4		**N=103**	**N=104**	**N=102**	**N=98**	**N=304**
Viral breakthrough[a]	n (%)	3 (2.9)	4 (3.8)	5 (4.9)	5 (5.1)	14 (4.6)
	95% CI	(0.6, 8.3)	(1.1, 9.6)	(1.6, 11.1)	(1.7, 11.5)	(2.5, 7.6)
Relapse[b]	n (%)	19 (18.4)	18 (17.3)	20 (19.6)	12 (12.2)	50 (16.4)
	95% CI	(11.5, 27.3)	(10.6, 26.0)	(12.4, 28.6)	(6.5, 20.4)	(12.5, 21.1)
GT-2, -3		**N=30**	**N=30**	**N=29**	**N=29**	**N=88**
Viral breakthrough[a]	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	95% CI	(0.0, 11.6)	(0.0, 11.6)	(0.0, 11.9)	(0.0, 11.9)	(0.0, 4.1)
Relapse[b]	n (%)	5 (16.7)	1 (3.3)	5 (17.2)	6 (20.7)	12 (13.6)
	95% CI	(5.6, 34.7)	(0.1, 17.2)	(5.8, 35.8)	(8.0, 39.7)	(7.2, 22.6)

a Subjects with a confirmed > 1-log increase in HCV RNA above nadir or confirmed HCV RNA ≥ LOQ after previously being confirmed undetectable
b Subjects confirmed undetectable upon completion of the full treatment period but who had an HCV RNA result ≥ LOQ during post-treatment follow-up
c 2-sided, 95% exact binomial confidence interval (Clopper-Pearson)

Cirrhotic GT-1: Among 24 cirrhotic GT-1 subjects treated with Lambda, no subject achieved RVR; 7 (29.2%) subjects achieved cEVR; and 8 (33.3%) achieved ETVR following 48 weeks of treatment. Four subjects (16.7%; 1 on 240 µg and 3 on 120 µg) achieved SVR24 and 4 subjects (16.7%; 3 on 180 µg and 1 on 120 µg) relapsed. Among 7 subjects treated with alfa-2a, none achieved RVR, 2 (28.6%) achieved cEVR, 3 (42.9%) achieved ETVR, none relapsed, and 3 (42.9%) achieved SVR24.

Cirrhotic GT-2, -3: Among 9 cirrhotic GT-2, -3 subjects treated with Lambda, 1 (11.1%) subject achieved RVR, 5 (55.6%) achieved cEVR, and 7 (77.8%) subjects achieved ETVR. Three subjects (33.3%) subsequently achieved

SVR24. Four subjects (57.1%; 1 on 240 µg, 1 on 180 µg, and 2 on 120 µg) relapsed. Among 2 alfa-2a–treated subjects, 1 achieved RVR and 1 achieved SVR24. One alfa-2a–treated subject (50.0%) relapsed.

Safety Results (Phase 2b):

Noncirrhotic GT-1, -4

A total of 407 noncirrhotic subjects with GT-1 or -4 HCV received study drug and were included in the safety analysis. A summary of safety in these subjects is presented in Table 6.

In summary:

- Three deaths were reported, all of which were assessed as not related to study drug. Two of the deaths were reported in Lambda-treated subjects: a fatal myocardial infarction occurring 2 months after the last dose of Lambda 120 µg and [redacted] in a subject in the Lambda 240-µg group. One subject in the alfa-2a group died due to sudden cardiac death.
- SAEs were reported with similar frequency between treatment groups (see Table 6). SAEs reported for at least 2 subjects in any group included hyperbilirubinemia (Lambda, 3 [1.0%]; alfa-2a, 1 [1.0%]); non-cardiac chest pain (Lambda, 2 [0.7%]; alfa-2a, 0); anemia (Lambda, 2 [0.7%]; alfa-2a, 0); [redacted] (Lambda, 1 [0.3%]; alfa-2a, 1 [1.0%]); and sarcoidosis (Lambda, 0; alfa-2a, 2 [1.9%]).
- The overall incidences of AEs of any grade and Grade 3 and 4 AEs were similar between treatment and dose groups (see Table 6)
- The most common AEs (reported by at least 20% of subjects) on Lambda overall were fatigue, headache, nausea, insomnia, and pruritus. The most common AEs with alfa-2a were fatigue, headache, myalgia, pyrexia, nausea, pruritus, insomnia, rash, chills, and arthralgia. Lambda was associated with fewer flu-like symptoms (arthralgia, myalgia, pyrexia, and chills) compared to alfa-2a (Table 6).
- The incidence of AEs by categories of interest are shown in Table 7. Psychiatric AEs and fatigue were reported in similar proportions of subjects in the overall Lambda and alfa-2a groups. Neurologic, musculoskeletal, and flu-like symptoms occurred in a numerically higher proportion of subjects in the alfa-2a group compared with Lambda overall or any Lambda dose group.
- The main treatment differences in clinical laboratory tests were increased incidences of Grade 3 or 4 elevated bilirubin in the Lambda 240- and 180-µg groups compared to the alfa-2a group, and increased incidences of Grade 3 or 4 hematologic toxicities in the alfa-2a group compared to with the Lambda groups (Table 6).
- The observed higher incidence of Grade 3 or 4 ALT, AST, and total bilirubin (TBili) elevations in the Lambda 240-µg group, without a corresponding increase in virologic response, resulted in April 2011 in discontinuation of the Lambda 240-µg dose for further investigation in Lambda studies.

Table 6: On-treatment Safety - Noncirrhotic Genotypes 1 and 4

	Alfa-2a + RBV (N=103)	Lambda + RBV			
		240 µg (N=104)	180 µg (N=102)	120 µg (N=98)	Total (N=304)
Subjects with SAE, n (%)	7 (6.8)	9 (8.7)	3 (2.9)	6 (6.1)	18 (5.9)
Discontinuations due to AE, n (%)	12 (11.7)	6 (5.8)	8 (7.8)	4 (4.1)	18 (5.9)
Subjects with AEs, n (%)	100 (97.1)	95 (91.3)	90 (88.2)	86 (87.8)	271 (89.1)
Maximum severity of AEs					
Grade 3 (Severe) AEs, n (%)	14 (13.6)	10 (9.6)	15 (14.7)	9 (9.2)	34 (11.2)
Grade 4 (Life-threatening) AEs, n (%)	4 (3.9)	4 (3.8)	2 (2.0)	3 (3.1)	9 (3.0)
Most common AEs (≥ 20% in group)					
Fatigue	44 (42.7)	39 (37.5)	47 (46.1)	37 (37.8)	123 (40.5)
Headache	43 (41.7)	29 (27.9)	28 (27.5)	26 (26.5)	83 (27.3)
Nausea	31 (30.1)	33 (31.7)	22 (21.6)	25 (25.5)	80 (26.3)
Insomnia	26 (25.2)	23 (22.1)	18 (17.6)	31 (31.6)	72 (23.7)
Pruritus	30 (29.1)	29 (27.9)	18 (17.6)	19 (19.4)	66 (21.7)
Rash	25 (24.3)	12 (11.5)	15 (14.7)	13 (13.3)	40 (13.2)
Arthralgia	21 (20.4)	10 (9.6)	6 (5.9)	14 (14.3)	30 (9.9)
Myalgia	34 (33.0)	13 (12.5)	6 (5.9)	10 (10.2)	29 (9.5)
Pyrexia	34 (33.0)	5 (4.8)	8 (7.8)	12 (12.2)	25 (8.2)
Chills	22 (21.4)	2 (1.9)	4 (3.9)	4 (4.1)	10 (3.3)
Selected Grade 3 laboratory abnormalities					
Hemoglobin low	32/103 (31.1)	7/102 (6.9)	6/101 (5.9)	11/97 (11.3)	24/300 (8.0)
Lymphocytes low	9/103 (8.7)	2/102 (2.0)	1/101 (1.0)	2/97 (2.1)	5/300 (1.7)
Neutrophils low	20/103 (19.4)	1/102 (1.0)	1/101 (1.0)	0/97 (0.0)	2/300 (0.7)
Platelets low	2/103 (1.9)	0/102 (0.0)	0/101 (0.0)	0/97 (0.0)	0/300 (0.0)
WBC low	7/103 (6.8)	0/102 (0.0)	1/101 (1.0)	0/97 (0.0)	1/300 (0.3)
ALT high	4/103 (3.9)	10/102 (9.8)	1/101 (1.0)	1/98 (1.0)	12/301 (4.0)
AST high	5/103 (4.9)	17/102 (16.7)	2/101 (2.0)	2/98 (2.0)	21/301 (7.0)
TBili high	4/103 (3.9)	8/102 (7.8)	5/101 (5.0)	2/98 (2.0)	15/301 (5.0)
Selected Grade 4 laboratory abnormalities					
Lymphocytes low	3/103 (2.9)	0/102 (0.0)	0/101 (0.0)	0/97 (0.0)	0/300 (0.0)
Neutrophils low	1/103 (1.0)	0/102 (0.0)	0/101 (0.0)	0/97 (0.0)	0/300 (0.0)
AST high	1/103 (1.0)	3/102 (2.9)	0/101 (0.0)	0/98 (0.0)	3/301 (1.0)
TBili high	1/103 (1.0)	2/102 (2.0)	2/101 (2.0)	0/98 (0.0)	4/301 (1.3)

Table 7: Adverse Events by Category of Interest - Noncirrhotic Genotypes 1 and 4

		Lambda + RBV		
	Alfa-2a + RBV (N=103)	**240 µg (N=104)**	**180 µg (N=102)**	**120 µg (N=98)**
Psychiatric	42 (40.8)	43 (41.3)	33 (32.4)	44 (44.9)
Constitutional symptoms	44 (42.7)	39 (37.5)	47 (46.1)	37 (37.8)
Neurologic	47 (45.6)	35 (33.7)	34 (33.3)	28 (28.6)
Musculoskeletal symptoms	48 (46.6)	22 (21.2)	16 (15.7)	21 (21.4)
Flu-like symptoms	47 (45.6)	8 (7.7)	13 (12.7)	17 (17.3)

Note: categories of interest are based on terms found in the alfa-2a label.

Psychiatric = depression, irritability, insomnia; Constitutional symptoms = fatigue; Neurologic = headache, dizziness; Musculoskeletal = arthralgia, myalgia, back pain; Flu-like symptoms = pyrexia, chills, pain.

Noncirrhotic GT-2, -3

A total of 118 noncirrhotic subjects with GT-2 or -3 HCV received study drug and were included in the safety analysis. A summary of safety in these subjects is presented in Table 8.

In summary:

- There were no deaths.
- SAEs were reported in a numerically higher proportion of subjects in the Lambda group (5/88 [5.7%]) than in the alfa-2a group (1/30 [3.3%]; see Table 8. Four of the 5 subjects with SAEs in the Lambda group were receiving the 240-µg dose and included 1 event each of hyperbilirubinemia, [redacted], [redacted], and [redacted]. The remaining subject with an SAE in the Lambda group received 180 µg and experienced chest pain and shortness of breath. In the alfa-2a group, benign intracranial hypertension considered possibly related to peginterferon treatment was reported as an SAE.
- The most common AEs reported for Lambda (reported by at least 20% of subjects) were nausea, fatigue, insomnia, pruritus, and headache; the most common AEs reported for alfa-2a were fatigue, nausea, headache, arthralgia, myalgia, pyrexia, insomnia, and chills. Consistent with findings in HCV GT-1, -4 subjects, Lambda was associated with fewer flu-like symptoms (arthralgias, myalgias, pyrexia, and chills) compared to alfa-2a.
- The incidence of AEs by categories of interest are shown in Table 9. Psychiatric symptoms in GT-2,-3 subjects occurred in a numerically higher proportion of subjects in the Lambda vs. alfa-2a groups. Fatigue was reported with similar incidence in the Lambda 240-µg and alfa-2a groups. Musculoskeletal and flu-like symptoms were reported in a numerically higher proportion of subjects in the alfa-2a group compared with the Lambda groups.
- With respect to laboratory abnormalities, consistent with observations in the GT-1, -4 subjects, Grade 3 or 4 hematologic toxicities were reported in a numerically higher proportion of subjects in the alfa-2a group, while Grade 3 or 4 elevated bilirubin was reported in a numerically higher proportion of subjects receiving Lambda.

Table 8: On-treatment Safety - Noncirrhotic Genotypes 2 and 3

	Alfa-2a + RBV (N=30)	Lambda + RBV			
		240 µg (N=30)	180 µg (N=29)	120 µg (N=29)	Total (N=88)
Subjects with SAE, n (%)	1 (3.3)	4 (13.3)	1 (3.4)	0	5 (5.7)
Discontinuations due to AE[b], n (%)	2 (6.7)	3 (10.0)	0	1 (3.4)	4 (4.5)
Subjects with AEs, n (%)	29 (96.7)	28 (93.3)	28 (96.6)	28 (96.6)	84 (95.5)
Maximum Severity of AEs, n (%)					
Grade 3 (Severe)	3 (10.0)	3 (10.0)	0	2 (6.9)	5 (5.7)
Grade 4 (Life-threatening)	0	2 (6.7)	0	0	2 (2.3)
Most common AEs (≥ 20% in any dose or treatment group)					
Nausea	11 (36.7)	18 (60.0)	8 (27.6)	13 (44.8)	39 (44.3)
Fatigue	16 (53.3)	15 (50.0)	8 (27.6)	12 (41.4)	35 (39.8)
Insomnia	6 (20.0)	9 (30.0)	8 (27.6)	8 (27.6)	25 (28.4)
Pruritus	3 (10.0)	8 (26.7)	6 (20.7)	8 (27.6)	22 (25.0)
Headache	10 (33.3)	7 (23.3)	6 (20.7)	7 (24.1)	20 (22.7)
Irritability	4 (13.3)	4 (13.3)	8 (27.6)	4 (13.8)	16 (18.2)
Pyrexia	7 (23.3)	6 (20.0)	5 (17.2)	3 (10.3)	14 (15.9)
Rash	2 (6.7)	6 (20.0)	2 (6.9)	3 (10.3)	11 (12.5)
Myalgia	10 (33.3)	3 (10.0)	3 (10.3)	5 (17.2)	11 (12.5)
Arthralgia	10 (33.3)	3 (10.0)	4 (13.8)	3 (10.3)	10 (11.4)
Alopecia	2 (6.7)	0	2 (6.9)	7 (24.1)	9 (10.2)
Chills	6 (20.0)	0	2 (6.9)	1 (3.4)	3 (3.4)
Selected Grade 3 Laboratory abnormalities					
Hemoglobin low	8/29 (27.6)	0/30 (0.0)	0/29 (0.0)	0/29 (0.0)	0/88 (0.0)
Lymphocytes low	3/29 (10.3)	0/30 (0.0)	0/29 (0.0)	0/29 (0.0)	0/88 (0.0)
Neutrophils low	7/29 (24.1)	0/30 (0.0)	0/29 (0.0)	0/29 (0.0)	0/88 (0.0)
WBC low	2/29 (6.9)	0/30 (0.0)	0/29 (0.0)	0/29 (0.0)	0/88 (0.0)
ALT high	4/29 (13.8)	4/30 (13.3)	2/29 (6.9)	1/29 (3.4)	7/88 (8.0)
AST high	1/29 (3.4)	3/30 (10.0)	1/29 (3.4)	0/29 (0.0)	4/88 (4.5)
TBili high	0/29 (0.0)	0/30 (0.0)	0/29 (0.0)	2/29 (6.9)	2/88 (2.3)
Selected Grade 4 Laboratory abnormalities					
Lymphocytes low	1/29 (3.4)	1/30 (3.3)	0/29 (0.0)	0/29 (0.0)	1/88 (1.1)
Neutrophils low	1/29 (3.4)	0/30 (0.0)	0/29 (0.0)	0/29 (0.0)	0/88 (0.0)
ALT high	0/29 (0.0)	1/30 (3.3)	0/29 (0.0)	0/29 (0.0)	1/88 (1.1)
TBili high	0/29 (0.0)	2/30 (6.7)	0/29 (0.0)	0/29 (0.0)	2/88 (2.3)

Table 9: Adverse Events by Category of Interest - Noncirrhotic Genotypes 2 and 3

		Lambda + RBV		
	Alfa-2a + RBV (N=30)	**240 µg (N=30)**	**180 µg (N=29)**	**120 µg (N=29)**
Psychiatric	10 (33.3)	12 (40.0)	12 (41.4)	13 (44.8)
Constitutional symptoms	16 (53.3)	15 (50.0)	8 (27.6)	12 (41.4)
Neurologic	10 (33.3)	11 (36.7)	7 (24.1)	8 (27.6)
Musculoskeletal symptoms	19 (63.3)	5 (16.7)	6 (20.7)	8 (27.6)
Flu-like symptoms	12 (40.0)	7 (23.3)	6 (20.7)	5 (17.2)

Note: categories of interest are based on terms found in the alfa-2a label.

Psychiatric = depression, irritability, insomnia; Constitutional symptoms = fatigue; Neurologic = headache, dizziness; Musculoskeletal = arthralgia, myalgia, back pain; Flu-like symptoms = pyrexia, chills, pain.

Cirrhotic subjects

A total of 31 cirrhotic subjects with GT-1 HCV and 11 cirrhotic subjects with GT-2 or -3 HCV received study drug and were included in the safety analysis; no subject with GT-4 was enrolled. In summary:

- There were no deaths.
- Among cirrhotic subjects with GT-1 HCV:
  - Two subjects reported 3 SAEs (ascites, liver disorder, and [redacted]). Both subjects were on Lambda 120 µg.
  - AEs leading to discontinuation were reported for 5/24 (20.8%) subjects on Lambda and 1/7 (14.3%) subjects on alfa-2a.
  - No Grade 4 AEs were reported. Eight subjects with GT-1 HCV reported Grade 3 AEs, including 4 on 240 µg Lambda and 4 on 120 µg Lambda. Grade 3 AEs assessed as related to treatment included hyperbilirubinemia in 3 subjects and peripheral edema, arthritis, [redacted] and ascites in 1 subject each.
  - Common AEs (reported by at least 20% of subjects) on Lambda included pruritus, insomnia, fatigue, irritability, nausea, and cough. Common AEs on alfa-2a included fatigue, insomnia, headache, nausea, decreased appetite, injection site reaction, arthralgia, [redacted] and muscle weakness.
  - There were no Grade 3 or Grade 4 elevations in ALT in any of the treatment groups. Grade 3 elevations in total bilirubin were reported for 3 Lambda-treated subjects (2 at 240 µg and 1 at 120 µg) and 1 alfa-2a–treated subject. Grade 3 low hemoglobin was reported for 2/24 (8.3%) Lambda-treated subjects (1 each on 180 µg and 120 µg) and 4/7 (57.1%) alfa-2a–treated subjects. Grade 3 low neutrophils were reported for 2/7 (28.6%) subjects in the alfa-2a group and none of the subjects in the Lambda groups.
- Among cirrhotic subjects with GT-2, -3 HCV:
  - No SAEs were reported.
  - AEs leading to discontinuation were reported for 1 subject (Lambda 180 µg) who discontinued prematurely due to Grade 3 influenza.
  - Two subjects reported Grade 3 AEs: 1 subject on alfa-2a (neutropenia) and 1 subject on 180 µg Lambda (influenza). Both events were considered related to peginterferon. No Grade 4 AEs were reported.
  - AEs reported by more than 1 subject overall were headache in 5/11 subjects (45.4%), nausea in 4/11 subjects (36.4%), and insomnia in 4/11 (36.4%).

– Grade 3 ALT elevation was reported for 1 subject in the Lambda 240-μg group. No Grade 3 or 4 elevations were reported for subjects in other Lambda groups or in the alfa-2a group. No Grade 3 elevations in total bilirubin were reported for any cirrhotic GT-2, -3 subject.

Pharmacokinetic Results (Phase 2b):

Trough concentrations were collected in the study up to end of treatment, through Week 48 for subjects with GT-1 and -4, and through Week 24 for subjects with GT-2 and -3 and subjects with cirrhosis GT-1, -2, -3, and -4. Following weekly administration of Lambda, mean trough concentrations indicated that steady state was achieved between 2 and 4 weeks after initiation of treatment. Comparing mean exposures over this timeframe within the dosing groups indicated that there was little to modest accumulation (< 25%) over this time period. There was high variability in the concentration measurements at each time point with %CV values greater than 50% in all dosing groups across genotypes.

PK data from the Phase 2a and 2b portions of the study were used to constuct a population PK model for Lambda. This model, along with clinical response data, including the primary endpoint data, were used to evaluate relationships between Lambda exposure and antiviral effect as part of Phase 3 dose selection. Details of these analyses are described in a separate report (Phase 3 dose selection document, [redacted]). Briefly, PK modeling results demonstrated that the PK of Lambda follow a 1-compartment model with first-order absorption with weight effects on clearance and volume. Weight effects were implemented as a power model, consistent with standard allometry. Although weight has a significant effect on clearance that overlaps the 0.8-1.25 bioequivalence window at the 5th and 95th percentiles of weight, the effect is small compared to the intersubject variability. The exposure-response relationship between Lambda serum concentrations and the HCV viral kinetics were evaluated using a pharmacokinetics-viral kinetics (PKVK) model. The Lambda PKVK model was described as an Emax exposure-response model using average concentration (Cavg) over the duration of treatment linked to viral decline. The impact of virus and host GT was evaluated, and the model accounted for differences in baseline viral load. The resulting model described the viral kinetics following administration of Lambda and was used to support Phase 3 dosing.

Pharmacodynamic Results (Phase 2b):

Six cytokines and chemokines (IP-10, MIG, MIP-1beta, MCP-1, and iTAC) were measured in the serum at baseline and Week 4 in the study. Most of these cytokines and chemokines (specifically IP-10 and iTAC) would generally be expected to decrease during treatment, coinciding with HCV RNA decline. IP-10, MIG, and MIP-1beta all decreased to varying levels from baseline to Week 4 with alfa-2a or Lambda treatment in GT-1, -4 and GT-2, -3 subjects. MCP-1 levels increased from baseline to Week 4 with alfa-2a, while minor increases or no change was observed with Lambda in GT-1, -4 and GT-2, -3 subjects. For iTAC, decreases from baseline to Week 4 were observed with Lambda regardless of HCV genotype while decreases from baseline to Week 4 were only observed in GT-1, -4 subjects and not GT-2, -3 subjects who received alfa-2a. Decreases in IL-8 from baseline to Week 4 were observed for both alfa-2a and Lambda in GT-1, -4 subjects, but not for GT-2, -3 subjects. **Immunogenicity Results (Phase 2b)**

Among noncirrhotic GT-1, -4 subjects in the Lambda group, 150/299 evaluable subjects (50.2%) developed anti-drug antibodies (ADA) at some time between Week 2 and the end-of-study (EOS) visit at Week 72. Most subjects became positive on or after Week 12. Four subjects (2.7%) were ADA positive at baseline and experienced an increase in titer of ≥ 1 unit following Lambda treatment. Of the 150 subjects who developed ADA, 83 (55.3% of ADA-positive subjects; 27.8% of total subjects) had ADA with neutralizing activity in an in vitro bioassay.

Among noncirrhotic GT-2, -3 subjects in the Lambda group, 43/88 evaluable subjects (48.9%) developed ADA between Week 2 and the EOS visit at Week 48. Most subjects became positive on or after Week 12. One subject was ADA positive at baseline and experienced an increase in titer of ≥ 1 unit following Lambda treatment. Of the 43 subjects who developed ADA, 20 (46.5% of ADA-positive subjects; 22.7% of total subjects) had neutralizing antibodies.

Among cirrhotic GT-1 subjects treated with Lambda, 9/24 evaluable subjects (37.5%) developed ADA between Week 2 and the EOS visit. All ADA-positive subjects seroconverted after receiving Lambda. Two of the 9 subjects with ADA (22.2% of ADA-positive patients; 8.3% of total subjects) had neutralizing antibodies.

Among cirrhotic GT-2, -3 subjects treated with Lambda, 4/9 evaluable subjects (44.4%) developed ADA between Week 2 and the EOS visit. All ADA-positive subjects seroconverted after receiving Lambda. Three of the 4 subjects with ADA (75.0% of ADA-positive patients; 33.3% of total subjects) had neutralizing antibodies.

CONCLUSIONS:

Phase 2a

- Lambda treatment was associated with rapid reduction in serum HCV RNA in the majority of subjects. Rates of virologic response (e.g., RVR, cEVR, SVR24) were similar between each of the highest 3 doses of Lambda (240 µg, 180 µg, 120 µg) and alfa-2a in both the GT-1, -4 and GT-2, -3 cohorts. As previously observed with treatment with alpha interferons, GT-1, -4 subjects in all treatment groups had lower virologic responses compared to GT-2, -3 subjects. Due to the small sample size in this Phase 2a study, the ability to interpret differences in treatment groups was limited.
- Virologic response was generally slower and less durable for subjects treated with 80 µg Lambda compared to other treatment groups. The 80-µg dose was therefore eliminated from further evaluation in Phase 2b.
- Safety was demonstrated at all dose levels of Lambda, sufficient to warrant continued evaluation in Phase 2b of the study. Most AEs were low-grade and self-limited, with the exception of 3 SAEs reported among Lambda-treated subjects considered related to peginterferon treatment, including bilateral pneumonitis, [redacted] and [redacted] in 1 subject each. These events are consistent with those reported among subjects treated with alfa-2a, and with SAEs observed on the alfa-2a arm in the present study (1 alfa-treated subject experienced a related SAE of [redacted]). Given the small samples sizes, no clear differences in the spectrum of commonly occurring AEs could be identified between Lambda and alfa-2a treatment or among the Lambda dose groups
- Elevations in serum transaminases occurred more commonly among Lambda-treated subjects, particularly among subjects at the highest 240-µg dose level, and were the most common reason for dose withholding or dose modifications among subjects in the Lambda groups.
- Treatment with Lambda resulted in fewer observed hematologic toxicities (neutrophils, platelets, and white blood cells [WBCs], in particular) than alfa-2a, consistent with limited expression of Lambda receptors in these cells and their precursers.
- In general, multiple dose exposure based on mean Cmax and AUC0-168h increased in an approximately dose-dependent manner.
- Induction of pro-inflammatory cytokines and chemokines were induced to a greater extent by alfa-2a than Lambda. Subjects in all study arms showed higher levels of the CXCR3 chemokines IP-10 and iTAC following a single dose of alfa-2a or Lambda with different kinetic profiles of induction.
- Mean CD4+ and CD8+ T cells decreased over time in subjects who received alfa-2a, but not in subjects receiving Lambda, likely reflecting the lack of expression of the interferon lambda receptor subunit IL28RA on peripheral cells as compared to the expression of the interferon alpha receptor subunits

Phase 2b

Noncirrhotic Subjects HCV GT-1, -4 and GT-2, -3

- The viral kinetics of Lambda 180 and 120 µg suggest a faster, earlier decline in HCV RNA compared to alfa-2a, with a significantly higher proportion of subjects with undetectable HCV RNA at Week 4 in the Lambda groups among both GT-1, 4 and GT-2,-3 subjects. Sustained virologic response and relapse rates were similar in the Lambda/RBV and alfa-2a/RBV groups regardless of genotype.
- Lambda 180 µg and 120 µg was generally tolerated. The rates of premature discontinuation and overall rates of SAEs and AEs were similar for the Lambda 180- and 120-µg groups compared with alfa-2a.
- Alfa-2a/RBV was associated with higher rates of flu-like symptoms (arthralgias, myalgias, chills, pyrexia) compared with Lambda. Lambda was associated with similar rates of fatigue, but with fewer events of flu-like symptoms compared with alfa-2a. Rates of neuropsychiatric events were generally similar.

- Transient elevation of hepatic transamininases and/or conjugated bilirubin increased with increasing dose of Lambda. Treatment with the highest dose (Lambda 240 µg) was discontinued in April 2011 following observed higher rates of hepatic laboratory abnormalities compared to alfa-2a and the 180-µg and 120-µg Lambda doses, without a significant increase in virologic response. Lambda 180-µg and 120-µg dose levels were associated with similar rates of AST and ALT elevations, and modestly greater rates of elevations of direct and total bilirubin compared to alfa-2a.
- Lambda was associated with less neutropenia or thrombocytopenia compared to alfa-2a, consistent with limited expression of Lambda receptors in the hematopoietic system. This translated into reduced rates of interferon dose modifications compared to alfa-2a.

Cirrhotic subjects with HCV GT-1, or GT -2, -3

- Among subjects with cirrhosis but no evidence of hepatic decompensation, no subjects achieved RVR. The rates of SVR were modest.
- Lambda was well tolerated by most subjects with compensated cirrhosis, and may have advantages over alfa-2a in patients at high risk for cytopenias. The pattern of AEs and laboratory abnormalities was similar to that observed in noncirrhotics. Specifically, compared to alfa-2a, treatment with Lambda was associated with fewer musculoskeletal and autoimmune AEs and less hematologic toxicity. As was the case in noncirrhotic subjects, elevation in bilirubin was the primary dose-related laboratory abnormality, with the majority of high-grade elevations occurring on the 240-µg Lambda dose, which has been discontinued. Overall, the proportion of Lambda-treated subjects who discontinued prematurely due to AEs was greater among cirrhotics than in the larger noncirrhotic population, consistent with a more vulnerable population.

Overall, the observations above suggest that Lambda may prove valuable in combination with RBV, with less hematologic toxicity, fewer flu-like symptoms, and less autoimmunity than is observed combinations that include alpha interferons.

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