CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206843Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	206,843 / S-0001 (**resubmission**)
Drug Name:	Daclatasvir (DCV) tablet: 30 mg or 60 mg (NDA 206,843);
Indication(s):	The treatment of Chronic Hepatitis C-3 Infection in Adults
Applicant:	Bristol-Myers Squibb (BMS)
Date(s):	Re-Submitted: February 13, 2015 Received: February 13, 2015 PDUFA Date: August 13, 2015 Draft Review Completed: June 17, 2015 Final Review Completed: June 29, 2015
Review Priority	Priority
Biometrics Division:	Division of Biometrics IV (HFD-725)
Statistical Reviewer:	Wen Zeng, Ph.D. (HFD-725)
Concurring Reviewers:	Fraser Smith, Ph.D. (HFD-725), Secondary Statistics Reviewer
Medical Division:	Division of Antiviral Drug Products (HFD-530)
Clinical Team:	Wendy Carter, D.O.; Medical Reviewer Kimberly Struble, PharmD.; Medical Team Leader
Project Manager:	Sohail Mosaddegh, RPh. Regulatory Project Manager

Keywords: HCV Infected Subjects, Daclatasvir (DCV), NS5A Replication Complex Inhibitor, HCV-3 Infection, Combination of DCV and Sofosbuvir (SOF), Cirrhosis Status at Baseline.

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1. EXECUTIVE SUMMARY

This review evaluates Bristol-Myers Squibb's resubmission to determine the efficacy of Daclatasvir.

Daclatasvir (BMS-790052; abbreviated as DCV) is a first-in-class highly selective nonstructural protein 5a (NS5A) replication complex inhibitor of HCV with broad genotypic coverage. NS5A is a non-enzymatic multifunctional protein with key functions in HCV replication, virus assembly, and the modulation of cellular signaling pathways. The proposed recommended dose is 60 mg once daily (QD) administrated with Sofosbuvir (SOF, or called Sovaldi^{TM}). DCV was submitted in NDA 206,843.

The original NDA 206,843 for Daclatasvir was submitted on March 31, 2014 along with the NDA 206,844 for Asunaprevir (BMS-650032; abbreviated as ASV). Both NDAs were supported by the same three phase 3 studies, AI447028 and AI447026 for DCV+ASV, and AI447029 for DCV+ASV+ Peglated Interferon+Ribavirin (P/R), for their efficacy claim. These three phase 3 studies mainly focused on HCV genotype 1 and 4 only. Please see the statistical review for the original NDA for the efficacy assessment of these three studies.

NDA 206,844 was withdrawn within the original review cycle by the applicant before the action date. On November 25, 2014, the agency issued a complete response letter (CRL) for NDA 206,843. This resubmission is in response to the CRL. Only data from one phase 3 study AI444218 (ALLY-3) was provided in the resubmission to support the use of DCV plus SOF for the treatment of HCV genotype 3 infected patients.

The primary objective of study AI444218 was to demonstrate that the combination therapy with DCV and SOF for 12 weeks is safe and effective in treatment-naïve (TN) or PR treatment-experienced (TE) subjects chronically infected with HCV GT-3 based upon SVR12, defined as HCV RNA < LLOQ [target not detected (TND) or target detected (TD)] at post treatment Week 12.

Study AI444218 was a global study that enrolled 152 subjects from 2 countries; 96% (146/152) of subjects were from US sites and only 4% (6/152) subjects were from Puerto Rico. The overall SVR12 was 89% (135/152) with 95% confidence interval (CI) of (83%, 93%). The SVR12 rate for the TN cohort was 90% (91/101) with 95% CI of (83%, 95%), and 86% (44/51) with 95% CI of (74%, 94%) in PR treatment-experienced cohort. Given the sample sizes in the trial, the SVR12 rates between TN and TE cohort were comparable.

The SVR12 rate was 63% (20/32) with 95% CI of (44%, 79%) for subjects with cirrhosis at baseline, and 96% (115/120) with 95% CI of (91%, 99%) for subjects without cirrhosis at baseline. Given the small sample sizes, the point estimate may be unstable. Given the confidence intervals for cirrhotics and non-cirrhotics did not overlap, this finding may suggest that the DCV/SOF 12-week regimen may not be the optimal regimen for subjects with cirrhosis at baseline.

The SVR12 rate was 54% (7/13) with 95% CI of (25%, 81%) for subjects with the NS5A Y93H baseline polymorphism, and 92% (128/139) with 95% CI of (86%, 96%) for subjects without the

Y93H NS5A baseline polymorphism. Given the small sample sizes, the point estimate may be unstable. Given the 95% confidence intervals for the two subgroups did not overlap this finding may suggest that patients with NS5A Y93H at baseline had a statistically significant lower SVR12 rate than patients without NS5A Y93H at baseline. The prevalence of NS5A Y93H baseline polymorphism is about 10% in the HCV-3 infected population according to the microbiology review.

The Study AI444218 protocol did not define the "win" criteria for the determination of efficacy. The current Standard-of-Care (SOC) for HCV-3 infected subjects is SOF/RBV for 24 weeks. During the review the statistical reviewer calculated the potential non-inferiority (NI) margins based on the historical data. The NI margin (M1) could be as low as -17% without any clinical consideration (i.e. clinical input that would be needed in order to determine M2). The SVR12 rate difference between the new regimen (DCV/SOF 12 weeks) and the SOC (SOF/RBV 24 weeks) is about 2% with 95% CI of (-4%, 9%). The lower bound of the 95% CI is -4% which is greater than the potential NI margin of -17%.

The applicant also submitted two interim reports from an Early Access Program (EAP) from two studies, AI444258 (France, ATU cohort) and AI444237 (UK), without any data. These two interim reports are not discussed in this review. On April 30, 2015, the applicant submitted two datasets, DM2 and VL2, which contain 44 HCV-3 infected subjects with cirrhosis at baseline from the EAP program. This data is limited and not conclusive to determine the appropriate regimen recommendation for subjects with cirrhosis at baseline.

In conclusion, Study AI444218 demonstrated the efficacy of DCV/SOF in HCV-3 infected subjects with the exception of subjects with cirrhosis and NS5A Y93H polymorphisms at baseline. These subjects had lower SVR12 rates than other subjects.

Key statistical issue: This reviewer identified two statistical issues in this resubmission. The first issue was the NI margin used to assess the efficacy for Study AI444218. Because the study protocol did not define the "win" criteria for the determination of efficacy, the statistical reviewer calculated the potential NI margins based on the historical data. Please see section 3.2.1 for details. The second issue was the percentage of subjects with baseline HCV RNA viral load greater or equal to 800,000 IU/mL. The applicant reported that the percentage was 71%, while the statistical reviewer got 76%. Please see section 3.1 for details.

2. INTRODUCTION

This review evaluates a resubmission from Bristol-Myers Squibb [BMS] to determine the efficacy of Daclatasvir.

2.1 Overview

Globally it is estimated that approximately 170 million people are infected with HCV, including approximately 3-5 million people in the United States (US) (http://www.epidemic.org/thefacts/theepidemic/worldPrevalence/). The most common HCV GT in the US is GT 1 (70-75%), followed by GT 2 and GT 3.

According to the clinical overview of the resubmission, genotype 3 (GT-3) is the second most prevalent GT in some European countries and India, and is associated with an increased likelihood of developing hepatic complications, from steatosis to HCC. In the US, the prevalence has been reported to be from 7.4% to 9.6%. In the US, GT-3 is more likely to be seen in the younger population (< 30 years old).

The two regimens approved for the treatment of HCV-3 infection are:

- Pegylated interferon + Ribavirin (PR) for 48 weeks;
- Sofosbuvir (SOF) + PR for 24 weeks;

Pegasys® (pegylated interferon alfa 2-a) and PegIntron® (pegylated interferon alfa-2-b), are immunostimulatory agents and are co-administered with RBV.

SOF (Sovaldi^{TM}) is approved and is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase and is incorporated into the HCV RNA by the NS5B polymerase and disrupts the viral replication by chain termination. These direct acting antiviral agents (DAA) are currently indicated for co-administration with PEG and RBV for the treatment of chronic HCV GT 3 infection.

In this NDA resubmission, BMS proposes use of DCV (Daklinza) in combination with sofosbuvir for the treatment of patients with genotype 3 chronic hepatitis C virus (HCV) infection.

2.1.1 Study Reviewed

The detailed description of the study is listed in Table 1. Only one phase 3 study, AI444218, was submitted and reviewed in the resubmission. Study AI444218 was conducted in the US and Puerto Rico.

In addition, the applicant submitted two interim reports for studies AI444237 and AI444258. AI444237 is conducted under a compassionate use program (CUP) in United Kingdom. AI444258 is an authorization for temporary use (ATU) study in France. Both studies were conducted under the expanded access program (EAP). There were no data submitted for either, and the studies were not reviewed in this review.

At the late review cycle, the applicant submitted two datasets (DM2 and VL2), which contain 44 HCV-3 infected subjects with cirrhosis at baseline from AI444258 on April 30, 2015. Only simple efficacy summaries are presented at the end of the review.

Table 1 List of Phase 3 study included in this review

Study	Phase and Design	Objectives/Primary Endpoints	Treatment Period	# of Subjects per Arm	Study Population
AI444218 (DCV/SOF in HCV-3)	Phase 3, Global, Open-label, single arm; Two cohorts: Treatment-naïve Treatment-experienced Chronic Hepatitis C Genotype **3** Infection	**SVR12:** -- To estimate the SVR12 rate, defined as HCV RNA < LLOQ target detected (TD) or target not detected (TND) at follow-up Week 12 in treatment-naive subjects treated with 12 weeks of DCV+SOF therapy. -- To estimate the SVR12 rate, defined as HCV RNA < LLOQ target detected (TD) or target not detected (TND) at follow-up Week 12 in treatment-experienced subjects treated with 12 weeks of DCV+SOF therapy.	12 weeks: DCV: 60 mg QD, + SOF 400 mg QD	TN cohort: (n=100, enrolled 101 subjects) TE cohort: (n=50, enrolled 51 subjects)	Treatment naïve and treatment experienced subjects with HCV-3 infection

The detailed design characteristics of the three phase 3 studies are described in section 3.2.1.

2.2 Data Sources

This resubmission contains the efficacy, safety, and some genotyping results for subjects in Study AI444218. The following tasks were done as part of the review process:

1. Reviewed protocols, statistical analysis plans, efficacy results and conclusions in the following submitted documents entitled "Statistics Section":
    - Module 1- labeling materials
    - Module 2- 2.5 Clinical Overview and 2.7.3 Summary of Clinical Efficacy
    - Module 5- Clinical Study Reports (CSRs) of the Phase III Study AI444218.

2. Converted SAS transport files '*.xpt' in the \analysis\legacy\datasets subfolder as analysis datasets, converted some of the raw datasets in the \tabulations\legacy subfolder into SAS datasets for verification based on the definitions in 'define.pdf', 'blankcrf.pdf', and the Statistical Analysis Plan in the CSR. In the \analysis\legacy\datasets subfolder, there are 12 SAS transport files for the phase 3 study. There are 26 SAS transport files in the \tabulations\legacy subfolder which are the input datasets for creating efficacy/safety analysis datasets. These files are under the CDER Electronic Document Room (EDR) directory of

    \\Cdsesub1\evsprod\NDA206843\0034\m5\datasets\ai444218

Two datasets for the ATU France study AI444258 can be found using the following link:

\\Cdsesub1\evsprod\NDA206843\0041\m5\datasets\ai444258-atu\analysis\legacy\datasets

There were no source data available and only simple efficacy summary statistics were generated based on the datasets submitted.

3. STATISTICAL EVALUATION

Study AI444218 is reviewed under each of following sections. All tables and figures were generated by the statistical reviewer unless otherwise cited. For Study AI444218, the treatment-naïve (TN) cohort is abbreviated as TN and the treatment-experienced (TE) cohort is abbreviated as TE. For Study AI444258, the actual regimens are used for the column titles in the summary tables.

3.1 Data and Analysis Quality

Overall, the reviewer reproduced primary efficacy variables in the primary efficacy analysis datasets, EFF and VFAIL, for Study AI444218. The only difference found was the baseline HCV RNA viral load summarized below:

Statistical issue #2: the baseline viral load data for 10 subjects were picked up incorrectly:

In the trial, 10 subjects enrolled into the PK sub-study and multiple viral load samples were taken on day 1 for these 10 subjects. The applicant used the last viral load sample on day 1 as the baseline HCV RNA viral load in their summary for these 10 subjects. This last viral load sample was after the first dose, not before the first dose. The first viral load sample on day 1 should be used as the baseline HCV RNA viral load. As a result, the applicant stated that 71% of subjects had baseline HCV RNA levels greater than or equal to 800,000 IU/mL, instead of the reviewer's estimate of 76%.

After discussing with the applicant, they agreed with it and the sentence of 76% of subjects had baseline HCV RNA levels greater or equal to 800,000 IU/mL is used in the label section 14.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

- **AI444218 (ALLY-3), a phase 3 study for HCV-3 subjects:**

Title: A Phase 3 Evaluation of Daclatasvir and Sofosbuvir in Treatment Naïve and Treatment Experienced Subjects with Genotype 3 Chronic Hepatitis C Infection.

This was a single arm study with two cohorts. Enrolled subjects received DCV (60 mg) plus SOF (100 mg) QD for 12 weeks. A total of 152 subjects were enrolled including 101 subjects in the TN cohort and 51 subjects in the TE cohort. See Figure 1 for the study design and planned sample size.

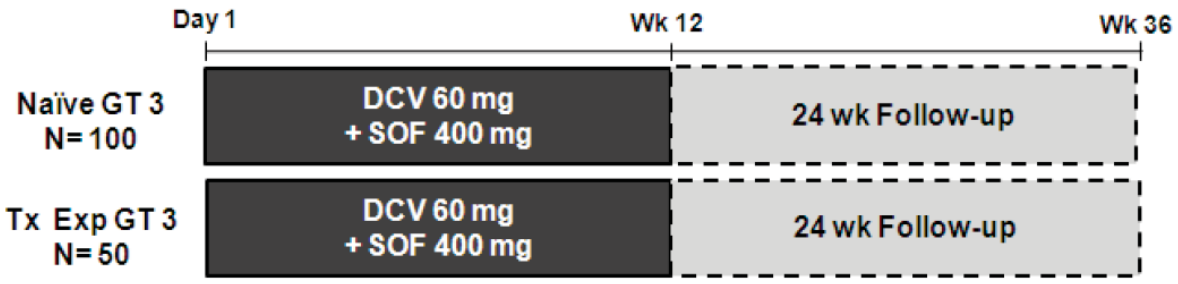


Figure 1: Study Diagram of AI444218

Research Hypothesis:

- Combination therapy with DCV and SOF for 12 weeks is safe and effective in treatment-naive or treatment-experienced subjects chronically infected with HCV GT-3 based upon SVR12 (defined as HCV RNA < LLOQ [TND or TD] at post treatment Week 12).

Primary Objectives:

- To estimate the SVR12 rate, defined as HCV RNA < LLOQ target detected (TD) or target not detected (TND) at follow-up Week 12 in treatment-naive subjects treated with 12 weeks of DCV+SOF therapy.

- To estimate the SVR12 rate, defined as HCV RNA < LLOQ target detected (TD) or target not detected (TND) at follow-up Week 12 in treatment-experienced subjects treated with 12 weeks of DCV+SOF therapy.

Statistical issue #1: the NI margin used to assess the efficacy:

Currently the SOC for HCV-3 infected subjects is SOF/RBV for 24 weeks. The efficacy results from the VALENCE study are listed below:

HCV-3	SOF/RBV x 24 weeks (n=250)	95% CI
Treatment- Naïve	**93% (98/105)**	**(87%, 97%)**
No Cirrhosis	**93% (86/92)**	**(86%, 98%)**
Cirrhosis	**92% (12/13)**	**(64%, 100%)**
Treatment-Exp	**77% (112/145)**	**(70%, 84%)**
No Cirrhosis	**85% (85/100)**	**(76%, 91%)**
Cirrhosis	**60% (27/45)**	**(44%, 74%)**
Overall (TN+TE)	**84% (210/250)**	**(79%, 88%)**

The DCV/SOF 12-week efficacy result will have to compare to this SOC. Considering the high SVR rate of the SOC, a NI type of comparison is warranted. The following will discuss the appropriate NI margin that can be used to assess this trial.

Because DCV and SOF both demonstrated effects in the previous trials, the regimen comparison is considered here instead of the component contribution for the NI margin.

A). Treatment naïve population:

- Using SOF/RBV 24 weeks vs. Placebo (assuming the SVR12 of Placebo is 10%).

  93% (98/105) vs. **10%** (constant)

  The NI margin M1=87%-10%=77%, which is very large.

- Using SOF/RBV 24 weeks vs. SOF monotherapy 12 weeks (in ELECTRON trial, HCV-3 only, cited from the stat review of Dr. Smith for IND (b) (4) SDN13):

  93% (98/105) vs. **57%** (4/7)

  The rate difference is 33% with an exact 95% CI of [-1%, 70%]. As a result, there is no NI margin. This M1 is very small due to the small sample size of SOF monotherapy.

- Using SOF/RBV 24 weeks vs. SOF/RBV 12 weeks by replacing 12 weeks of SOF monotherapy (now SOF is common to both the DCV/SOF and SOF/RBV arms and RBV is the putative placebo), the NI margin can be calculated below:

  In the Sofosbuvir label, the results of SVR from the FISSION study are shown below:

HCV-3, TN	**SOF/RBV x 12 weeks (n=256)**		**PR x 24 weeks (n=243)**	
	SVR12	**95% CI**	**SVR12**	**95% CI**
Treatment- Naïve	**56%** (102/183)	(48%, 63%)	**63%** (110/176)	(55%, **70%**)
No Cirrhosis	61% (89/145)	(53%, 69%)	71% (99/139)	(63%, 79%)
Cirrhosis	34% (13/38)	(20%, 51%)	30% (11/37)	(16%, 47%)

  93% (98/105) vs. **56%** (102/183)

  The rate difference is 38% with 95% CI [28%, 46%]. The M1 is 28% without any clinical consideration.

- Using SOF/RBV 24 weeks vs. PR 24 weeks by viewing PR 24 weeks as putative placebo, the NI margin can be calculated below:

  93% (98/105) vs. **63%** (110/176)

  The rate difference is 28% with 95% CI [17%, 37%]. The M1 is 17% here without any clinical consideration.

Consequently, an appropriate NI margin will be between 17% to 28% for the TN population without any clinical consideration.

B). Treatment experience population:

The SVR results for HCV-3 TE population can be found in the original FUSION study in the Sofosbuvir label.

HCV-3	**SOF/RBV x 12 weeks (n=64)**		**SOF/RBV x 16 weeks (n=63)**	
	SVR12	**95% CI**	**SVR12**	**95% CI**
Treatment-Exp	30% (19/64)	(19%, 42%)	62% (39/63)	(49%, 74%)
No Cirrhosis	37% (14/38)	(22%, 54%)	63% (25/40)	(46%, 77%)
Cirrhosis	19% (5/26)	(7%, 39%)	61% (14/23)	(39%, 80%)

- Using SOF/RBV 24 weeks vs. SOF/RBV 12 weeks by using this regimen as putative placebo, the NI margin can be calculated below:

  TE: 77% (112/145) vs. **30%** (19/64)

  The rate difference is 48% with 95% CI [34%, 60%]. The M1 is 34% here without any clinical consideration (i.e. clinical input that would be needed in order to determine M2).

C). Treatment naïve and Treatment experience population:

Then combine TN and TE together:

- Using SOF/RBV 24 weeks vs. SOF/RBV 12 weeks by using this regimen as putative placebo, the NI margin can be calculated below:

  TN: 93% (98/105) vs. **56%** (102/183)
  TE: 77% (112/145) vs. **30%** (19/64)

  With MH strata-adjustment, the rate difference is 42% with 95% CI [34%, 49%]. The M1 is 34% without any clinical consideration.

D). considering TN vs. TE and Cirrhosis status at baseline all together:

- Using SOF/RBV 24 weeks vs. SOF/RBV 12 weeks by using this regimen as putative placebo, the NI margin can be calculated below:

  TN w/ Cirr: 92% (12/13) vs. **34%** (13/38)
  TN w/o Cirr: 93% (86/92) vs. **61%** (89/145)
  TE w/ Cirr: 60% (27/45) vs. **19%** (5/26)
  TE w/o Cirr: 85% (85/100) vs. **37%** (14/38)

  With MH strata-adjustment, the rate difference is 40% with 95% CI [32%, 47%]. The M1 is 32% here without any clinical consideration.

Note:
- Some data are from different studies, and are used directly for NI margin calculation without any adjustment;
- NI margins presented here are M1 without any clinical consideration. The new regimen is DCV/SOF 12 weeks, which is only half of duration of the SOC (SOF/RBV 24 weeks) and without RBV.

In summary, depending on the selection of the placebo arm, the NI margin could be as low as 17% without any clinical consideration.

In NDA 206,843 resubmission, the SVR results from ALLY-3 are the following:

HCV-3	**DCV/SOF x 12 weeks (N=152)**	**95% CI**
Treatment- Naïve	90% (91/101)	**(83%,** 95%)
No Cirrhosis	98% (80/82)	(91%, 100%)
Cirrhosis	58% (11/19)	(34%, 80%)
Treatment-Exp	86% (44/51)	**(74%,** 94%)
No Cirrhosis	92% (35/38)	(79%, 98%)
Cirrhosis	69% (9/13)	(39%, 91%)

If comparing DCV/SOF 12 weeks vs. SOC (SOF/RBV 24 weeks) from VALENCE study, the results for TN and TE populations are the following:

TN: DCV/SOF -- SOF/RBV = 90% - 93% = - 3% with 95% CI of (-11%, 5%)

TE: DCV/SOF -- SOF/RBV = 86% - 77% = 9% with 95% CI of (-4%, 20%)

For the combination of (TN + TE) comparison:

Using the stratum-adjusted Mantel-Haenszel (MH) approach to adjust the strata effect of TN vs. TE, the result is the following:

(TN+TE): DCV/SOF -- SOF/RBV = 2% with 95% CI of (-5%, 7%)

Using the stratum-adjusted Mantel-Haenszel (MH) approach to adjust the strata effect of both TN vs. TE and Cirrhosis status at baseline, the result is the following:

(TN+TE): DCV/SOF -- SOF/RBV = 2% with 95% CI of (-4%, 9%)

The lower bound of rate difference ranges from -11% to -4%, and it is higher than -17% of the low NI margin generated above. It demonstrated that the new regimen (DCV/SOF 12 weeks) is non-inferior to the SOC (SOF/RBV 24 weeks).

Also, if comparing DCV/SOF 12 weeks vs. SOF/RBV 12 weeks, or PR 24 weeks from FISSION study, the results are the following:

TN: DCV/SOF 12 weeks -- SOF/RBV 12 weeks= 90%-56% = 34% with 95% CI of (24%, 43%)

TN: DCV/SOF 12 weeks – PR 24 weeks = 90%-63% = 28% with 95% CI of (18%, 36%)

DCV/SOF (TN+TE) 12 weeks – PR 24 weeks (TN) = 89%-63% = 26% with 95% CI of (17%, 35%)

Because the lower bounds of rate differences are above 0% what demonstrated the DCV contribution to DCV/SOF by comparing DCV/SOF 12 weeks against SOF/RBV 12 weeks. The DCV/SOF 12 weeks'

regimen is superior to SOF/RBV 12 week's regimen in TN population. It also demonstrated that DCV/SOF 12 week's regimen is superior to PR 24 week's regimen in TN population.

Sample Size:

There was no formal sample size calculation. The target sample sizes of 100 treatment-naive subjects and 50 treatment-experienced subjects provide 95% confidence that the observed SVR12 rate can be estimated to within 9.7% and 14.2% of the estimates respectively when the observed SVR12 rate is 75% or higher.

Populations for Analyses:

- **Enrolled subjects** are those who signed an informed consent form and were assigned a Patient Identification Number (PID)
- **Treated subjects** are enrolled subjects who received at least 1 dose of study therapy.

Results were presented by cohort (TN and TE) and overall for treated subjects. For binary efficacy endpoints, response rates and two-sided 95% CIs based on the normal approximation to the binomial distribution will be presented.

Analysis Windows

Day 1 is the first dose of active study therapy. The analysis windows are listed in Table 2 below.

Table 2 Analysis Windows for Phase 3 Study

Study Period Label		Visit Label	Visit Number	Target Day from Start of Study Period	Visit Window
PRE-TREAT		PRE-TREAT	1	1	< 1 day[a]
ON-TREAT		DAY 1	2	1	1 - 4 days
		WEEK 1	3	7	5 days - 11 days
		WEEK 2	4	14	12 days - 3 weeks
		WEEK 4	5	28	> 3 weeks - 5 weeks
		WEEK 6	6	42	> 5 - 7 weeks
		WEEK 8	7	56	> 7 - 10 weeks
		WEEK 12	8	84	> 10 - 14 weeks
		WEEK 12 EXT	9	140	> 14 weeks
FOLLOW-UP		F/U WEEK 4	10	21	> 1 - 8 weeks
		F/U WEEK 12	11	77	> 8 - 18 weeks
		F/U WEEK 24	12	161	> 18 - 30 weeks
		F/U WEEK 24 EXT	13	245	> 30 weeks

Source: copied from the Table 8.1-1 in the SAP for the study.

❖ **AI444258:**

AI444258 was an authorization for temporary use (ATU) study in France. Only efficacy results of the cirrhosis subgroup are mentioned in the subgroup analysis section.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

3.2.2.1 Disposition

Table 3 describes the subject disposition for the phase 3 study. Almost all treated subjects (99%) completed the designed 12-week treatment period except for one subject who became pregnant and discontinued study drug at week 8. The subject entered the follow-up period and achieved SVR12. The statistical reviewer was able to reproduce the applicant's disposition results for the study.

Table 3: Subjects Disposition for study AI444218 (Treated Subjects)

	TN	TE	Total
Treated:	101	51	152
Completed Treatment Period			
YES	100(99.0%)	51(100.0%)	151(99.3%)
NO	1(1.0%)	.(. %)	1(0.7%)
Reasons of NOT completed treatment			
PREGNANCY	1(1.0%)	.(. %)	1(0.7%)
Subject Continue in the Study			
YES	101(100.0%)	51(100.0%)	152(100.0%)

3.2.2.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics were generally comparable between TN and TE cohort. The percentage of males was slightly higher than females (59% male vs. 41% female). The mean age was approximately 52 years old with approximately 7% of the subjects age 65 and over. The mean BMI was 27 kg/m^2, and 32% of subjects had BMI $\leq$ 25 kg/m^2 at baseline. Twenty-one percent (21%) of subjects were cirrhotic at baseline, 40% of subjects had the IL28B CC genotype at baseline, and 9% of subjects had the NS5A Y93H polymorphism. The majority of subjects were white (90%). Most of subjects (96%) were from the US and 4% were from Puerto Rico. Please see Table 13 in the Appendix for details.

3.2.3 Statistical Methodologies

Ninety-five percent (95%) CIs were calculated for the SVR rates for each cohort separately within the study. Binary antiviral activity endpoints were assessed by the applicant using the treated population.

3.2.4 Results and Conclusions

3.2.4.1 Summary of Applicant's Results

In Study AI444218, SVR12 rates were 90% in TN subjects and 86% in TE subjects (Table 4). Of the 152 GT-3 subjects treated with DCV/SOF, 17 (11%) met the protocol-defined criteria for virologic failure by follow-up Week 12; this included 16 relapsers and one other on-treatment failure (AI444218-32-163) with HCV RNA > LLOQ at EOT (Table 5).

SVR12 with DCV/SOF was higher in non-cirrhotic subjects than in cirrhotic subjects (96% vs 63% overall; 97% vs 58%, respectively, in TN subjects and 94% vs 69%, respectively, in TE subjects). SVR12 in subjects with baseline NS5A-Y93H were lower than SVR in subjects without this baseline polymorphism [54% (7/13) vs 92% (123/134)]. (Please see Table 6.)

Note that there were 11 subjects whose baseline cirrhosis statuses were not reported in Table 6. These subjects are treated as no cirrhosis at baseline in the reviewer's analyses. Also there were 5 subjects without NS5A-Y93 polymorphism information in Table 6. These subjects were treated as no NS5A-Y93H polymorphism at baseline in the reviewer's analysis. The SVR12 rates were similar either including or excluding these subjects in the analyses.

Mean HCV RNA changes from baseline in Study AI444218 for treated subjects measured in log10 IU/mL are shown in Figure 2 below.

Table 4: Applicant's SVR12 Results for Study AI444218 (Treated Subjects)

Table 7.1-1: Key HCV RNA Endpoints: Treated Subjects

Category Endpoint	Naive N=101	Experienced N=51
PRIMARY ENDPOINT		
SUSTAINED VIROLOGIC RESPONSE AT FOLLOW-UP WEEK 12		
RESPONDER/EVALUABLE (%)	91/101 (90.1)	44/51 (86.3)
95% CI	(82.5, 95.1)	(73.7, 94.3)
OTHER KEY EFFICACY ENDPOINTS		
RAPID VIROLOGIC RESPONSE (RVR)		
RESPONDER/EVALUABLE (%)	64/101 (63.4)	37/51 (72.5)
95% CI	(53.2, 72.7)	(58.3, 84.1)
EXTENDED RAPID VIROLOGIC RESPONSE (ERVR)		
RESPONDER/EVALUABLE (%)	63/101 (62.4)	37/51 (72.5)
95% CI	(52.2, 71.8)	(58.3, 84.1)
COMPLETE EARLY VIROLOGIC RESPONSE (CEVR)		
RESPONDER/EVALUABLE (%)	99/101 (98.0)	51/51 (100.0)
95% CI	(93.0, 99.8)	(93.0, 100.0)
END OF TREATMENT RESPONSE (HCV RNA < LLOQ TND AT EOT)		
RESPONDER/EVALUABLE (%)	100/101 (99.0)	51/51 (100.0)
95% CI	(94.6, 100.0)	(93.0, 100.0)

HCV RNA measurements are excluded after the start of non-study anti-HCV medication on-treatment or during follow-up.
Primary endpoint SVR12 is based on Next Value Carried Backwards approach.

Source: study AI444218 CSR, Table 7.1-1.

Table 5: Applicant's SVR12 Outcomes for Study AI444218 (Treated Subjects)

Table 7.3.2-1: SVR12 Outcomes: Treated Subjects

Number of Subjects (%)	Naive N=101	Experienced N=51	Total N=152
RESPONDER (SVR12)	91/101 (90.1)	44/ 51 (86.3)	135/152 (88.8)
NON-RESPONDER (NON-SVR12)	10/101 (9.9)	7/ 51 (13.7)	17/152 (11.2)
NON-RESPONDER WITH HCV RNA < LLOQ TND AT EOT	9/101 (8.9)	7/ 51 (13.7)	16/152 (10.5)
RELAPSER	9/100 (9.0)	7/ 51 (13.7)	16/151 (10.6)
OTHER NON-RESPONDER [1]	0	0	0
ON-TREATMENT FAILURE	1/101 (1.0)	0	1/152 (0.7)
VIROLOGIC BREAKTHROUGH	0	0	0
OTHER ON-TREATMENT FAILURE [2]	1/101 (1.0)	0	1/152 (0.7)
NO HCV RNA ON TREATMENT	0	0	0

Source: study AI444218 CSR, Table 7.3.2-1.

Table 6: Applicant's SVR12 Subgroup Analyses by Baseline Cirrhosis and Baseline NS5A-Y93H Polymorphisms for Study AI444218 (Treated Subjects)

Table 7.3.3.1-1: SVR12 by Baseline Cirrhosis, Fibrosis, and Platelet Count: Treated Subjects

Category Subgroup	Naive N=101	Experienced N=51	Total N=152
BASELINE CIRRHOSIS STATUS			
ABSENT			
RESPONDERS/TREATED (%)	73/75 (97.3)	32/34 (94.1)	105/109 (96.3)
95% CI	(90.7, 99.7)	(80.3, 99.3)	(90.9, 99.0)
PRESENT			
RESPONDERS/TREATED (%)	11/19 (57.9)	9/13 (69.2)	20/32 (62.5)
95% CI	(33.5, 79.7)	(38.6, 90.9)	(43.7, 78.9)
NOT REPORTED			
RESPONDERS/TREATED (%)	7/7 (100.0)	3/4 (75.0)	10/11 (90.9)
95% CI	(59.0, 100.0)	(19.4, 99.4)	(58.7, 99.8)
NS5A-Y93 RESISTANCE			
YES			
RESPONDERS/TREATED (%)	2/6 (33.3)	5/7 (71.4)	7/13 (53.8)
95% CI	(4.3, 77.7)	(29.0, 96.3)	(25.1, 80.8)
NO			
RESPONDERS/TREATED (%)	85/91 (93.4)	38/43 (88.4)	123/134 (91.8)
95% CI	(86.2, 97.5)	(74.9, 96.1)	(85.8, 95.8)
NOT REPORTED			
RESPONDERS/TREATED (%)	4/4 (100.0)	1/1 (100.0)	5/5 (100.0)
95% CI	(39.8, 100.0)	(2.5, 100.0)	(47.8, 100.0)

Source: study AI444218 CSR, Table 7.3.3.1-1 and 7.3.3.2-2

Figure 7.3.1-1: Mean (95% CI) Change from Baseline in log_{10} HCV RNA: Treat Subjects

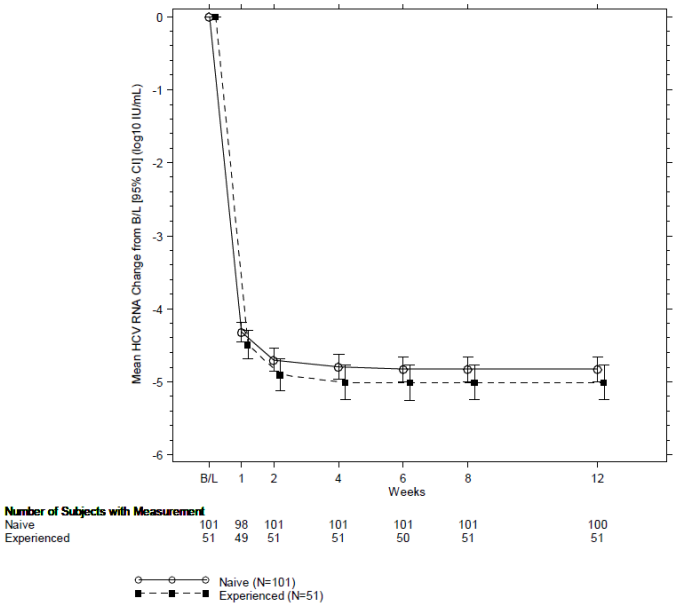


Figure 2: Mean HCV RNA Change from Baseline for Study AI444218 **(Observed Values for Treated Subjects)** Source: study AI444218 CSR, Figure 7.3.1-1.

3.2.4.2 Study AI444218 Primary Efficacy Results

- **Primary Efficacy Analysis Results**

The pre-specified primary efficacy endpoint for this study was SVR12. The statistical reviewer obtained the same SVR12 (<LOQ) results as the applicant. Overall, the SVR12 rate was 89% (Table 7 and Figure 3). The SVR12 rates in both cohorts were 90% in TN subjects and 86% in TE subjects, while relapse rates were 9% in TN subjects and 14% in TE subjects. One subject in the TN cohort had on-treatment failure other than virologic relapse.

Table 7: SVR12 and Virologic Failure Rates for Study AI444218 **(Treated Subjects)**

Cohort	TN N=101	TE N=51	Total N=152
Responder (SVR12)	**91(90.1%)**	**44(86.3%)**	**135(88.8%)**
95% CI	**(82.5%, 95.1%)**	**(73.7%, 94.3%)**	**(82.7%, 93.3%)**
Reasons of Virologic Failure	10(9.9%)	7(13.7%)	17(11.2%)
Other on-Treatment Failure	1(11.5%)	0(0%)	1(0.7%)
RELAPSE*	9	7	16
Relapse rate**	**9/100(9.0%)**	**7/51(13.7%)**	**16/151(10.6%)**

*: Notes that there was no % for the relapse row. Please see the last row for the relapse rates.
**: Relapse rates were calculated with a denominator of subjects with undetectable HCV RNA at the end of treatment (EOT).

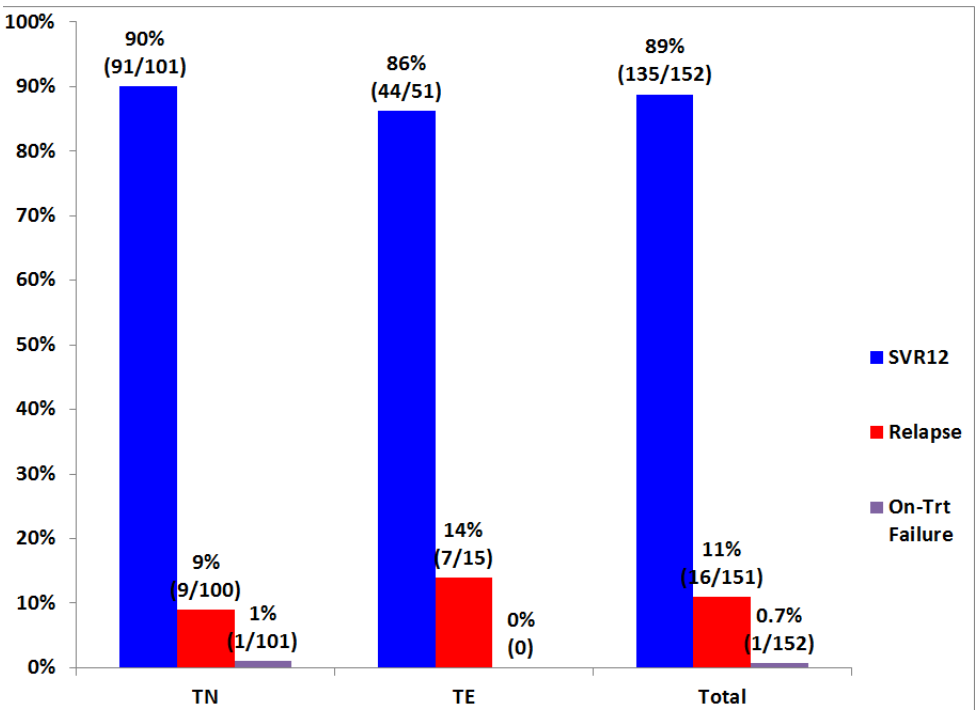


Figure 3: Study AI444218 SVR12, Relapse, On-Treatment Failure (Treated Subjects)

- **Secondary Efficacy Analysis Results**

Results of some secondary efficacy endpoints are listed in Table 8 below. These results are the same as the CSR reported.

Table 8: Secondary Efficacy Results for Study AI444218 (Treated Subjects)

Treated Subjects Parameters analyzed	Treatment-Naïve (N=101) n (%) (95% CI)*	Treatment-Experienced (N=51) n (%) (95% CI)	Total (N=152) n (%) (95% CI)
SVR12	**91 (90.1)** **(82.5, 95.1)**	**44 (86.3)** **(73.7, 94.3)**	**135 (88.8)** **(82.7, 93.3)**
EOT	100 (99.0) (94.6, 100.0)	51 (100.0) (93.0, 100.0)	151 (99.3) (96.4, 100.0)
Relapse rate	**9/100 (9.0)**	**7/51 (13.7)**	**16/151(10.6%)**
RVR at WK 4	64 (63.4) (53.2, 72.7)	37 (72.5) (58.3, 84.1)	101 (66.4) (58.3, 73.9)
cEVR at WK 12	99 (98.0) (93.0, 99.8)	51 (100.0) (93.0, 100.0)	150 (98.7) (95.3, 99.8)
eRVR at WK 4 & 12	63 (62.4) (52.2, 71.8)	37 (72.5) (58.3, 84.1)	100 (65.8) (57.7, 73.3)

*: 95% CI is the Clopper-Pearson CI from SAS StatXact PROCs' Exact method.

3.3 Evaluation of Safety

See the clinical review for the evaluation of safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Note that subgroup analyses need to be interpreted with caution because they were post-hoc (with the exception of gender, race, age and geographic region), with no multiple comparison adjustments, had small sample sizes within subgroups, and lacked active-control. In addition, there was only one study conducted and thus, there is no replication of the findings.

For HCV-3 subjects, the baseline cirrhosis status and NS5A polymorphisms of Y93H had a significant impact on the SVR12 efficacy results. No other baseline factors had statistically significant effects on the SVR12 efficacy results.

4.1 Baseline Cirrhosis Status

There were 11 subjects whose cirrhosis statuses at baseline were not reported in the analysis datasets submitted. These 11 subjects are treated as having no cirrhosis at baseline in the label.

The SVR12 rate for subjects with cirrhosis at baseline was only 63% (20/32) with 95% CI of (44%, 79%) compared to 96% (115/120) with 95% CI of (91%, 99%) of the SVR12 for subjects without cirrhosis at baseline (Table 9). Given the small sample sizes, the point estimate may be unstable. Given the confidence intervals for cirrhotics and non-cirrhotics did not overlap, this finding may suggest that the DCV/SOF 12 week's regimen may not be the optimal regimen for subjects with cirrhosis at baseline.

Table 9: Subgroup Analysis of SVR12 for Study AI447026 by Baseline Cirrhosis Status and NS5A-Y93H Polymorphism (Treated Subjects)

Treatment Outcomes	TN (N=101)	TE (N=51)	Total (N=152)
SVR			
All	90% (91/101)	86% (44/51)	89% (135/152)
No cirrhosis[a]	98% (80/82) (91%, 100%)	92% (35/38) (79%, 98%)	96% (115/120) (91%, 99%)
With cirrhosis	58% (11/19) (34%, 80%)	69% (9/13) (39%, 91%)	63% (20/32) (44%, 79%)
No cirrhosis[b]	97% (73/75) (91%, 100%)	94% (32/34) (80%, 99%)	96% (105/109) (91%, 99%)

[a:] The 11 subjects whose cirrhosis statuses at baseline were not reported in the analysis datasets submitted were included in the analysis.
[b:] The 11 subjects whose cirrhosis statuses at baseline were not reported in the analysis datasets submitted were excluded from the analysis. These were the results that the applicant presented in CSR.

During the latter portion of the review cycle (April 20, 2015), the applicant submitted two datasets (DM2 and VL2), which contained 44 HCV-3 infected subjects with cirrhosis at baseline from AI444258. The purpose of this additional submission was to determine if the data from this authorization for temporary use (ATU) study in France could be used to identify the optimal regimen for subjects with cirrhosis at baseline.

Because only two derived datasets were submitted without any raw datasets, only simple efficacy summaries are presented here by using the datasets submitted without any verification from raw datasets.

All of these 44 subjects had cirrhosis at baseline and none of them had a liver transplant. The regimens used among these 44 subjects were different, DCV/SOF 12 or 24 weeks, or DCV/SOF+RBV 12 or 24 weeks (Table 10). If the duration of treatment was less than 14 weeks, the applicant assigned patients to the 12 week regimen. If the duration of treatment was greater than or equal to 14 weeks, the applicant assigned patients to the 24 week regimen. There were 8 subjects who missed their treatment ending date, and because of this we do not know the duration of their treatment. Please see Figure 5 in the Appendix for the details in terms of treatment duration for these 44 subjects.

Because the sample size under each regimen was very small, we concluded that the findings were inconclusive. As a result, the optimal regimen for subjects with cirrhosis at baseline is unknown even though the longer duration, say 24 weeks of DCV/SOF, or additional component, say RBV, could potentially improve the SVR12 rate. Please see the clinical review for a discussion on this.

Table 10: SVR12 Summary by Regimen for 44 subjects who had Cirrhosis at Baseline from Study AI444258

	DCV/SOF			DCV/SOF+RBV			Total
	DCV/SOF	DCV/SOF 12 wks.	DCV/SOF 24 wks.	DCV/SOF +RBV	DCV/SOF +RBV 12 wks.	DCV/SOF +RBV 24 wks.	
SVR12	3/5 (60.0%)	11/14 (78.6%)	13/15 (86.7%)	2/3 (66.7%)	2/2 (100%)	5/5 (100%)	36/44 (81.8%)
95% CI	(14.7%, 94.7%)	(49.2%, 95.3%)	(59.5%, 98.3%)	(9.4%, 99.2%)	(15.8%, 100%)	(47.8%, 100%)	(67.3%, 91.8%)

4.2 Baseline NS5A Polymorphism Y93H

Out of 152 subjects enrolled in the study, 148 subjects had NS5A sequence information at the baseline. Among these 148 subjects, 13 subjects had NS5A-Y93H polymorphism at baseline. There were 4 subjects who did not have NS5A sequence information at baseline according to the microbiological reviewer, and they were included in the no NS5A-Y93H polymorphism in the analysis here.

Given the small sample size here, the SVR12 rate for subjects who had the NS5A-Y93H polymorphism was 54% overall, which was much lower than the SVR12 rate of 92% among

subjects who did not have the NS5A-Y93H polymorphism at baseline. The similar trend exists in both TN and TE cohorts (Table 11).

Table 11: Subgroup Analysis of SVR12 for Study AI447026 by Baseline NS5A-Y93H Polymorphism (Treated Subjects)

Treatment Outcomes	TN (N=101)	TE (N=51)	Total (N=152)
SVR			
All	90% (91/101)	86% (44/51)	89% (135/152)
No Y93H Polymorphism[a]	94% (89/95) (87%, 98%)	89% (39/44) (75%, 96%)	92% (128/139) (86%, 96%)
With Y93H Polymorphism	33% (2/6) (4%, 78%)	71% (5/7) (29%, 96%)	54% (7/13) (25%, 81%)

[a:] According to the microbiological reviewer that there were 4 subjects who did not have NS5A sequence information. These 4 subjects were treated as no Y93H polymorphism here. In CSR, there were 5 subjects instead of 4 because 1 subject was identified after CSR. Please see microbiological review for more details. In this analysis, these

Although the sample sizes were too small to make any statistical conclusions, the observed SVR12 rate (25%) for subjects with both Cirrhosis and NS5A-Y93H polymorphism at baseline was even lower than the SVR12 (68%) rate for subjects who only had cirrhosis at baseline, or the SVR12 (67%) rate for subjects who only had NS5A-Y93H polymorphism at baseline (Table 12). Please see the microbiology review for more information in terms of baseline polymorphism.

Table 12: Subgroup Analysis of SVR12 for Study AI447026 by Baseline Cirrhosis and NS5A-Y93H Polymorphism (Treated Subjects)

Study Population	SVR12 with Y93H	SVR12 without Y93H[b]
All Subjects	54% (7/13)	92% (128/139)
No Cirrhosis[a]	67% (6/9)	98% (109/111)
With Cirrhosis	25% (1/4)	68% (19/28)

[a]: Including 11 subjects with missing or inconclusive cirrhosis status
[b]: Including 4 subjects who did not have NS5A sequence information

4.3 Gender, Race, Age, and Geographic Region

For Study AI444218, separate subgroup analyses were conducted on the all treated subject set, subjects without NS5A Y93H polymorphisms at baseline and subjects without cirrhosis at baseline.

Among the 152 treated subjects, there were no statistically significant gender differences in SVR rates, but there was a slightly higher SVR12 rate for subjects who were less than age 65 (90%) comparing to subjects who were 65 years of age and older (70%). However the sample sizes for subjects who were 65 years of age and older were very small. Because 90% of subjects were

white and 88% of subjects were from US, there is no enough data to access the impact of race and geographic region on the SVR12 rate. Please see Table 16 in the Appendix for details.

Among 139 subjects without Y93H polymorphisms at baseline, the trends for gender, race, age and geographic region were similar to the overall population. Please see Table 15 in the Appendix for details.

Among 120 subjects without cirrhosis at baseline, the trends for gender, race, age and geographic region were similar to the overall population. Please see Table 14 in the Appendix for details.

4.4 Other Special/Subgroup Populations

The subgroup analysis for other baseline covariates were conducted on the all treated subject set, on subjects without Y93H polymorphisms at baseline and on subjects without cirrhosis at baseline.

No other baseline factors, such as HCV RNA viral load at baseline, IL28B, or prior treatment, had a strong impact on the SVR12 rates. Please see Table 14, 15, and 16 in the Appendix for details.

The following forest plot shows that only cirrhosis status at baseline and NS5A-Y93H polymorphism had a significant impact on the SVR12 rates.

Figure 7.3.4.1-1: Forest Plot of Odds Ratios for Baseline Predictors

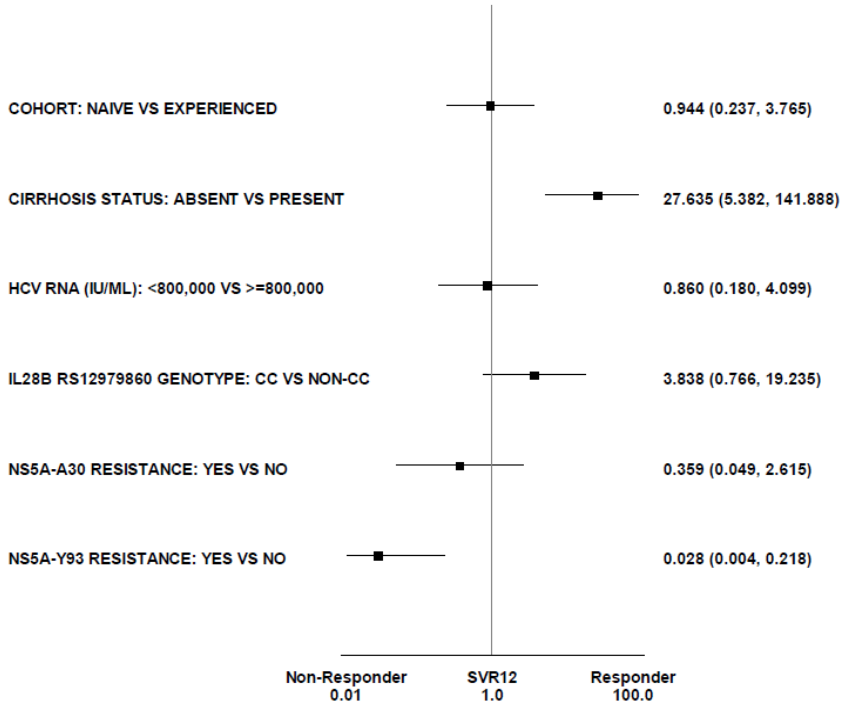


Figure 4: Forest Plot of Odds Ratios for Baseline Predictors of SVR12 for Study AI444218 (Treated Subjects) Source: copied from CSR Figure 7.3.4.1-1.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were two statistical issues identified during the review, the NI margin used to access the efficacy and the viral load data for 10 subjects who enrolled in the PK sub-study.

For the first issue, the protocol did not define the criteria for efficacy claim. The current Standard-of-Care (SOC) for HCV-3 infected subjects is SOF/RBV for 24 weeks. During the review the statistical reviewer calculated the potential non-inferiority (NI) margins based on the historical data. Depending on the selection of the placebo arm, the NI margin could be as low as -17% without any clinical consideration. The SVR12 rate difference between the new regimen (DCV/SOF 12 weeks) and SOC (SOF/RBV 24 weeks) is about 3% with 95% CI of (-4%, 9%). The lower bound of 95% CI is -4% which is less than the potential NI margin of -17%. Thus, if this -17% NI margin is used, the single study demonstrates that DCV/SOF12 weeks was non-inferior to SOF/RBV 24 weeks for HCV-3 infected population even though the optimal regimen for subjects who had cirrhosis at baseline is still undetermined.

For the percentage of subjects having baseline HCV RNA viral load greater or equal to 800,000 IU/mL (the stat reviewer got 76% while the applicant got 71%), the applicant confirmed the results generated by the statistical reviewer and it is reflected in the label.

Only data from one phase 3 Study AI444218 was submitted in the resubmission to support the use of DCV plus SOF for the treatment of HCV genotype 3 infected patients.

The overall SVR12 was 89% (95% CI of [83%, 93%]). The SVR12 rate for subjects with cirrhosis at baseline was 63% (95% CI of [44%, 79%]), and 96% (95% CI of [91%, 99%]) for subjects without cirrhosis at baseline. Given the sample sizes in the trial, subjects with cirrhosis at baseline had significantly lower SVR12 rate than subjects without cirrhosis at baseline, which suggested that the DCV/SOF 12 week's regimen may not be the optimal regimen for subjects with cirrhosis at baseline.

The SVR12 rate for subjects with Y93H NS5A baseline polymorphism was 54% (95% CI of [25%, 81%]), and 92% (95% CI of [86%, 96%]) for subjects without Y93H NS5A baseline polymorphism. Given the sample sizes in the trial, the Y93H NS5A baseline polymorphism had a significant impact on the SVR12 rate. The prevalence of Y93H NS5A baseline polymorphism is about 10% in HCV-3 infected population according to the microbiological review.

The applicant also submitted two interim reports from Early Access Program (EAP) from two studies, AI444258 (France, ATU cohort) and AI444237 (UK), without any data. These two interim reports are not discussed in this review. On April 30, 2015, the applicant submitted two datasets, DM2 and VL2, which contain 44 HCV-3 infected subjects with cirrhosis at baseline from the EAP program. Because this data is limited the findings were inconclusive to determine the appropriate regimen recommendation for subjects with cirrhosis at baseline.

5.2 Conclusions and Recommendations

In conclusion, Study AI444218 demonstrated the efficacy of DCV/SOF in HCV-3 infected subjects with the exception of subjects with cirrhosis and Y93H NS5A polymorphisms at baseline. These subjects had significantly lower SVR12 rates than other subjects.

5.3 Labeling Recommendations

In the section 14 of the label, those 11 subjects who missed cirrhosis status at baseline are included in the analysis as having no cirrhosis at baseline.

According to the microbiology reviewer, those 4 subjects who missed NS5A sequence information are excluded from the NS5A-Y93H subgroup analysis table. The final table in the label resembles the table below.

Subgroup Analysis of SVR12 for Study AI447026 by Baseline Cirrhosis and NS5A-Y93H Polymorphism (Treated Subjects)

Study Population	**SVR12 with Y93H**	**SVR12 without Y93H[b]**
All Subjects	54% (7/13)	92% (124/135)
No Cirrhosis[a]	67% (6/9)	98% (105/107)
With Cirrhosis	25% (1/4)	68% (19/28)

[a]: Including 11 subjects with missing or inconclusive cirrhosis status
[b]: Excluding 4 subjects who did not have NS5A sequence information

Please see the clinical review for details in terms of dosage and administration section of the label.

APPENDICES

Table 13: Demographics and Baseline Characteristics for Study AI444218 (Treated Subjects)

Subgroup	TN	TE	Total
Treated (ITT)			
N	101	51	152
Gender			
FEMALE	43(42.6%)	19(37.3%)	62(40.8%)
MALE	58(57.4%)	32(62.7%)	90(59.2%)
Race			
AMERICAN INDIAN/ALASKA NATIVE	.(. %)	2(3.9%)	2(1.3%)
ASIAN INDIAN	3(3.0%)	1(2.0%)	4(2.6%)
ASIAN OTHER	2(2.0%)	1(2.0%)	3(2.0%)
BLACK/AFRICAN AMERICAN	4(4.0%)	2(3.9%)	6(3.9%)
WHITE	92(91.1%)	45(88.2%)	137(90.1%)
Ethnicity			
HISPANIC/LATINO	17(16.8%)	8(15.7%)	25(16.4%)
NOT HISPANIC/LATINO	84(83.2%)	43(84.3%)	127(83.6%)
Age (Year)			
Mean (SE)	50 (1.1)	56 (0.9)	52 (0.8)
Median	53	58	55
Range	(24, 67)	(40, 73)	(24, 73)
Standard Deviation	10.7	6.6	9.9
Age Category			
< 65	95(94.1%)	47(92.2%)	142(93.4%)
>= 65	6(5.9%)	4(7.8%)	10(6.6%)
Baseline HCV RNA log10 (IU/mL)			
Mean (SE)	6.28 (0.082)	6.55 (0.094)	6.37 (0.064)
Median	6.37	6.61	6.49
Range	(3.40, 7.52)	(4.67, 7.52)	(3.40, 7.52)
Standard Deviation	0.827	0.669	0.786
Baseline HCV RNA Category 1 (IU/mL)			
<800,000	28(27.7%)	9(17.6%)	37(24.3%)
>=800,000	73(72.3%)	42(82.4%)	115(75.7%)
Baseline HCV RNA Category 2 (IU/mL)			
<600,000	23(22.8%)	8(15.7%)	31(20.4%)
>=600,000	78(77.2%)	43(84.3%)	121(79.6%)
Baseline HCV RNA Category 3 (IU/mL)			
<2,000K	45(44.6%)	13(25.5%)	58(38.2%)
>=2,000K, <4,000K	18(17.8%)	12(23.5%)	30(19.7%)
>=4,000K, <6,000K	10(9.9%)	3(5.9%)	13(8.6%)
>=6,000K, <8,000K	5(5.0%)	4(7.8%)	9(5.9%)
>=8,000K, <10,000	3(3.0%)	2(3.9%)	5(3.3%)
>=10,000K, <12,00	3(3.0%)	5(9.8%)	8(5.3%)

>=12,000K	17(16.8%)	12(23.5%)	29(19.1%)
Baseline Genotype			
3	94(93.1%)	49(96.1%)	143(94.1%)
3A	7(6.9%)	2(3.9%)	9(5.9%)
Baseline BMI (kg/m^2)			
Mean (SE)	26.55 (0.423)	28.22 (0.527)	27.11 (0.337)
Median	26.20	28.50	27.15
Range	(18.30, 36.80)	(18.50, 35.30)	(18.30, 36.80)
Standard Deviation	4.253	3.767	4.160
Baseline BMI Category (kg/m2)			
<=25	38(37.6%)	11(21.6%)	49(32.2%)
25<=, <30	42(41.6%)	22(43.1%)	64(42.1%)
>=30	21(20.8%)	18(35.3%)	39(25.7%)
Baseline Cirrhosis Status			
NO	75(74.3%)	34(66.7%)	109(71.7%)
YES	19(18.8%)	13(25.5%)	32(21.1%)
Not Reported	7(6.9%)	4(7.8%)	11(7.2%)
IL28B genotype			
CC	40(39.6%)	20(39.2%)	60(39.5%)
CT	47(46.5%)	21(41.2%)	68(44.7%)
TT	14(13.9%)	10(19.6%)	24(15.8%)
Prior Response Category			
BREAKTHROUGH		2(3.9%)	
HCV RNA NEVER UNDETECTABLE		2(3.9%)	
INDETERMINATE		1(2.0%)	
INTOLERANCE		6(11.8%)	
NULL RESPONDER		7(13.7%)	
PARTIAL RESPONDER		2(3.9%)	
RELAPSER		31(60.8%)	
Prior Treatment			
INTERFERON		4(7.8%)	
INTERFERON/RIBAVIRIN		38(74.5%)	
OTHER		2(3.9%)	
SOFOSBUVIR/RIBAVIRIN		7(13.7%)	
Y93H Mutation			
N	95(94.1%)	44(86.3%)	139(91.4%)
Y	6(5.9%)	7(13.7%)	13(8.6%)
Sub-Cohort Classification			
F0	35(35.7%)	10(19.6%)	45(30.2%)
F1	22(22.4%)	11(21.6%)	33(22.1%)
F2	5(5.1%)	9(17.6%)	14(9.4%)
F3	14(14.3%)	13(25.5%)	27(18.1%)
F4	22(22.4%)	8(15.7%)	30(20.1%)
Country			
PRICO	5(5.0%)	1(2.0%)	6(3.9%)
USA	96(95.0%)	50(98.0%)	146(96.1%)

Region			
NORTH AMERICA	101(100.0%)	51(100.0%)	152(100.0%)

Table 14: Subgroup Analyses of SVR12 for Study AI444218 (120 Subjects without Cirrhosis at Baseline)

Efficacy Parameter	TN	TE	Total
120 Subjects who did not have cirrhosis at baseline			
N	80/ 82(97.6)	35/ 38(92.1)	115/120(95.8)
Gender			
FEMALE	36 / 38 (94.7)	16 / 16 (100)	52 / 54 (96.3)
MALE	44 / 44 (100)	19 / 22 (86.4)	63 / 66 (95.5)
Race			
AMERICAN INDIAN	. / . (.)	1 / 1 (100)	1 / 1 (100)
ASIAN INDIAN	3 / 3 (100)	1 / 1 (100)	4 / 4 (100)
ASIAN OTHER	2 / 2 (100)	1 / 1 (100)	3 / 3 (100)
BLACK/AFRICAN AMERICAN	4 / 4 (100)	2 / 2 (100)	6 / 6 (100)
WHITE	71 / 73 (97.3)	30 / 33 (90.9)	101 /106 (95.3)
Ethnicity			
HISPANIC/LATINO	14 / 14 (100)	5 / 5 (100)	19 / 19 (100)
NOT HISPANIC/LATINO	66 / 68 (97.1)	30 / 33 (90.9)	96 /101 (95.0)
Age Group			
< 65	77 / 79 (97.5)	33 / 36 (91.7)	110 /115 (95.7)
>= 65	3 / 3 (100)	2 / 2 (100)	5 / 5 (100)
Median Age Split			
<52	39 / 39 (100)	9 / 9 (100)	48 / 48 (100)
>=52	41 / 43 (95.3)	26 / 29 (89.7)	67 / 72 (93.1)
HCV RNA BSL <600K			
<600,000	22 / 22 (100)	7 / 7 (100)	29 / 29 (100)
>=600,000	58 / 60 (96.7)	28 / 31 (90.3)	86 / 91 (94.5)
HCV RNA BSL <800K			
<800,000	26 / 26 (100)	8 / 8 (100)	34 / 34 (100)
>=800,000	54 / 56 (96.4)	27 / 30 (90.0)	81 / 86 (94.2)
BMI category			
<=25	31 / 32 (96.9)	11 / 11 (100)	42 / 43 (97.7)
25<=, <30	34 / 34 (100)	15 / 16 (93.8)	49 / 50 (98.0)
>=30	15 / 16 (93.8)	9 / 11 (81.8)	24 / 27 (88.9)
Y93H Mutation			
N	79 / 79 (100)	30 / 32 (93.8)	109 /111 (98.2)
Y	1 / 3 (33.3)	5 / 6 (83.3)	6 / 9 (66.7)
IL28B Genotype			

CC	31 / 32 (96.9)	15 / 15 (100)	46 / 47 (97.9)
CT	37 / 38 (97.4)	13 / 16 (81.3)	50 / 54 (92.6)
TT	12 / 12 (100)	7 / 7 (100)	19 / 19 (100)
Prior Response Category			
BREAKTHROUGH		1 / 1 (100)	
INDETERMINATE		1 / 1 (100)	
INTOLERANCE		6 / 6 (100)	
NULL RESPONDER		7 / 7 (100)	
PARTIAL RESPONDER		1 / 1 (100)	
RELAPSER		19 / 22 (86.4)	
Country			
PRICO	4 / 4 (100)	1 / 1 (100)	5 / 5 (100)
USA	76 / 78 (97.4)	34 / 37 (91.9)	110 /115 (95.7)
Prior Treatment			
INTERFERON		4 / 4 (100)	
INTERFERON/RIBA		25 / 27 (92.6)	
SOFOSBUVIR/RIBA		4 / 5 (80.0)	
OTHER		2 / 2 (100)	
Fibrosis Score Category -- 1			
F0 - F2	60 / 60 (100)	27 / 27 (100)	87 / 87 (100)
F3 - F4	17 / 19 (89.5)	8 / 11 (72.7)	25 / 30 (83.3)
missing	3 / 3 (100)	. / . (.)	3 / 3 (100)
Fibrosis Score Category -- 2			
F0 - F3	69 / 70 (98.6)	32 / 34 (94.1)	101 /104 (97.1)
F4	8 / 9 (88.9)	3 / 4 (75.0)	11 / 13 (84.6)
missing	3 / 3 (100)	. / . (.)	3 / 3 (100)

Table 15: Subgroup Analyses of SVR12 for Study AI444218 (139 Subjects without Baseline Y93H Polymorphism)

Efficacy Parameter	TN	TE	Total
139 Subjects who had baseline polymorphism information but not Y93H			
N	89/ 95(93.7)	39/ 44(88.6)	128/139(92.1)
Gender			
FEMALE	37 / 38 (97.4)	14 / 14 (100)	51 / 52 (98.1)
MALE	52 / 57 (91.2)	25 / 30 (83.3)	77 / 87 (88.5)
Race			
AMERICAN INDIAN	. / . (.)	2 / 2 (100)	2 / 2 (100)
ASIAN INDIAN	3 / 3 (100)	1 / 1 (100)	4 / 4 (100)
ASIAN OTHER	2 / 2 (100)	1 / 1 (100)	3 / 3 (100)
BLACK/AFRICAN AMERICAN	4 / 4 (100)	2 / 2 (100)	6 / 6 (100)
WHITE	80 / 86 (93.0)	33 / 38 (86.8)	113 /124 (91.1)

Ethnicity			
HISPANIC/LATINO	15 / 17 (88.2)	7 / 7 (100)	22 / 24 (91.7)
NOT HISPANIC/LATINO	74 / 78 (94.9)	32 / 37 (86.5)	106 /115 (92.2)
Age Group			
< 65	86 / 90 (95.6)	35 / 40 (87.5)	121 /130 (93.1)
>= 65	3 / 5 (60.0)	4 / 4 (100)	7 / 9 (77.8)
Median Age Split			
<52	40 / 41 (97.6)	10 / 10 (100)	50 / 51 (98.0)
>=52	49 / 54 (90.7)	29 / 34 (85.3)	78 / 88 (88.6)
HCV RNA BSL <600K			
<600,000	22 / 23 (95.7)	7 / 7 (100)	29 / 30 (96.7)
>=600,000	67 / 72 (93.1)	32 / 37 (86.5)	99 /109 (90.8)
HCV RNA BSL <800K			
<800,000	26 / 28 (92.9)	8 / 8 (100)	34 / 36 (94.4)
>=800,000	63 / 67 (94.0)	31 / 36 (86.1)	94 /103 (91.3)
BMI category			
<=25	34 / 35 (97.1)	10 / 10 (100)	44 / 45 (97.8)
25<=, <30	36 / 41 (87.8)	15 / 17 (88.2)	51 / 58 (87.9)
>=30	19 / 19 (100)	14 / 17 (82.4)	33 / 36 (91.7)
Baseline Cirrhosis Category			
NO	72 / 72 (100)	28 / 29 (96.6)	100 /101 (99.0)
YES	10 / 16 (62.5)	9 / 12 (75.0)	19 / 28 (67.9)
No Reported	7 / 7 (100)	2 / 3 (66.7)	9 / 10 (90.0)
Fibrosis Score Category -- 1			
F0 - F2	60 / 60 (100)	25 / 26 (96.2)	85 / 86 (98.8)
F3 - F4	26 / 32 (81.3)	14 / 18 (77.8)	40 / 50 (80.0)
missing	3 / 3 (100)	. / . (.)	3 / 3 (100)
Fibrosis Score Category -- 2			
F0 - F3	71 / 72 (98.6)	34 / 36 (94.4)	105 /108 (97.2)
F4	15 / 20 (75.0)	5 / 8 (62.5)	20 / 28 (71.4)
missing	3 / 3 (100)	. / . (.)	3 / 3 (100)
IL28B Genotype			
CC	35 / 37 (94.6)	15 / 15 (100)	50 / 52 (96.2)
CT	41 / 44 (93.2)	14 / 19 (73.7)	55 / 63 (87.3)
TT	13 / 14 (92.9)	10 / 10 (100)	23 / 24 (95.8)
Prior Response Category			
BREAKTHROUGH		2 / 2 (100)	
HCV RNA NEVER UNDETECTABLE		1 / 2 (50.0)	
INDETERMINATE		1 / 1 (100)	
INTOLERANCE		6 / 6 (100)	
NULL RESPONDER		7 / 7 (100)	
PARTIAL RESPONDER		2 / 2 (100)	
RELAPSER		20 / 24 (83.3)	

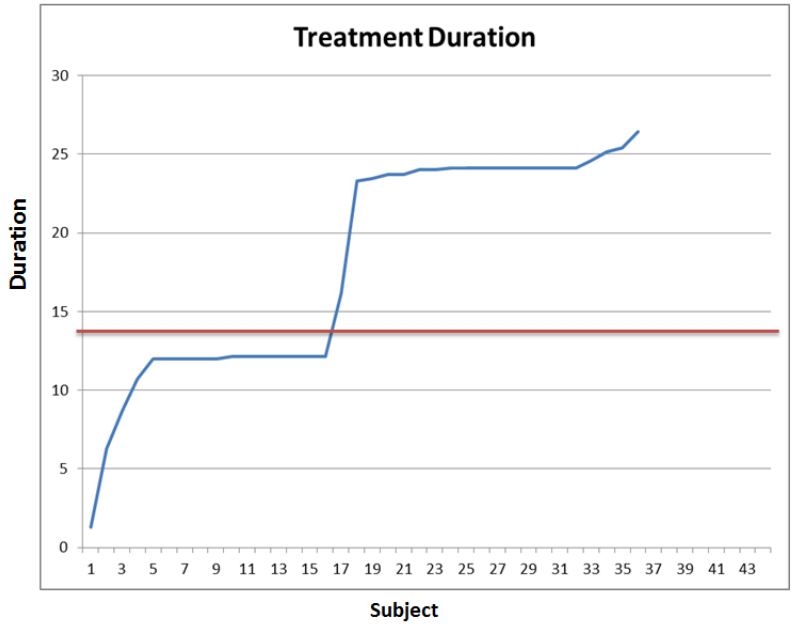
Country			
PRICO	5 / 5 (100)	1 / 1 (100)	6 / 6 (100)
USA	84 / 90 (93.3)	38 / 43 (88.4)	122 /133 (91.7)
Prior Treatment			
INTERFERON		4 / 4 (100)	
INTERFERON/RIBAVIRIN		28 / 32 (87.5)	
SOFOSBUVIR/RIBAVIRIN		5 / 6 (83.3)	
OTHER		2 / 2 (100)	

Table 16: Subgroup Analyses of SVR12 for Study AI444218 (Treated Subjects)

Efficacy Parameter	TN	TE	Total
Treated (ITT)			
N	91/101(90.1)	44/ 51(86.3)	135/152(88.8)
Gender			
FEMALE	39 / 43 (90.7)	19 / 19 (100)	58 / 62 (93.5)
MALE	52 / 58 (89.7)	25 / 32 (78.1)	77 / 90 (85.6)
Race			
AMERICAN INDIAN	. / . (.)	2 / 2 (100)	2 / 2 (100)
ASIAN INDIAN	3 / 3 (100)	1 / 1 (100)	4 / 4 (100)
ASIAN OTHER	2 / 2 (100)	1 / 1 (100)	3 / 3 (100)
BLACK/AFRICAN AMERICAN	4 / 4 (100)	2 / 2 (100)	6 / 6 (100)
WHITE	82 / 92 (89.1)	38 / 45 (84.4)	120 /137 (87.6)
Ethnicity			
HISPANIC/LATINO	15 / 17 (88.2)	8 / 8 (100)	23 / 25 (92.0)
NOT HISPANIC/LATINO	76 / 84 (90.5)	36 / 43 (83.7)	112 /127 (88.2)
Age Group			
< 65	88 / 95 (92.6)	40 / 47 (85.1)	128 /142 (90.1)
>= 65	3 / 6 (50.0)	4 / 4 (100)	7 / 10 (70.0)
Median Age Split			
<52	41 / 43 (95.3)	11 / 11 (100)	52 / 54 (96.3)
>=52	50 / 58 (86.2)	33 / 40 (82.5)	83 / 98 (84.7)
HCV RNA BSL <600K			
<600,000	22 / 23 (95.7)	8 / 8 (100)	30 / 31 (96.8)
>=600,000	69 / 78 (88.5)	36 / 43 (83.7)	105 /121 (86.8)
HCV RNA BSL <800K			
<800,000	26 / 28 (92.9)	9 / 9 (100)	35 / 37 (94.6)
>=800,000	65 / 73 (89.0)	35 / 42 (83.3)	100 /115 (87.0)
BMI category			
<=25	36 / 38 (94.7)	11 / 11 (100)	47 / 49 (95.9)
25<=, <30	36 / 42 (85.7)	19 / 22 (86.4)	55 / 64 (85.9)

>=30	19 / 21 (90.5)	14 / 18 (77.8)	33 / 39 (84.6)
Fibrosis Score Category -- 1			
F0 - F2	61 / 62 (98.4)	29 / 30 (96.7)	90 / 92 (97.8)
F3 - F4	27 / 36 (75.0)	15 / 21 (71.4)	42 / 57 (73.7)
missing	3 / 3 (100)	. / . (.)	3 / 3 (100)
Fibrosis Score Category -- 2			
F0 - F3	72 / 76 (94.7)	39 / 43 (90.7)	111 /119 (93.3)
F4	16 / 22 (72.7)	5 / 8 (62.5)	21 / 30 (70.0)
missing	3 / 3 (100)	. / . (.)	3 / 3 (100)
IL28B Genotype			
CC	36 / 40 (90.0)	19 / 20 (95.0)	55 / 60 (91.7)
CT	42 / 47 (89.4)	15 / 21 (71.4)	57 / 68 (83.8)
TT	13 / 14 (92.9)	10 / 10 (100)	23 / 24 (95.8)
Country			
PRICO	5 / 5 (100)	1 / 1 (100)	6 / 6 (100)
USA	86 / 96 (89.6)	43 / 50 (86.0)	129 /146 (88.4)
Prior Response Category			
BREAKTHROUGH		2 / 2 (100)	2 / 2 (100)
HCV RNA NEVER UNDETECTABLE		1 / 2 (50.0)	1 / 2 (50.0)
INDETERMINATE		1 / 1 (100)	1 / 1 (100)
INTOLERANCE		6 / 6 (100)	6 / 6 (100)
NULL RESPONDER		7 / 7 (100)	7 / 7 (100)
PARTIAL RESPONDER		2 / 2 (100)	2 / 2 (100)
RELAPSER		25 / 31 (80.6)	25 / 31 (80.6)
Prior Treatment			
INTERFERON		4 / 4 (100)	4 / 4 (100)
INTERFERON/RIBAVIRIN		33 / 38 (86.8)	33 / 38 (86.8)
SOFOSBUVIR/RIBAVIRIN		5 / 7 (71.4)	5 / 7 (71.4)
OTHER		2 / 2 (100)	2 / 2 (100)

Treatment Duration



If duration <14 weeks, it will be classified as 12 weeks of treatment;
If duration >=14 weeks, it will be classified as 24 weeks of treatment;

Figure 5: The Treatment Duration of 44 Subjects in the AI444258 ATU Study at France

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2. SAS Version 9.3, SAS Inc.
3. Sofosbuvir label;
4. Dr. Karen Qi's review for NDA 204,671 of Sofosbuvir;
5. Dr. Fraser Smith's stat review for IND (b) (4) SDN13;

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/s/

WEN ZENG
06/26/2015

FRASER B SMITH
06/26/2015

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

ADDENDUM OF
STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/BLA Serial Number:	206,843 / S-0000 & 206,844 / S-0000
Drug Name:	Daclatasvir (DCV) tablet: 30 mg or 60 mg (NDA 206,843); Asunaprevir (ASV) (b) (4) (NDA 206,844)
Indication(s):	The treatment of Chronic Hepatitis C Infection in Adults
Applicant:	Bristol-Myers Squibb (BMS)
Date(s):	Submitted: March 31, 2014 Received: March 31, 2014 PDUFA Date: November 30, 2014 Draft Addendum Completed: October 21, 2014 Final Addendum Completed: November 10, 2014
Review Priority	Priority
Biometrics Division:	Division of Biometrics IV (HFD-725)
Statistical Reviewer:	Wen Zeng, Ph.D. (HFD-725)
Concurring Reviewers:	Fraser Smith, Ph.D. (HFD-725), Secondary Statistics Reviewer Greg Soon, Ph.D. (HFD-725), Statistical Team Leader
Medical Division:	Division of Antiviral Drug Products (HFD-530)
Clinical Team:	Wendy Carter, D.O.; Medical Reviewer Kimberly Struble, PharmD.; Medical Team Leader
Project Manager:	Sohail Mosaddegh, RPh. Regulatory Project Manager

Keywords: HCV Infected Subjects, Daclatasvir (DCV), NS5A Replication Complex Inhibitor, Asunaprevir (ASV), NS3 Protease Inhibitor, HCV-1b, HCV-1 and HCV-4.

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1. The Purpose of this Addendum

After finalized the original statistical review, some additional analyses were conducted for the label and originally planned AC meeting. The analyses include the concordance between SVR12 and SVR24 in three phase 3 studies which is used in the section 14 of the label, and ALT elevation from nadir during the treatment phase as a part of the AC safety discussion. These analyses results are summarized here. Also, the applicant did a multivariable logistic regression analyses on the ALT elevation and will be summarized briefly at the end.

Note that the applicant withdrew the NDA 206,844 for Asunaprevir on Oct. 6, 2014. As a result, the planned AC meeting was cancelled.

2. Analyses Results

2.1 The Concordance between SVR12 and SVR24

- **For AI447026:** Ninety-five percent (95%) of the subjects (212/222) in trial AI447026 had observed SVR24 measurements.

Table 1: Relapse Rate at Follow-up Week 24 from Follow-up Week 12 for Study AI447026

Treated Subjects Parameters analyzed	Prior Non-responders (N=87)	IFN Ineligible-Naïve/Intolerant (N=135)	Total (N=222)
SVR24	**70 (80.5%)**	**118 (87.4%)**	**188 (84.7%)**
SVR24 –observed	**70/77 (90.9%)**	**118/135 (87.4%)**	**188/212 (88.7%)**
SVR12	70 (80.5%)	**119 (88.1%)**	189 (85.1%)
SVR12 (imputed)	**70 (80.5%)**	**119 (88.1%)**	**188 (84.7%)**
Relapse at FW24 from FW12*	0%	0.8% (1/119)	0.5% (1/212)

*: imputed SVR12 was used for the relapse rate calculation (b) (4).

The Pearson correlation between imputed SVR12 and SVR24 was 0.976.

- **For AI447028:** Eighty-three percent (83%) (536/643) of the subjects in trial AI447028 had observed SVR24 measurements.

Table 2: Relapse Rate at Follow-up Week 24 from Follow-up Week 12 for Study AI447028

Treated Subjects Parameters analyzed	Prior Non-responders (N=205)	IFN Ineligible-Naïve/Intolerant (N=235)	Treatment-Naïve (randomized) (N=203)	Total (N=643)
SVR24 (LOQ)	**152 (74.2%)**	**168 (71.5%)**	**155 (76.4%)**	**475 (73.9%)**
SVR24 (LOQ) – observed only	**152/170 (89.4%)**	**168/198 (84.9%)**	**155/168 (92.3%)**	**475/536 (84.9%)**
SVR12 (LOQ)	168 (82.0%)	192 (81.7%)	182 (89.7%)	542 (84.3%)
SVR12 (LOQ) - imputed	**169 (82.4%)**	**194 (82.6%)**	**184 (90.6%)**	**547 (85.1%)**
Relapse at FW24 from FW12*	**0%**	**0.5% (1/198)**	**0%**	**0.2% (1/536)**

*: imputed SVR12 was used for the relapse rate calculation (b) (4).

The Pearson correlation between imputed SVR12 and SVR24 was 0.991.

- **For AI447029:** Ninety-four percent (94%) (374/398) of the subjects in trial AI447029 had observed SVR24 measurements.

Table 3: Relapse Rate at Follow-up Week 24 from Follow-up Week 12 for Study AI447029

Treated Subjects Parameters analyzed	GT1a (N=176)	GT1b (N=178)	GT4 (N=44)	Total (N=398)
SVR24 (LOQ)	**140 (79.6%)**	**173 (97.2%)**	**42 (95.5%)**	**355 (89.2%)**
SVR24 (LOQ) –observed only	**140/158 (88.6%)**	**173/174 (99.4%)**	**42/42 (100%)**	**355/374 (94.9%)**
SVR12 (LOQ)	153 (86.9%)	176 (98.9%)	43 (97.7%)	372 (93.5%)
SVR12 (LOQ) - imputed	**154 (87.5%)**	**176 (98.9%)**	**44 (100%)**	**374 (94.0%)**
Relapse at FW24 from FW12*	**2.5% (4/158)**	**0%**	**0%**	**1% (4/374)**
Relapse at FW24 from FW12**	**1.9% (3/158)**	**0%**	**0%**	**1% (3/374)**

*: imputed SVR12 was used for the relapse rate calculation [redacted] (b) (4).
**: one subject AI447029-3-90099 had SVR36 data as success instead of relapse at SVR24. So total was 3/158 in GT-1a.

The Pearson correlation between imputed SVR12 and SVR24 was 0.884.

If combining all three studies together, the relapse rate is 0.446% (5/1122), based on the 1122/1263=88.8% observed cases.

2.2 The ALT Elevation from the Nadir during the Treatment Phase

Because some subjects had their ALT nadir at the baseline, the analyses either included these subjects or excluded them from the analyses. After talking to the medical reviewer, the analyses excluding these subjects may be more reasonable. All analyses were kept here for completion purposes.

- **For AI447026:** There was no subject in the study who had its ALT nadir value at baseline. As a result, all subjects were included in the analysis.

Table 4: Percentage of Subjects who had ALT Elevation 2, 5, or 10 Times Nadir during the Treatment Phase in Study AI447026

AI447026	Prior Non-responders (N=87)	Intolerant /Ineligible TN (N=135)	DUAL total (N=222)
Overall	**87**	**135**	**222**
>2x Nadir	29 (33%)	54 (40%)	83 (37%)
>5x Nadir	11 (13%)	28 (21%)	39 (18%)
>10x Nadir	6 (7%)	17 (13%)	23 (10%)

Table 5: The Median and Range of Nadirs for Subjects who had ALT Elevation 2, 5, or 10 Times Nadir during the Treatment Phase in Study AI447026

AI447026 Median (min, max) of nadir	Prior Non-responders (N=87)	Intolerant /Ineligible TN (N=135)	DUAL total (N=222)
Overall	**24 (9, 697)**	**25 (7, 683)**	**24 (7, 697)**
2x Nadir	67 (18, 697)	84.5 (16, 683)	71 (16, 697)
5X Nadir	155 (76, 697)	158 (49, 683)	155 (49, 697)
10x Nadir	203 (155, 697)	227 (100, 683)	223 (100, 697)

- **For AI447028:** In study AI447028, two subjects were not randomized, but treated with DUAL in the TN cohort. That is why there were 645 subjects in DUAL cohort in study AI447028. Either including or excluding these two subjects did not make any difference for the results summarized below. Since this is a safety analysis, these two subjects were included in the analyses.

There were 28 subjects in study AI447028 whose baseline ALT value was their nadir value.

- Ten were in the DUAL treated group. One had a 23 fold increase for ALT (SVR12=1) and another had a 2 fold increase from nadir (SVR12=1). Out of these 10 subjects, 7 subjects achieved HCV suppression (SVR12=1).
- Eighteen were in the Placebo group, and two had a 7-8 fold increase from nadir. All 18 subjects were non-responders (SVR12=0);

The results listed in Table 6 and 7 below included all subjects in the analyses.

Table 6: Percentage of Subjects who had ALT Elevation 2, 5, or 10 Times Nadir during the Treatment Phase in Study AI447028

AI447028	Prior Non-responders (N=205)	Intolerant /Ineligible TN (N=235)	Treatment-naïve (N=205)	DUAL total (N=645)	Placebo (N=102)
Overall *	**205**	**235**	**205**	**645**	**102**
>2x Nadir	49 (24%)	69 (29%)	61 (30%)	179 (28%)	4 (4%)
>5x Nadir	17 (8%)	20 (9%)	29 (14%)	66 (10%)	2 (2%)
>10x Nadir	8 (4%)	6 (3%)	10 (5%)	24 (4%)	

*: all subjects were counted regardless if the nadir was the baseline ALT observation or not.

Table 7: The Median and Range of Nadirs for Subjects who had ALT Elevation 2, 5, or 10 Times Nadir during the Treatment Phase in Study AI447028

AI447028 Median (min, max) of nadir	Prior Non-responders (N=205)	Intolerant /Ineligible TN (N=235)	Treatment-naïve (N=205)	DUAL total (N=645)	Placebo (N=102)
Overall *	**17 (5, 54)**	**17 (5, 70)**	**15 (4, 65)**	**17 (4, 70)**	**42 (8, 177)**
2x Nadir	16 (5, 35)	17 (5, 33)	14 (6, 42)	16 (5, 42)	28.5 (8, 56)
5X Nadir	13 (7, 33)	16 (7, 26)	15 (8, 33)	15 (7, 33)	28.5 (19, 38)
10x Nadir	12 (7, 17)	16 (7, 26)	17.5 (9, 33)	14.5 (7, 33)	0

*: all subjects were counted regardless if the nadir was the baseline ALT observation or not.

The results listed in Table 8 and 9 below included only subjects whose nadir value was not the baseline ALT in the analyses.

Table 8: Percentage of Subjects who had ALT Elevation 2, 5, or 10 Times Nadir during the Treatment Phase in Study AI447028 (Excluded 28 subjects from the analysis)

AI447028	Prior Non-responders (N=205)	Intolerant /Ineligible TN (N=235)	Treatment-naïve (N=205)	DUAL total (N=645)	Placebo (N=102)
Overall *	**200**	**233**	**202**	**635**	**84**
>2x Nadir	47 (24%)	69 (30%)	61 (30%)	177 (28%)	2 (2%)
>5x Nadir	16 (8%)	20 (9%)	29 (14%)	65 (10%)	0
>10x Nadir	7 (4%)	6 (3%)	10 (5%)	23 (4%)	0

*: Subjects whose nadir was the baseline ALT value were excluded.

Table 9: The Median and Range of Nadirs for Subjects who had ALT Elevation 2, 5, or 10 Times Nadir during the Treatment Phase in Study AI447028 (Excluded 28 subjects from the analysis)

AI447028 Median (min, max) of nadir	Prior Non-responders (N=200)	Intolerant /Ineligible TN (N=233)	Treatment-naïve (N=202)	DUAL total (N=635)	Placebo (N=84)
Overall *	**17 (5, 54)**	**17 (5, 70)**	**15 (4, 65)**	**16 (4, 70)**	**42 (8, 177)**
2x Nadir	16 (5, 35)	17 (5, 33)	14 (6, 42)	16 (5, 42)	32 (8, 56)
5X Nadir	13.5 (8, 33)	16 (7, 26)	15 (9, 33)	15 (7, 33)	0
10x Nadir	13 (8, 17)	16 (7, 26)	17.5 (9, 33)	15 (7, 33)	0

*: Subjects whose nadir was the baseline ALT value were excluded.

- **For AI447029:** There were 8 subjects in study AI447029 whose baseline ALT value was their nadir value. Out of these 8 subjects, 7 subjects achieved HCV suppression (SVR12=1). One subject had a 14 fold increase for ALT from nadir, one had a 6 fold, one had a 3 fold, and two had two fold increases for ALT from their nadir which was their baseline ALT value.

The results listed in Table 10 and 11 below included all subjects in the analyses.

Table 10: Percentage of Subjects who had ALT Elevation 2, 5, or 10 Times Nadir during the Treatment Phase in Study AI447029

AI447029	GT1a (N=176)	GT1b (N=178)	GT4 (N=44)	DUAL+PR total (N=398)
Overall *	**176**	**178**	**44**	**398**
>2x Nadir	32 (18%)	34 (19%)	10 (23%)	76 (19%)
>5x Nadir	10 (6%)	9 (5%)	2 (5%)	21 (5%)
>10x Nadir	3 (2%)	2 (1%)	2 (5%)	7 (2%)

*: all subjects were counted regardless if the nadir was the baseline ALT observation or not.

Table 11: The Median and Range of Nadirs for Subjects who had ALT Elevation 2, 5, or 10 Times Nadir during the Treatment Phase in Study AI447029

AI447029 Median (min, max) of nadir	GT1a (N=176)	GT1b (N=178)	GT4 (N=44)	DUAL+PR total (N=398)
Overall *	**24 (5, 133)**	**21 (6, 193)**	**28 (7, 159)**	**23 (5, 193)**
2x Nadir	21 (12, 116)	20.5 (6, 59)	37.5 (15, 159)	21 (6, 159)
5X Nadir	21 (16, 53)	15 (6, 28)	28 (22, 34)	20 (6, 53)
10x Nadir	21 (18, 21)	17 (13, 21)	28 (22, 34)	21 (13, 34)

*: all subjects were counted regardless if the nadir was the baseline ALT observation or not.

The results listed in Table 12 and 13 below included only subjects whose nadir value was not the baseline ALT value in the analyses.

Table 12: Percentage of Subjects who had ALT Elevation 2, 5, or 10 Times Nadir during the Treatment Phase in Study AI447029 (Excluded 8 subjects from the analysis)

AI447029	GT1a (N=176)	GT1b (N=178)	GT4 (N=44)	DUAL+PR total (N=398)
Overall *	**172**	**175**	**43**	**390**
>2x Nadir	29 (17%)	33 (19%)	9 (21%)	71 (18%)
>5x Nadir	9 (5%)	9 (5%)	1 (2%)	19 (5%)
>10x Nadir	3 (2%)	2 (1%)	1 (2%)	6 (2%)

*: Subjects whose nadir was the baseline ALT value were excluded.

Table 13: The Median and Range of Nadirs for Subjects who had ALT Elevation 2, 5, or 10 Times Nadir during the Treatment Phase in Study AI447029 (Excluded 8 subjects from the analysis)

AI447029 Median (min, max) of nadir	GT1a (N=172)	GT1b (N=175)	GT4 (N=43)	DUAL+PR total (N=390)
Overall *	**23.5 (5, 133)**	**21 (6, 193)**	**28 (7, 159)**	**23 (5, 193)**
2x Nadir	21 (12, 85)	21 (6, 59)	41 (15, 159)	21 (6, 159)
5X Nadir	21 (16, 50)	15 (6, 28)	22 (22, 22)	19 (6, 50)
10x Nadir	21 (18, 21)	17 (13, 21)	22 (22, 22)	21 (13, 22)

*: Subjects whose nadir was the baseline ALT value were excluded.

- **Three Study Combined:** If combining three study's results together, the final results are listed in Table 14 and 15. Overall the Japanese trial 7026 had proportionately the most subjects with increases from nadir. Generally the dual regimen (in trial 7026 and to a lesser extent in trial 7028) had a higher proportion of subjects with increases in ALT from nadir compared to the quad regimen.

Table 14: Percentage of Subjects who had ALT Elevation 2, 5, or 10 Times Nadir during the Treatment Phase

	AI447026	AI447028		AI447029
Shift from Nadir Number of subject (%)	**DCV 60mg QD + ASV 100 mg BID (24W) N=222**	**DCV 60mg QD + ASV 100 mg BID (24W) N=645**	**PLACEBO (12W) N=102**	**DCV 60mg + ASV 100mg BID+ PegIFN + RBV (24W) N=398**
>2x Nadir	83 (37%)	179 (28%)	4 (4%)	76 (19%)
>5x Nadir	39 (18%)	66 (10%)	2 (2%)	21 (5%)
>10x Nadir	23 (10%)	24 (4%)	0	7 (2%)

Table 15: The Median and Range of Nadirs for Subjects who had ALT Elevation 2, 5, or 10 Times Nadir during the Treatment Phase

	AI447026	AI447028		AI447029
Median ALT Nadir Value (Min, Max) U/L	**DCV 60mg QD + ASV 100 mg BID (24W) N=222**	**DCV 60mg QD + ASV 100 mg BID (24W) N=645**	**PLACEBO (12W) N=102**	**DCV 60mg + ASV 100mg BID+ PegIFN + RBV (24W) N=398**
Overall Median ALT Nadir	**24 (7, 697)**	**17 (4, 70)**	**42 (8, 177)**	**23 (5, 193)**
Median 2x Nadir ALT U/L	71 (16, 697)	16 (5, 42)	28.5 (8, 56)	21 (6, 159)
Median 5X Nadir ALT U/L	155 (49, 697)	15 (7, 33)	28.5 (19, 38)	20 (6, 53)
Median 10x Nadir ALT U/L	223 (100, 697)	14.5 (7, 33)	n/a	21 (13, 34)

If only including subjects whose nadir was not the baseline ALT value, 28 subjects in AI447028 and 8 subjects in AI447029 were excluded from the analyses. The results are listed in Table 16 and 17.

Table 16: Percentage of Subjects who had ALT Elevation 2, 5, or 10 Times Nadir during the Treatment Phase (Excluded subjects whose nadir value was the baseline value from the analysis)

	AI447026	AI447028		AI447029
Shift from Nadir	**DCV 60mg QD + ASV 100 mg BID (24W) N=222**	**DCV 60mg QD + ASV 100 mg BID (24W) N=635**	**PLACEBO (12W) N=84**	**DCV 60mg + ASV 100mg BID+ PegIFN + RBV (24W) N=390**
>2x Nadir	83 (37%)	177 (28%)	2 (2%)	71 (18%)
>5x Nadir	39 (18%)	65 (10%)	0	19 (5%)
>10x Nadir	23 (10%)	23 (4%)	0	6 (2%)

Table 17: The Median and Range of Nadirs for Subjects who had ALT Elevation 2, 5, or 10 Times Nadir during the Treatment Phase (Excluded subjects whose nadir value was the baseline value from the analysis)

	AI447026	AI447028		AI447029
Median ALT Nadir Value (Min, Max) U/L	**DCV 60mg QD + ASV 100 mg BID (24W) N=222**	**DCV 60mg QD + ASV 100 mg BID (24W) N=635**	**PLACEBO (12W) N=84**	**DCV 60mg + ASV 100mg BID+ PegIFN + RBV (24W) N=390**
Overall Median ALT Nadir	**24 (7, 697)**	**16 (4, 70)**	**42 (8, 177)**	**23 (5, 193)**
Median 2x Nadir ALT U/L	71 (16, 697)	16 (5, 42)	32 (8, 56)	21 (6, 159)
Median 5X Nadir ALT U/L	155 (49, 697)	15 (7, 33)	n/a	19 (6, 50)
Median 10x Nadir ALT U/L	223 (100, 697)	15 (7, 33)	n/a	21 (13, 22)

2.3 Multivariable Logistic Regression for the ALT Elevation from the Nadir during the Treatment Phase

The following analyses were conducted by the applicant, not the statistical reviewer.

To further understand potential signals of hepatotoxicity, the applicant conducted a multivariate logistic regression analysis looking at several baseline factors and their possible association with elevations in liver enzymes. As part of our preliminary analysis, the applicant defined elevation of liver enzymes as an on treatment ALT > 3 times the upper limit of normal (3xULN) and this was set to be the dependent variable in the initial model. Therefore a subject who had at

least one laboratory assessment of ALT > 3xULN was deemed to have met the definition of an elevation of liver enzymes.

To check the robustness of the results from this first set of analyses, the applicant examined other definitions of ALT elevation. Baseline factors were selected based on clinical judgment and questions from the FDA regarding which factors, if any, could identify specific populations, such as subjects enrolled from Japanese sites, which are more likely to result in elevated ALT. No model selection methods were used to identify any additional factors so as to minimize spurious findings. The following factors were considered:

Independent Variables:

- *Age category (<65, >=65)*
- *BMI (either as continuous or categorical with categories of < 20, 20-25, 25-30, >30). Weight was considered as a different measure of body size in place of BMI.*
- *Country (Japan vs Non Japan). Also considered was Japan vs. Non-Japanese Asians vs. Others)*
- *Treatment (ASV containing regimens, DCV containing regimens but without ASV, Placebo (PBO) or placebo with Pegylated Interferon and Ribavirin (PBO/P/R)*
- *Gender (Male vs. Female)*
- *Cirrhotic status (Present vs. Absent*
- *Interaction terms*
  - *Treatment by Country*
  - *Treatment by Cirrhosis status.*

The analysis data set included subjects from the phase 2 and 3 programs included in the submission package and treated at the recommended dose (b) (4) *for DCV the dose was 60 mg BID). Additionally, in order to maximize the number of subjects from Japan, the applicant also included subjects from a phase 3 comparative study, AI447031, who were treated with Dual therapy (ASV/DCV). This resulted in an analysis data set compromising 2710 subjects.*

Simple descriptive statistics of these variables are listed below. The applicant considered the rates of ALT elevations of 10% to be relatively low. In the population, 16% of the subjects were cirrhotic, 61% (Note: the applicant stated 37%, and it seems not right) *of the subjects received at least one dose of ASV,* (b) (4) *% of the subjects where from Japan.*

- *ALT Elevation*
  - *278 (10.3%) ALT > 3x ULN*
  - *2432(89.7%) ALT < 3x ULN*

- *Treatment*
  - *1646 treated with ASV + Other*
    - *189 ASV/P/R*
    - *1008 DCV + ASV (100mg* (b) (4) *BID)*
    - *398 DCV + ASV + P + R*

        - *51 DCV + ASV (200mg pills BID)*
    - *716 treated with DCV w/o ASV*
        - *211 DCV + SOF*
        - *505 DCV/P/R*
    - *348 PBO or PBO/P/R*
        - *102 PBO*
        - *246 PBO/P/R*
- *Country*
    - *448 Japan*
    - *2262 Non Japan*
        - *264 Non Japanese Asians*
        - *1998 Non Japanese Others*
- *Age*
    - *378 > = 65 yrs*
    - *2332 < 65 yrs*
- *Cirrhosis Status*
    - *2268 Non-cirrhotics.*
    - *435 Cirrhotics*
    - *7 missing*
- *BMI*
    - *165 < 20 kg/m2*
    - *1078 20 - < 25 kg/m2*
    - *999 25 -< 30 kg/m2*
    - *466 >=30 kg/m2*
    - *2 Missing*

The preliminary results the applicant listed are the following:

- *Overall ALT elevations appeared to be nearly* (b) (4) *containing regimens compared to subjects treated with DCV w/o ASV containing regimens (12% vs. 6%).*

- *Subjects from Japan seemed to be at even higher risk of ALT elevation with* (b) (4) *compared to subjects from Non-Japanese sites (10%). This country difference does not appear for DCV w/o ASV containing regimens with rates nearly identical (6% vs. 6% respectively).*

- *There was also no meaningful difference for DCV w/o ASV compared to PBO or PBO/P/R (5.7% vs. 8.9%), irrespective of Japan vs. Non-Japanese sites.*

- *There seemed to be minimal differences in rates of ALT elevations across age groups and categories of BMI.*

- *A suggestion of a small trend towards higher rates in males and slightly lower rates in subjects without cirrhosis s observed.*

Note that in the applicant's analysis, the ASV-contained regimen in the treatment factor includes DUAL, DUAL+PR, and ASV+PR. As a result, almost 90% (1457/1646) of the subjects who received ASV also received DCV.

Also, no Japanese subjects were treated with ASV+PR or DUAL+PR, only 36 Japanese received DCV w/o ASV and only 16 Japanese were treated with PR only. As a result, the numbers of subjects in some sub-categories were very small or even ZERO.

Two documents, the analysis plan and preliminary results, are located in the folder below:

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Please see the documents for details.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WEN ZENG
12/16/2014
This is the addendum to the original statistical review.

FRASER B SMITH
12/16/2014

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	206,843 / S-0000 & 206,844 / S-0000
Drug Name:	Daclatasvir (DCV) tablet: 30 mg or 60 mg (NDA 206,843); Asunaprevir (ASV) [redacted] (b) (4) (NDA 206,844)
Indication(s):	The treatment of Chronic Hepatitis C Infection in Adults
Applicant:	Bristol-Myers Squibb (BMS)
Date(s):	Submitted: March 31, 2014 Received: March 31, 2014 PDUFA Date: November 30, 2014 Draft Review Completed: August 8, 2014 Final Review Completed: August 29, 2014
Review Priority	Priority
Biometrics Division:	Division of Biometrics IV (HFD-725)
Statistical Reviewer:	Wen Zeng, Ph.D. (HFD-725)
Concurring Reviewers:	Fraser Smith, Ph.D. (HFD-725), Secondary Statistics Reviewer Greg Soon, Ph.D. (HFD-725), Statistical Team Leader
Medical Division:	Division of Antiviral Drug Products (HFD-530)
Clinical Team:	Wendy Carter, D.O.; Medical Reviewer Kimberly Struble, PharmD.; Medical Team Leader
Project Manager:	Sohail Mosaddegh, RPh. Regulatory Project Manager

Keywords: HCV Infected Subjects, Daclatasvir (DCV), NS5A Replication Complex Inhibitor, Asunaprevir (ASV), NS3 Protease Inhibitor, HCV-1b, HCV-1 and HCV-4.

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1. EXECUTIVE SUMMARY

Daclatasvir (Bristol-Myers Squibb [BMS])-790052; abbreviated as DCV) is a first-in-class highly selective nonstructural protein 5a (NS5A) replication complex inhibitor of HCV with broad genotypic coverage. NS5A is a non-enzymatic multifunctional protein with key functions in HCV replication, virus assembly, and the modulation of cellular signaling pathways. The recommended dose is 60 mg once daily (QD) with the corresponding recommended dose for the combination agent. DCV was submitted in NDA 206,843.

Asunaprevir (Bristol-Myers Squibb [BMS])-650032; abbreviated as ASV) is an NS3 protease inhibitor of HCV with broad genotype coverage. (b) (4) ASV was submitted in NDA 206,844.

Both NDAs were supported by the same three phase 3 studies, AI447028 and AI447026 for DCV+ASV, and AI447029 for DCV+ASV+ Peglated Interferon+Ribavirin (P/R), for their efficacy claim. These three studies will be the focus of this statistical review. There are additional phase 2 studies that supported either the DCV contribution (six studies for DCV+P/R), ASV contribution (one study for ASV+P/R), or DCV+ASV contribution (two studies DCV+ASV±P/R). These phase 2 studies were listed as Table 36 in Appendix and will not be reviewed here.

The primary objective of study AI447028 was to evaluate the efficacy of DCV+ASV for 24 weeks for the treatment of chronic HCV genotype 1b infection using SVR12, defined as HCV RNA< lower limit of quantitation (LLOQ) (<25 IU/mL) [target detected (TD) or target not detected (TND)] at post-treatment Week 12.

Study AI447028 was a global study that enrolled subjects from 18 countries; only 19% of subjects were from US sites. The overall SVR12 was 84% (542/643) with 95% confidence interval (CI) of (81%, 87%). The SVR12 rates for treatment-naïve (TN), prior non-responders, and Intolerant/Ineligible cohorts were 90% (182/203) with 95% CI of (85%, 94%), 82% (168/205) with 95% CI of (76%, 87%), and 82% (192/235) with 95% CI of (76%, 86%) respectively.

The primary endpoints for Study AI447028 were the SVR12 rates for subjects who were prior null or partial responders to P/R or were treatment-naive. As defined in the protocol, for the treatment naive cohort: "to determine whether the SVR12 rate in subjects treated with Dual therapy (DCV+ASV) is similar to the historical SVR rate for Telaprevir (TVR) in combination with P/R in previously untreated, genotype 1b, HCV patients, where similar efficacy is defined as the lower bound of the 95% confidence interval for the SVR12 rate being greater than 68%."

The benchmark set for the HCV-1b prior non-responders cohort was the lower bound of the 95% CI of SVR12 had to be greater than 59%, and had to be greater than 30% for the intolerant/ineligible-naïve HCV-1b cohort. These benchmarks were determined by using Telaprevir ADVANCE trial results and were accepted by the DAVP before the enrollment of the Study.

The primary objective of study AI447026 was to evaluate the efficacy of DCV+ASV for 24 weeks for the treatment of chronic HCV genotype 1b infection using SVR24, defined as HCV RNA <LLOQ (<15 IU/mL) [target detected or not detected] at Week 24 of post treatment follow-up. Since SVR12 was almost identical to SVR24 in the study, SVR12 was used here in order to be consistent with other two studies.

Study AI447026 was a Japanese study, and all subjects were from Japan. The overall SVR12 rate was 85% (189/222) with 95% confidence interval (CI) of (80%, 90%). The SVR12 rates for prior non-responders and Intolerant/Ineligible cohorts were 80% (70/87) with 95% CI of (71%, 88%) and 81% (119/135) with 95% CI of (81%, 93%) respectively. This study protocol was not reviewed by the DAVP since it was not under the IND.

For study AI447026, the benchmark set for the HCV-1b prior non-responders cohort was the lower bound of the 95% CI of SVR12 had to be greater than 45%, and had to be greater than 30% for the intolerant/ineligible-naïve HCV-1b cohort.

The primary objective of study AI447029 was to evaluate the efficacy of DCV+ASV+P/R for 24 weeks for the treatment of chronic HCV genotype 1 and genotype 4 prior non-responders using SVR12, defined as HCV RNA <LLOQ (<25 IU/mL) [target detected (TD) or target not detected (TND)] at post treatment Week 12.

Study AI447029 was a global study that enrolled subjects from 15 countries; only 29% of subjects were from US sites. The overall SVR12 was 93% (372/398) with 95% CI of (91%, 96%) for these prior non-responders. The SVR12 rates for HCV-1a, HCV-1b, and HCV-4 were 87% (153/176) with 95% CI of (81%, 92%), 99% (176/178) with 95% CI of (96%, 100%), and 98% (43/44) with 95% CI of (88%, 100%) respectively.

In conclusion, studies AI447028 and AI447026 demonstrated the efficacy of DCV+ASV in HCV-1b infected subjects with the exception of subjects with L31F/I/M/CV or Y93H polymorphisms at baseline who had much lower SVR12 rates and much higher virologic failure rates than other subjects. After excluding these subjects, there were no other baseline factors that appeared to have a statistically significant impact on SVR12 or virologic failure rates.

Study AI447029 demonstrated the efficacy of DCV+ASV+P/R in HCV-1 and HCV-4 infected subjects. Efficacy for HCV-1b subjects was much higher in study AI447029 than in the other DUAL studies but the tradeoff was that higher efficacy required the use of P/R for 24 weeks. There were no baseline factors that appeared to have a statistically significant impact on SVR12 or virologic failure rates.

Key statistical issue: There were no major statistical issues identified in this submission.

2. INTRODUCTION

2.1 Overview

Globally it is estimated that approximately 170 million people are infected with HCV, including approximately 3 million people in the United States (US) (http://www.epidemic.org/thefacts/theepidemic/worldPrevalence/). The most common HCV GT in the US is GT 1 (70-75%), followed by GT 2 and GT 3.

The currently approved drugs for the treatment of HCV infection are listed in Table 1.

Pegasys® (pegylated interferon alfa 2-a) and PegIntron® (pegylated interferon alfa-2-b), are immunostimulatory agents and are co-administered with RBV. RBV is a guanosine nucleoside analog. RBV is a prodrug, which when metabolized resembles purine RNA nucleotides. In this form it interferes with RNA metabolism required for viral replication. The exact effects of RBV on viral replication are unclear; many mechanisms have been proposed but not established. RBV has shown an effect in decreasing post-treatment relapse following treatment and multiple mechanisms of action may be involved.

Telaprevir (Incivek®), boceprevir (Victrelis®) and simeprevir (Olysio™) are NS3/4A protease inhibitors and inhibit the HCV NS3/4A protease which is essential for viral replication. SOF (Sovaldi™) is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase and is incorporated into the HCV RNA by the NS5B polymerase and disrupts the viral replication by chain termination. These direct acting antiviral agents (DAA) are currently indicated for co-administration with PEG and RBV for the treatment of chronic HCV GT 1 infection.

Table 1: Currently US Approved Agents for Treatment of Chronic HCV Genotype 1 Infection

Drug Class	Generic Name	Trade Name	Genotype in Indication
Pegylated interferons	Peginterferon alfa-2a	Pegasys®	
	Peginterferon alfa-2b	PegIntron®	
Interferons	Interferon alfa-2a	Roferon-A®*	
	Interferon alfa-2b	Intron-A®	
Nucleoside Analogue	Ribavirin	Rebetol®, Copegus®	
Protease Inhibitors	Boceprevir	Victrelis®	With PR for HCV-1 only
	Telaprevir	Incivek®	With PR for HCV-1 only
	Simeprevir	Olysio™	Combining with PR for HCV-1. Restriction for NS3 Q80K polymorphism in HCV-1a patients.
NS5B Inhibitor	Sofosbuvir	Sovaldi™	Combining with PR for HCV-1 and -4. Combining with R for HCV-2 and -3.

* Voluntarily withdrawn from U.S. market 10/1/2007; not due to safety or efficacy concerns.
Source: copied from the clinical review of this NDA with little modification.

In these two DNAs, three phase 3 studies were submitted to request approval of daclatasvir (DCV) and asunaprevir (ASV) for the proposed indication for treatment of chronic hepatitis C (CHC) in adults.

2.1.1 Studies Reviewed

The detailed description of the three studies is listed in Table 2. Study AI447026 was conducted in Japan only, and Study AI447028 was conducted in the US as well as other 17 countries or regions (Argentina, Australia, Austria, Canada, France, Germany, Ireland; Israel, Italy, Korea, Netherlands, New Zealand, Poland, Russia, Spain, Taiwan, United Kingdom). The regimen used in both studies was DCV+ASV (DUAL) in HCV-1b infected subjects only. Study AI447029 enrolled HCV-1 and HCV-4 infected subjects, treated with DCV+ASV+PR (QUAD), and conducted in Argentina, Canada, Denmark, France, Germany, Italy, Korea, Mexico, Netherlands, Russia, Spain, Sweden, Switzerland, Taiwan, and United States.

Table 2 List of Phase 3 studies included in this review

Study	Phase and Design	Objectives/Primary Endpoint	Treatment Period	# of Subjects per Arm	Study Population
AI447026 (DCV/ASV in HCV-1b)	Phase 3, Japan, Open-label, single arm; Two cohorts: Prior Non-responders and IFN-ineligible-TN/intolerants Chronic Hepatitis C Genotype **1b** Infection	**SVR24:** as determined by the proportion of subjects with SVR24, defined as below LLOQ (<15 IU/mL) (target detected or not detected) HCV RNA at Week 24 of post treatment follow-up for each population. DCV/ASV for 24 weeks for HCV GT-1b infection can achieve SVR24 rate whose lower bound of the estimated 95% CI is >45% for non-responder and > 30% for IFN-based therapy ineligible naive/intolerant subjects;	24 weeks ASV: 100 mg* BID DCV: 60 mg QD, If Rescue, 48 weeks	DCV/ASV for 24 weeks: A: Prior Non-responder (n=87) B: Intolerant/ineligible (n=135)	Japanese subjects with Chronic HCV Genotype 1b (Non-responder, IFN therapy ineligible naive/ intolerant)

AI447028 (DCV/ASV in HCV-1b)	Phase 3, Global, TN- randomized; Intolerant or Ineligible to P/R Subjects – Not randomized (open label); TE (Null/Partial Responders P/R) – Not randomized (open label); Chronic Hepatitis C Genotype **1b** Infection	**SVR12**, defined as HCV RNA <LLOQ (target detected or not detected) at post treatment Week 12, for subjects who are prior null or partial responders to P/R or are treatment-naive. Efficacy analyses will not be assessed for treatment naive subjects on PBO. TN: is to determine whether the SVR12 rate in subjects treated with DCV/ASV therapy is greater than 68%. The 68% benchmark was determined using the historical SVR rates of TVR in combination with P/R.	24 weeks ASV: 100 mg* BID DCV: 60 mg QD If Rescue, up to 48 weeks 12 weeks; then enrolled in open label treatment trial	A: TN (2:1 Randomization) -- PBO for 12 weeks (N=102); -- DCV/ASV for 24 weeks (n=205) B: Intolerant/ineligible DCV/ASV for 24 weeks (n=235); C: Non-responder (Null/Partial) DCV/ASV for 24 weeks (n=205);	Chronic HCV Genotype 1b (Null / partial responders, and IFN therapy ineligible naive/ intolerant) *and* Chronic HCV Genotype 1b (Treatment-naive)
AI447029 (DCV/ASV /PR in HCV-1 & -4)	Phase 3, Open-Label, Single arm,Global; Chronic Hepatitis C Genotypes **1 or 4** Infection	**SVR12**, defined as HCV RNA <LLOQ (target detected or not detected) at post treatment Week 12, for subjects who are prior null or partial responders to P/R. The historical threshold was not set-up in the protocol.	24 weeks ASV: 100 mg* BID DCV: 60 mg QD plus PR	DCV/ASV/PR for 24 weeks: Non responder (n=398)	Chronic HCV Genotype 1a, 1b, and 4 (Null/partial responders)

The detailed design characteristics of the three phase 3 studies are described in section 3.2.1.

2.2 Data Sources

The submission under NDA 206,843 and NDA 206,844 contains the efficacy, safety, and some genotyping results for subjects in Studies AI447026, AI447028 and AI447029. This reviewer conducted efficacy analyses to verify the applicant's results.

1. Reviewed protocols, statistical analysis plans, efficacy results and conclusions in the following submitted documents entitled "Statistics Section":
   - Module 1- labeling materials
   - Module 2- 2.5 Clinical Overview and 2.7.3 Summary of Clinical Efficacy
   - Module 5- Clinical Study Reports (CSRs) of 3 Phase III Studies AI447026, AI447028 and AI447029.

2. Converted SAS transportable files '*.xpt' in \analysis\legacy\datasets subfolder as analysis datasets, some of the raw datasets in \tabulations\legacy subfolder into SAS data files for verification based on the definitions in 'define.pdf', 'blankcrf.pdf', and Statistical Analysis Plan (SAP) in the CSR. In \analysis\legacy \datasets subfolder, there are about 16 SAS transportable files for each of three phase 3 studies. There are

approximately 29 SAS transportable files in \tabulations\legacy subfolder which are the input datasets for creating efficacy/safety analysis datasets. These files are under CDER Electronic Document Room (EDR) directory of

\\Cdsesub1\evsprod\NDA206843\0001\m5\datasets\ai447026
\\Cdsesub1\evsprod\NDA206843\0001\m5\datasets\ai447028
and \\Cdsesub1\evsprod\NDA206843\0001\m5\datasets\ai447029

3. STATISTICAL EVALUATION

Studies AI447026, AI447028 and AI447029 will be reviewed separately under each of following sections. All tables and figures were generated by the statistical reviewer unless otherwise cited.

For Studies AI447026 and AI447028, the prior non-responder cohort will be abbreviated as Prior, the treatment-naïve intolerant/ineligible cohort will be abbreviated as TN_IN, and the treatment-naïve (TN) cohort will be abbreviated as TN. For Study AI447029, all subjects were prior non-responders, and the HCV genotype/subtype will be used to represent the corresponding cohorts, GT-1a, GT-1b, or GT-4.

3.1 Data and Analysis Quality

Overall, the reviewer reproduced primary efficacy variables in the primary efficacy analysis datasets, EFF and VFAIL, for three studies.

The reviewer guides, SAPs and the comments in the SAS programs submitted were very helpful.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

❖ **AI447028, a phase 3 study for HCV-1b subjects:**

Title: A Phase 3 Study with Asunaprevir and Daclatasvir (DUAL) for Null or Partial Responders to Peginterferon Alfa and Ribavirin (P/R), Intolerant or Ineligible to P/R Subjects and Treatment-Naive Subjects with Chronic Hepatitis C Genotype 1b Infection.

A total of 725 subjects were enrolled into three cohorts. Subjects in the TN cohort were randomized in a 2:1 ratio to either receive the designed treatment or placebo (Figure 1).

Treatment Arm:

- Experimental Treatment (three cohorts): BMS-790032 (ASV) + BMS-790052 (DCV) for 24 weeks for Null or partial responders to P/R (N=200), intolerant or ineligible (N=225), and TN (N=200);
- Placebo of ASV and DCV for 12 weeks (N=100);

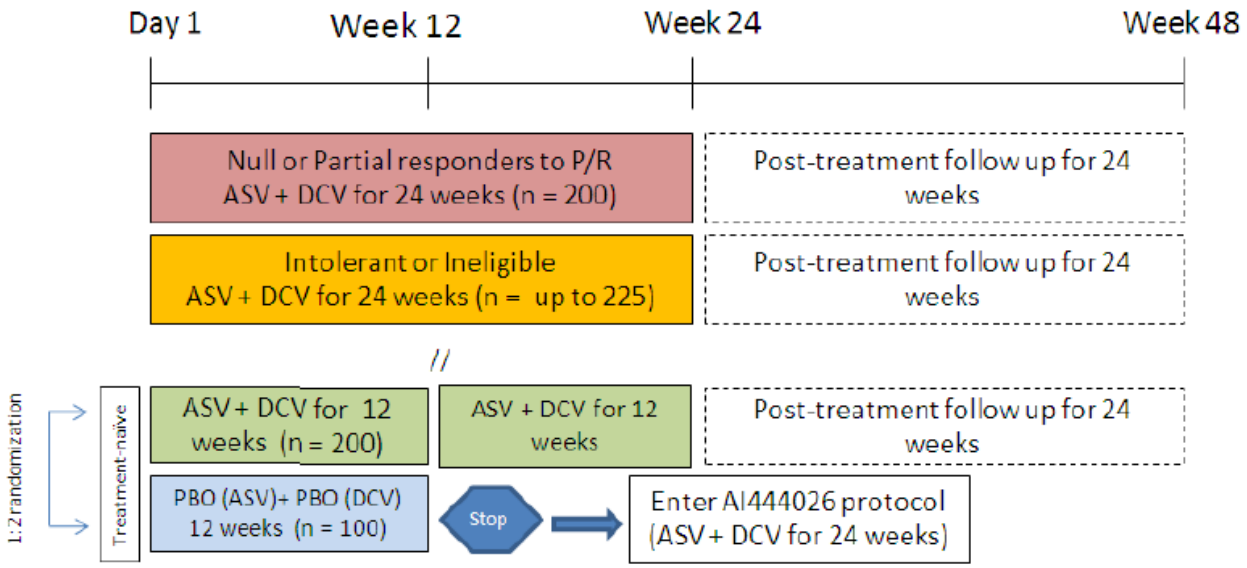


Figure 1: Study Diagram of AI447028

Research Hypothesis:

- In subjects who were prior null or partial responders to P/R or are intolerant or ineligible to P/R, the co-administration of ASV and DCV for 24 weeks for the treatment of chronic HCV genotype 1b infection is safe, tolerable and efficacious where efficacy is based on SVR12, defined as HCV RNA < LOQ [target detected (TD) or target not detected (TND)] at post-treatment Week 12.

- In the TN cohort, Dual therapy was expected to have similar efficacy to what has been observed for TVR in combination with P/R in genotype 1b patients, where similar efficacy was defined as the lower bound of the 95% confidence interval for the SVR12 rate being greater than 68%.

The justification of the benchmark of 68% for TN cohort was the following:

At the time of reviewing the protocol, only TVR and BOC were approved for HCV-1b TN population. From the TVR trial, the SVR24 results for HCV-1b TN subjects were following:

Results from Tom's review were the following:

TRIAL_108_12_WK_TVR_VS_PBO

	Mean	95%_Limits		TVR_12_wk	Placebo	P-Homog
Covariate	Diff	Lower	Upper			
1a	31.4%	21.2%	41.6%	158/213=74.0%	89/208=43.0%	0.32
1b	**34.3%**	23.1%	45.4%	128/149=**86.0%**	78/151=**52.0%**	

For genotype 1b TN subjects the dual therapy was estimated by the sponsor to preserve at least 50% of the historical treatment effect of TVR relative to P/R alone if the SVR rate exceeded 68%, based upon SVR24 rates from the ADVANCE trial of 85% for TVR+P/R and 51% for placebo. (See the Statistical Review of IND (b) (4) SN 028, SDN 031 for details.) Based on the results above, it was possible to conclude that the threshold should have been at

least 86% since TVR + P/R was the standard of care. However the 68% benchmark was acceptable because of the benefits of the interferon-free DUAL regimen over the SOC at the time of study initiation, which was TVR+P/R or BOC+P/R.

Obviously, these calculations are out of date right now with the approval of Sofosbuvir. However Dual therapy with ASV+DCV still has an advantage over currently approved Sofosbuvir treatment since the Dual is interferon free for genotype 1b subjects.

In the original protocol submitted, the benchmark for prior non-responders cohort was 59%, while the benchmark for the intolerant/ineligible cohort was 30% (See the Statistical Review of IND (b) (4) SN 001, SDN 004 for details). However, these benchmarks were deleted from the updated protocol as noted in the Statistical Review of IND (b) (4) SN 028, SDN 031.

The reason of 59% benchmark for the prior non-responder cohort seems OK for prior non-responders is based on the TVR trial results. As shown in the table below, in the TVR study 216 the TVR 12-week arm had an SVR24 rate for combined prior non-responders of 43% with 95% CI of (34%, 52%).

TRIAL_216_12_WK_TVR

Population	SVR_{24} in TVR 12 Week Arm	95% CI
Null	30.6% (22/72)	[20.2%, **42.5%**]
Partial	61.2% (30/49)	[46.2%, **74.8%**]
Null/Partial	43% (52/121)	[34.0%, **52.3%**]
Relapser	84.1% (122/145)	[77.2%, 89.7%]

At the time of reviewing the protocol, there was no available treatment for the intolerant/ineligible subjects. As a result, the benchmark could be any number above 0%; 30% was most likely chosen because it was the minimum threshold the applicant considered to be clinically meaningful.

Primary Endpoint: Proportion of treated subjects with SVR12, defined as HCV RNA < LOQ at post-treatment Week 12, for subjects who were prior null or partial responders to P/R or were treatment-naive.

Note that the LLOQ used in this study was 25 IU/mL. While the LOQ used in the study AI477026 was 15 IU/mL. The LOQ in the study AI477029 was 25 IU/mL.

Some Secondary Endpoints:

- Proportion of treated subjects with SVR12, defined as HCV RNA < LOQ at post-treatment Week 12, for subjects who were intolerant or ineligible to P/R;

Populations for Analyses:

- **Enrolled subjects** are those who signed an informed consent form and were assigned a Patient Identification Number (PID)
- **Treated subjects** are enrolled subjects who received at least 1 dose of study therapy (ASV, DCV).
- **Treatment naive subjects on PBO:** naive subjects that were randomized to placebo who received at least 1 dose of placebo. Only demographics, baseline characteristics and safety data through Week 12 will be analyzed for these subjects.

Results were presented by cohort (P/R null or partial responders, intolerant or ineligible to P/R and treatment-naive subjects) and overall for treated subjects, as well as by the subgroup of intolerant or ineligible subjects (Anemia/neutropenia, F3/F4 with thrombocytopenia, depression).

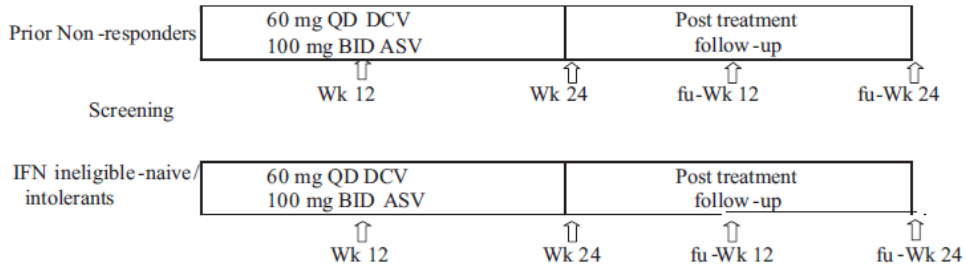
Efficacy analyses were not assessed for treatment naive subjects on PBO; since it is well known that there was no efficacy for untreated subjects the PBO arm was only used to assess safety. For binary efficacy endpoints, response rates and two-sided 95% CIs based on the normal approximation to the binomial distribution will be presented.

❖ **AI447026, a phase 3 study for HCV-1b subjects:**

Title: A Phase 3 Japanese Study of BMS-790052 plus BMS-650032 Combination Therapy in Chronic Hepatitis C Genotype 1b Infected Subjects Who are Non Response to Interferon plus Ribavirin and Interferon Based Therapy Ineligible Naive/Intolerant.

A total of approximately 200 subjects (approximately 80 previous non-responders, plus a maximum of 120 IFN-based therapy ineligible naive/intolerant subjects), who were infected with HCV GT-1b, were to receive 60mg of BMS-790052 QD and 100mg of BMS-650032 BID in combination for 24 weeks and were to be followed for 24 weeks, regardless of HCV RNA status at the EOT. Thus, the maximum duration of the study was 24 weeks (Figure 2).

There were a total of 222 subjects enrolled in the study; 87 subjects were in the prior non-responder cohort and 135 subjects were in the intolerant/ineligible cohort.



Abbreviations: BID - twice daily, BMS-650032 - asunaprevir, BMS-790052 - daclatasvir, fu-Wk - follow-up Week, QD - once daily

Figure 2: Study Diagram of AI447026

Study Population: Males and females 20 to 75 years of age with GT-1b chronic HCV infection who are non-responders to alfa/RBV or beta/RBV, and IFN based therapy ineligible naive/intolerant subjects.

Non-responders were defined as subjects who never attained undetectable HCV RNA levels after a minimum of 12 weeks of alfa/RBV or beta/RBV IFN-based therapy.

Ineligible naive/intolerant subjects were defined as follows:

- IFN-based therapy ineligible naive patients have never been exposed to any HCV therapy with IFN based therapy, and cannot receive IFN based therapy and have no plans to use IFN based therapy in next 12 months because of meeting either of the following criteria; advanced age, anemia, neutropenia, thrombocytopenia, depression, or other complications.

- IFN-based therapy intolerant subjects received IFN based therapy for less than 12 weeks and previously discontinued from the therapy due to the toxicities associated with IFN and/or RBV.

Research Hypothesis:

❖ Co-administration of BMS-790052 and BMS-650032 for 24 weeks for chronic hepatitis C virus (HCV) genotype (GT) 1b infection can achieve sustained virologic response at 24 weeks post-treatment (SVR24) [defined as HCV RNA below LLOQ of 15 IU/mL (target detected or not detected) at Week 24 of post treatment follow-up] rate whose lower bound of the estimated 95% CI is > 45% for non-responder to peg interferon (IFN) alfa plus ribavirin (RBV) (hereinafter, alfa/RBV) or IFN beta plus RBV (hereinafter, beta/RBV) and > 30% for IFN-based therapy ineligible naive/intolerant subjects;

❖ Co-administration of BMS-790052 and BMS-650032 for 24 weeks is safe for the treatment of HCV GT-1b infection among subjects who are non-response to alfa/RBV or beta/RBV and IFN-based therapy ineligible naive/intolerant subjects.

Primary Objective: To assess antiviral activity, as determined by the proportion of subjects with SVR24 for each population.

Primary endpoint: SVR24. The LLOQ used in study AI477026 was 15 IU/mL.

Note that SVR24 in the study is almost identical to SVR12. In order to be consistent with other studies in these NDAs, SVR12 was the primary efficacy endpoint in this review. The lower bound of 95% CI should be higher than the benchmarks listed above in order to claim efficacy. Also, this protocol was not reviewed by the DAVP under the IND.

Analysis populations are the same as for the previous study.

❖ **AI447029, a phase 3 study for HCV-1 and HCV-4 prior non-responder subjects:**

Title: A Phase 3, open-label Study with Asunaprevir and Daclatasvir plus Peg-interferon alfa-2a (Pegasys) and Ribavirin (Copegus) (P/R) (QUAD) for Subjects who are Null or Partial Responders to Peg-interferon Alfa 2a or 2b plus Ribavirin with Chronic Hepatitis C Genotype 1 or 4 Infection.

Approximately 390 HCV subjects (approximately 350 genotype 1 and approximately 40 genotype 4), who failed prior P/R treatment, were treated in this single arm, open-label study. Genotype 1 subjects were comprised of subtypes 1a and 1b. At least 40% of the subjects were to be genotype 1a and at least 40% were to be genotype 1b. All subjects were treated for 24 weeks and were to receive 100 mg BID of ASV (b) (4), 60 mg QD of DCV, and P/R for 24 weeks and followed by 24 weeks of follow-up after completion of treatment or early discontinuation (Figure 3).

Following completion of the post-treatment period of the study, subjects were then asked to enroll into a separate observational study (AI444046) for an additional 3-year follow-up to assess long-term SVR, natural history of the HCV resistance and liver-related complications.

There were 398 subjects enrolled in the study.

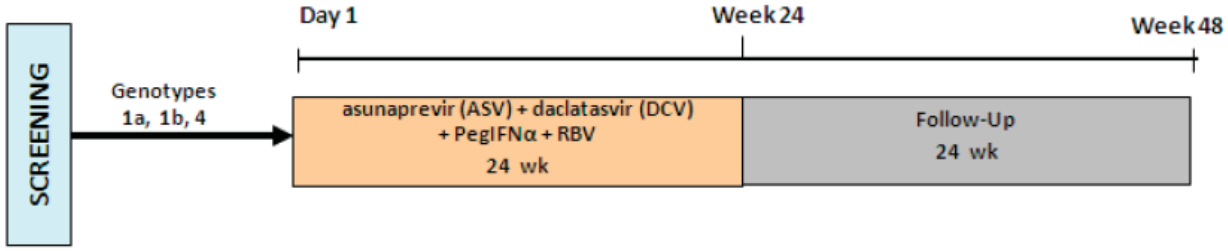


Figure 3: Study Diagram of AI447029

Research Hypothesis:

In subjects who were prior null or partial responders to P/R, co-administration of DCV and ASV with P/R for 24 weeks for the treatment of chronic HCV genotype 1 infection is safe, tolerable and efficacious where efficacy is based on SVR12, defined as HCV RNA < LOQ at post-treatment Week 12.

Primary Endpoint: Proportion of genotype 1 subjects with SVR12, defined as HCV RNA < LOQ at post-treatment Week 12, for all subjects infected with HCV-1. The LLOQ in study AI477029 was 25 IU/mL.

Note that there was no formal sample size calculation. There was no formal hypothesis testing since the expected SVR rate was believed to be much higher than that of the current standard of care (i.e. TVR/pegIFN/RBV) at the time of protocol review.

In statistical review for IND (b) (4) SN241, SDN 244, it stated that "there are 22/23 prior null responders in AI447017 plus AI447011 reached SVR; SVR=96% with 95% CI of [78%, 100%], and BMS anticipates a lower limit of the 95% CI with QUAD in null responders to be 93% using exact methods given the sample size; this is well above the 59% upper limit of the 95% CI for TVR + pegIFNα/RBV.

Reviewer Comment: No formal hypothesis testing or benchmark was proposed from this trial; however, the benchmark of 59% for the non-responder cohort from trial 7028 could be applied to this same prior non-responder population. The efficacy rates for all subgroups (e.g. genotype 1a, 1b and 4, cirrhotic and non-cirrhotic) of trial 7029 far exceed the prior standard of care benchmark.

SVR12 rates were analyzed via proportions and two-sided, 95% confidence intervals. The confidence intervals were based on normal approximations.

The primary analysis of the SVR12 rate was based on treated subjects. Subjects with missing post-treatment week 12 measurements and subjects who received non-study anti-HCV medication prior to post-treatment week 12 were counted as non-responders.

Analysis populations were the same as in the previous studies.

Analysis Windows

Day 1 is the first dose of active study therapy. The analysis windows are listed in Table 3 below.

Table 3 Analysis Windows for Phase 3 Studies

Study Period Label	Visit Label	Visit Number	Target Day from Start of Study Period	Visit Window
PRE-TREAT	PRE-TREAT	1	1	< 1 day[a]
ON-TREAT	DAY 1	2	1	1 - 4 days
	WEEK 1	3	7	5 days - 11 days
	WEEK 2	4	14	12 days - 3 weeks
	WEEK 4	5	28	> 3 weeks - 5 weeks
	WEEK 6	6	42	> 5 - 7 weeks
	WEEK 8	7	56	> 7 - 11 weeks
	WEEK 12	8	84	> 11 - 14 weeks
	WEEK 16	9	112	> 14 - 18 weeks
	WEEK 20	10	140	> 18 - 22 weeks
	WEEK 24	11	168	> 22 - 26 weeks
	WEEK 24 EXT	12	224	> 26 weeks
FOLLOW-UP	F/U WEEK 4	13	21	> 1 - 6 weeks
	F/U WEEK 12	14	77	> 6 - 18 weeks
	F/U WEEK 24	15	161	> 18 - 30 weeks
	F/U WEEK 24 EXT	16	245	> 30 weeks

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

3.2.2.1 Disposition

The statistical reviewer was able to reproduce the applicant's disposition results for the three studies.

Tables 4, 5 and 6 describe subject disposition for the phase 3 trials. Overall, the majority of subjects (87% and 89% in studies 7026 and 7028 respectively) completed dual therapy while 95% completed quad therapy. Across all three trials, the main reason for not completing

treatment was due to lack of efficacy with 7%, 8% and 3% of subjects having this reason in trials 7026, 7028 and 7029, respectively. Adverse Events led to discontinuation in 2% of the subjects in trials 7028 and 7029, and 5% of the subjects in trial 7026.

Table 4: Subjects Disposition for study AI447026 (Treated Subjects)

	Prior	TN_IN	Total
Treated	87	135	222
Completed Treatment Period			
YES	73(83.9%)	121(89.6%)	194(87.4%)
NO	14(16.1%)	14(10.4%)	28(12.6%)
Reasons for NOT completing treatment			
LACK OF EFFICACY	11(12.6%)	4(3.0%)	15(6.8%)
ADVERSE EVENT	2(2.3%)	9(6.7%)	11(5.0%)
SUBJECT REQUEST TO DISCONTINUE TREATMENT	1(1.1%)	1(0.7%)	2(0.9%)
NUMBER OF SUBJECTS USING RESCUE-TREATMENT	9(10.3%)	0	9(4.0%)
Completed Rescue-Treatment			
YES	7(8.0%)	.(. %)	7(3.2%)
NO (LACK OF EFFICACY)	2(2.3%)	.(. %)	2(0.9%)

Table 5: Subjects Disposition for study AI447028 (Treated Subjects)

	Prior	TN_IN	TN	Total
Treated	205	235	203	643
Completed Treatment Period				
YES	177(86.3%)	208(88.5%)	188(92.6%)	573(89.1%)
NO	28(13.7%)	27(11.5%)	15(7.4%)	70(10.9%)
Reasons for NOT completing treatment				
ADVERSE EVENT	2(1.0%)	2(0.9%)	6(3.0%)	10(1.6%)
LACK OF EFFICACY	26(12.7%)	20(8.5%)	8(3.9%)	54(8.4%)
LOST TO FOLLOW-UP	.(. %)	.(. %)	1(0.5%)	1(0.2%)
SUBJECT REQUEST TO DISCONTINUE	.(. %)	1(0.4%)	.(. %)	1(0.2%)
SUBJECT WITHDREW CONSENT	.(. %)	4(1.7%)	.(. %)	4(0.6%)

Table 6: Subjects Disposition for study AI447029 (Treated Subjects)

	GT1a	GT1b	GT4	Total
Treated	176	178	44	398
Completed Treatment Period				
YES	163(92.6%)	172(96.6%)	44(100.0%)	379(95.2%)
NO	13(7.4%)	6(3.4%)	.(. %)	19(4.8%)
Reasons for NOT completing treatment				
ADVERSE EVENT	2(1.1%)	5(2.8%)	.(. %)	7(1.8%)
LACK OF EFFICACY	10(5.7%)	1(0.6%)	.(. %)	11(2.8%)
LOST TO FOLLOW-UP	1(0.6%)	.(. %)	.(. %)	1(0.3%)

3.2.2.3 Demographic and Baseline Characteristics

❖ **Study AI447026**

The percentage of females was somewhat higher in prior non-responders (55% female vs. 45% male), and much higher for TN_IN subjects (72% female vs. 28% male). Mean age was approximately 61 years old with approximately 40% of the subjects age 65 and over. At baseline 92% of prior non-responders and 81% of TN_IN subjects had baseline HCV RNA≥800,000 copies/ml. Approximately 80% of subjects in both cohorts had BMI ≤ 25 kg/m^2 at baseline. Thirteen percent (13%) of prior non-responders and 8% of TN-IN subjects were cirrhotic at baseline. The majority of prior non-responders (76%) had the IL28B CT genotype while the majority of TN_IN subjects (70%) had the IL28B CC genotype. Ineligibility for interferon was primarily due to thrombocytopenia (21%) followed by advanced age (9%) and anemia (9%). Prior non-responders consisted of 55% who were null responders and 41% who were partial responders. Please see Table 16 in the Appendix for details.

Median drug compliance was 100% with 84% of prior non-responders and 89% of TN_IN subjects having at least 95% compliance. The duration of treatment compliance was 93% in both cohorts.

❖ **Study AI447028**

Slightly more than half of the subjects were female, while 70% of the subjects were white, 11% were Chinese, 10% were Korean and 5% were Black/African American. Only 4% of the subjects were Hispanic/Latino. Mean age was 57 years old with 21% of the subjects age 65 and over. The percentage of subjects who had baseline HCV RNA≥800,000 copies/ml ranged from 74% in TN subjects to 87% in prior non-responders. Forty-seven percent of subjects had BMI ≤ 25 kg/m^2 at baseline. The percentage of subjects who were cirrhotic at baseline ranged from 16% in TN subjects to 47% in TN_IN subjects. The majority of subjects had the IL28B CT genotype (ranging from 45% of TN_IN subjects to 61% in prior non-responders). Ineligibility for interferon was primarily due to anemia or neutropenia (37%) followed by compensated advanced fibrosis/cirrhosis (33%) and depression (30%). The majority of subjects were from Europe (43%) followed by N. America (24%) and Asia (22%). Please see Table 17 in the Appendix for details.

❖ **Study AI447029**

Unlike the other two trials, the majority of subjects (69%) were male, while 76% of the subjects were white, 9% were black/African American, and 7% were Native Hawaiian/Other Pacific Islanders. Nine percent (9%) of the subjects were Hispanic/Latino, ranging from 4.5% of GT 4 subjects to 10% of GT 1a subjects. Mean age was 53 years old with 9% of the subjects age 65 and over. The percentage of subjects who had baseline HCV RNA≥800,000 copies/ml ranged from 66% in GT 4 subjects to 91% in GT 1a subjects. The majority of subjects (42%) had

25≤BMI<30 kg/m^2 at baseline. The percentage of subjects who were cirrhotic at baseline ranged from 16% in GT 1b subjects to 45% in GT 4 subjects. The majority of subjects (66%) had the IL28B CT genotype. Two-thirds (67%) were prior null responders while the remaining 33% were partial responders. The majority of GT 1a subjects were from N. America (52%) while the majority of GT 1b and GT 4 subjects were from Europe (53% and 66% respectively). Please see Table 18 in the Appendix for details.

3.2.3 Statistical Methodologies

Ninety-five percent (95%) CIs were calculated for the SVR rates for each cohort separately within each study. Binary antiviral activity endpoints were assessed by the applicant using modified intent-to-treat (ITT) population and only subjects with observed values. The numerator was based on subjects meeting the response criteria. For modified ITT (mITT), the denominator was based on all treated subjects. For observed values, the denominator was based on subjects with available measurements at the analysis week(s). The applicant presented response rates with two-sided 95% exact binomial confidence intervals (CIs).

3.2.4 Results and Conclusions

3.2.4.1 Summary of Applicant's Results

❖ **Study AI447026**

In Japanese study AI447026, SVR24 rates were 80.5% and 87.4% for prior non-responders and IFN Ineligible-Naïve/Intolerant subjects (Table 7). Relapse rates were approximately 8% in both cohorts while more prior non-responders had virologic breakthroughs (11.5%) compared to only 3% for IFN Ineligible-Naïve/Intolerant subjects.

SVR12 rates were 80.5% and 88.1% for prior non-responders and IFN Ineligible-Naïve/Intolerant subjects, which were almost identical to the SVR24s except one subject in the IFN Ineligible-Naïve/Intolerant cohort.

In this study, HCV RNA LLOQ was 15 IU/mL while in studies 7028 and 7029 the LLOQ were 25 IU/mL.

Mean HCV RNA changes from baseline in study AI447026 treated subjects measured in $\log_{10}$ IU/mL are shown in Figure 4 below.

Table 7: Applicant's SVR12 Results for Study AI447026 (Treated Subjects)

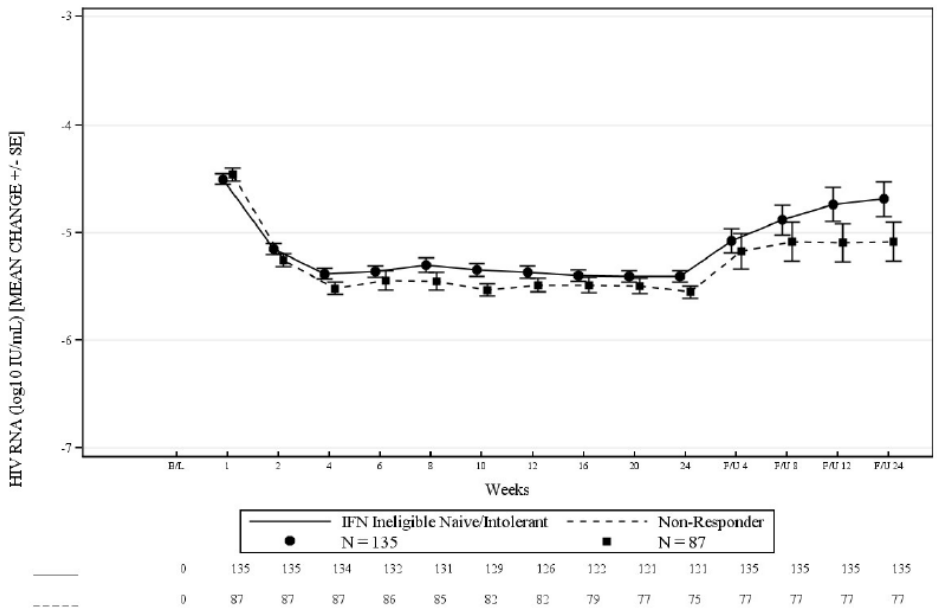
Table 4: Efficacy Results: All Treated Subjects

Modified ITT	Prior Non-responder (N = 87)	IFN Ineligible-Naive/Intolerant (N = 135)	Total (N = 222)
Virologic Endpoints (Responder /N) %			
Primary Endpoint			
SVR24	70 (80.5)	118 (87.4)	188 (84.7)
95% CI	(72.1, 88.8)	(81.8, 93.0)	(79.9, 89.4)
Secondary and Other Efficacy Endpoints			
RVR	53 (60.9)	114 (84.4)	167 (75.2)
95% CI	(50.7, 71.2)	(78.3, 90.6)	(69.5, 80.9)
cEVR	77 (88.5)	125 (92.6)	202 (91.0)
95% CI	(81.8, 95.2)	(88.2, 97.0)	(87.2, 94.8)
eRVR	48 (55.2)	106 (78.5)	154 (69.4)
95% CI	(44.7, 65.6)	(71.6, 85.4)	(63.3, 75.4)
EOTR	76 (87.4)	129 (95.6)	205 (92.3)
95% CI	(80.4, 94.3)	(92.1, 99.0)	(88.8, 95.8)
SVR12	70 (80.5)	119 (88.1)	189 (85.1)
95% CI	(72.1, 88.8)	(82.7, 93.6)	(80.5, 89.8)
Total with Virologic Failure	17 (19.5)	17 (12.6)	34 (15.3)
On-Treatment Virologic Failure	11 (12.6)	6 (4.4)	17 (7.7)
Virologic Breakthrough	10 (11.5)	4 (3.0)	14 (6.3)
Detectable HCV RNA at EOT	1 (1.1)	2 (1.5)	3 (1.4)
Relapse (in subjects who were HCV RNA < LLOQ, TND at EOT)	6/76 (7.9)	11/129 (8.5)	17/205 (8.3)

Abbreviations: cEVR - complete early virologic response (HCV RNA < LLOQ, TND at Week 12), CI - confidence interval, DCV - daclatasvir, EOT - end of treatment, EOTR - HCV RNA < LLOQ, TND at EOT, eRVR - extended rapid virologic response (HCV RNA < LLOQ, TND at both Week 4 and 12), HCV - hepatitis C virus, ITT - intent-to-treat, < LLOQ - less than the lower limit of quantitation, RNA - ribonucleic acid, RVR - rapid virologic response (HCV RNA < LLOQ, TND at Week 4), SVR12/SVR24 - sustained virologic response (< LLOQ [< 15 IU/mL], TD or TND HCV RNA) at follow-up Weeks 12 and 24, respectively, TD - target detected, TND - target not detected

Source: study AI447026 CSR, Table 4.

Figure 7.3.4-1: Mean HCV RNA Changes from Baseline, Treated Subjects



(Source: study CSR, Figure 7.3.4-1)

Figure 4: Mean HCV RNA Change from Baseline for Study AI447026 **(Observed Values for Treated Subjects)**

❖ **Study AI447028**

According to the applicant, the two treatment naive subjects assigned rather than randomized to DCV/ASV were excluded from the treatment-naive cohort in efficacy tables but included in tables covering other domains because efficacy analyses were done following the intent-to-treat (ITT) principle (grouping as randomized).

In study AI447028, SVR12 rates were 82% for prior null or partial responders and intolerant/ineligible cohorts and 90% for TN subjects (Table 8). Relapse rates ranged from 4-6% while on-dual treatment failure rates were higher in prior null or partial responders and intolerant/ineligible cohorts (14% and 12% respectively) compared to only 6% for TN subjects).

Mean HCV RNA changes from baseline in study AI447028 treated subjects ranged from 4 to 5 $\log_{10}$ IU/mL after 12 and 24 weeks of post-treatment follow-up as shown in Figure 5.

Table 8: Applicant's SVR12 Results for Study AI447028 (Treated Subjects)

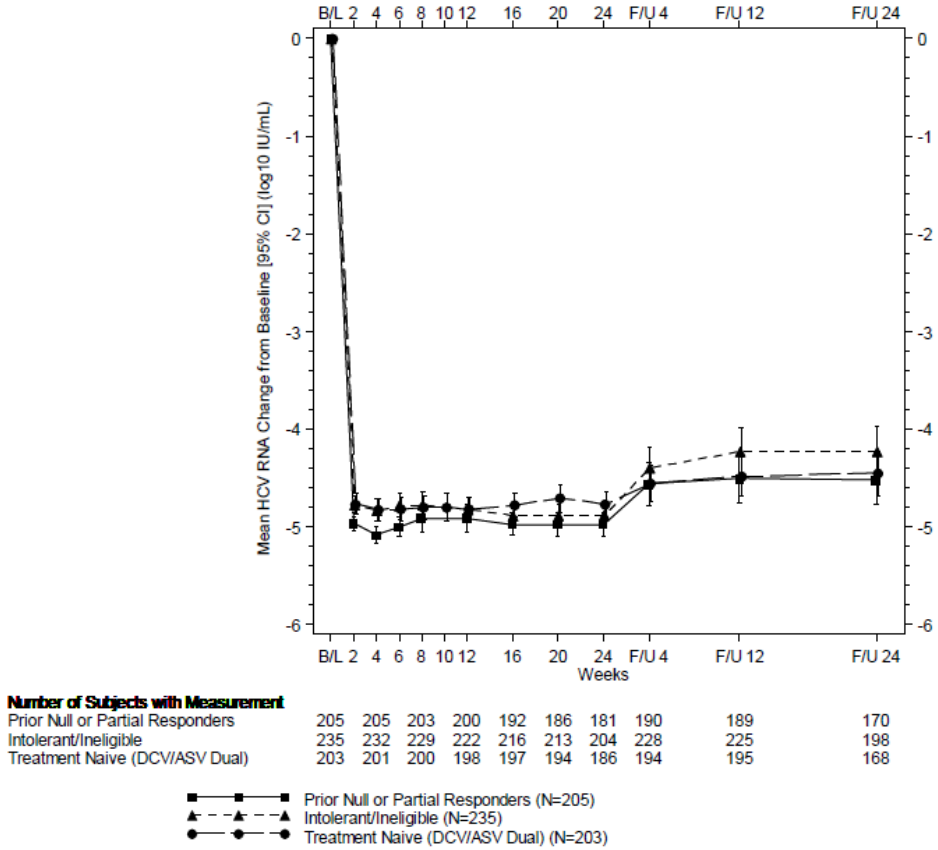
Table 7.2-1: Summary of SVR12 Responder and Non-responder Outcomes to Active DCV/ASV, Treated Subjects

Number of Subjects (%)	Prior Null or Partial Responders N=205	Intolerant/ Ineligible N=235	Treatment Naive (DCV/ASV Dual) N=203	Total N=643
RESPONDER (SVR12)	168/205 (82.0)	192/235 (81.7)	182/203 (89.7)	542/643 (84.3)
RESPONDER (SVR12 - IMPUTATION FOR MISSING VALUES) [1]	169/205 (82.4)	194/235 (82.6)	184/203 (90.6)	547/643 (85.1)
VIROLOGIC FAILURE (NON-SVR12)	37/205 (18.0)	43/235 (18.3)	21/203 (10.3)	101/643 (15.7)
NON-RESPONDERS WITH HCV RNA < LLOQ TND AT EOT	8/205 (3.9)	14/235 (6.0)	8/203 (3.9)	30/643 (4.7)
RELAPSER [2]	7/174 (4.0)	12/204 (5.9)	5/189 (2.6)	24/567 (4.2)
RELAPSER [CONFIRMED]	7/174 (4.0)	12/204 (5.9)	5/189 (2.6)	24/567 (4.2)
OTHER NON-RESPONDER [3]	1/174 (0.6)	2/204 (1.0)	3/189 (1.6)	6/567 (1.1)
ON-DUAL TREATMENT FAILURE	29/205 (14.1)	29/235 (12.3)	13/203 (6.4)	71/643 (11.0)
BREAKTHROUGH [4]	26/205 (12.7)	20/235 (8.5)	9/203 (4.4)	55/643 (8.6)
FUTILITY [5]	0/205 (0.0)	1/235 (0.4)	0/203 (0.0)	1/643 (0.2)
OTHER ON-TREATMENT FAILURE [6]	3/205 (1.5)	8/235 (3.4)	4/203 (2.0)	15/643 (2.3)

HCV RNA measurements after the start of rescue therapy or the start of non-study anti-HCV medication are excluded.
[1] Imputation algorithm: similar to the primary analysis, except SVR12 status for subjects with missing post-treatment Week 12 HCV RNA is imputed using the first available HCV RNA measurement after the post-treatment Week 12 window.
[2] Relapse occurs when HCV RNA < LLOQ TND at EOT followed by HCV RNA >= LLOQ at any post treatment visit; confirmed relapse occurs when HCV RNA < LLOQ TND at EOT followed by confirmed HCV RNA >= LLOQ, where confirmed is 2 consecutive measurements >= LLOQ or last available measurement >= LLOQ; relapse and Other Non-Responder rates computed among all subjects with HCV RNA < LLOQ TND at EOT, not just non-responders with HCV RNA < LLOQ TND at EOT.
[3] Other Non-Responder is made up of subjects whose HCV RNA < LLOQ TND at EOT but who are missing post-treatment week 12 HCV RNA.
[4] Breakthrough is confirmed > 1 log10 IU/ml HCV RNA on treatment increase from nadir, or confirmed increase in HCV RNA >= LLOQ if HCV RNA previously declined to < LLOQ TD or TND.
[5] Confirmed HCV RNA >= LLOQ at week 8.
[6] Includes non-responders with missing or detectable HCV RNA at EOT.

Source: study AI447028 CSR, Table 7.2-1.

Figure 7.3.5-1: Mean HCV RNA Changes from Baseline, Treated Subjects



HCV RNA measurements after the start of rescue therapy or the start of non-study anti-HCV medication are excluded.

Figure 5: Mean HCV RNA Change from Baseline in Study AI447028 (Observed Values for Treated Subjects) (Source: study CSR, Figure 7.3.5-1)

❖ Study AI447029

In study AI447029, SVR24 rates were 93% for genotype 1 subjects and 98% for Genotype 4 subjects. Relapse and on-treatment failure rates were 2% and 4% for genotype 1 subjects while none of the genotype 4 subjects relapsed or were on-treatment failures (Table 9).

Mean HCV RNA changes from baseline in study AI447029 treated subjects ranged from 4 to 5 $\log_{10}$ IU/mL after 12 and 24 weeks of post-treatment follow-up as shown in Figure 6.

Note that in Table 9, <LOQ was used to generate SVR12 rates, while <LOD was used for the secondary and other endpoints.

Table 9: Applicant's SVR12 Results for Study AI447029 (Treated Subjects)

Table 4: Efficacy Results Summary - Treated Subjects

	Responder/Evaluable (%), N = 354		
	GT-1 (N = 354)[a]	GT-4 (N = 44)	Overall (N = 398)
Primary Endpoint[b]			
SVR12 (mITT)	329/354 (92.9)	43/44 (97.7)	372/398 (93.5)
95% CI	(90.3, 95.6)	(93.3, 100.0)	(91.0, 95.9)
SVR12 (Imputation for missing values[c])	330/354 (93.2)	44/44 (100.0)	374/398 (94.0)
95% CI	(90.6, 95.8)	(100.0, 100.0)	(91.6, 96.3)
Secondary and Other Endpoints (mITT)[b]			
Rapid Virologic Response (RVR)	292/354 (82.5)	36/44 (81.8)	328/398 (82.4)
95% CI	(78.5, 86.4)	(70.4, 93.2)	(78.7, 86.2)
Extended Rapid Virologic Response (eRVR)	284/354 (80.2)	36/44 (81.8)	320/398 (80.4)
95% CI	(76.1, 84.4)	(70.4, 93.2)	(76.5, 84.3)
Complete Early Virologic Response (cEVR)	337/354 (95.2)	44/44 (100.0)	381/398 (95.7)
95% CI	(93.0, 97.4)	(100.0, 100.0)	(93.7, 97.7)
End of Treatment Response (EOTR)	337/354 (95.2)	43/44 (97.7)	380/398 (95.5)
95% CI	(93.0, 97.4)	(93.3, 100.0)	(93.4, 97.5)
SVR24	313/354 (88.4)	42/44 (95.5)	355/398 (89.2)
95% CI	(85.1, 91.8)	(89.3, 100.0)	(86.1, 92.2)
Total With Virologic Failure[b]			
Virologic failure (Non-SVR12)	25/354 (7.1)	1/44 (2.3)	26/398 (6.5)
Non-responders with HCV RNA < LLOQ, TND at EOT	12/354 (3.4)	1/44 (2.3)	13/398 (3.3)
Relapser[d]	8/337 (2.4)	0/43 (0.0)	8/380 (2.1)
Relapser (confirmed)	8/337 (2.4)	0/43 (0.0)	8/380 (2.1)
Other non-responder[e]	4/337 (1.2)	1/43 (2.3)	5/380 (1.3)
On-treatment failure	13/354 (3.7)	0/44 (0.0)	13/398 (3.3)
Breakthrough[f]	11/354 (3.1)	0/44 (0.0)	11/398 (2.8)
Futility[g]	0/354 (0.0)	0/44 (0.0)	0/398 (0.0)
Other on-treatment failure[h]	2/354 (0.6)	0/44 (0.0)	2/398 (0.5)

Source: study AI447026 CSR, Table 4.

Figure 7.3.6-1: Mean HCV RNA Changes from Baseline - Treated Subjects

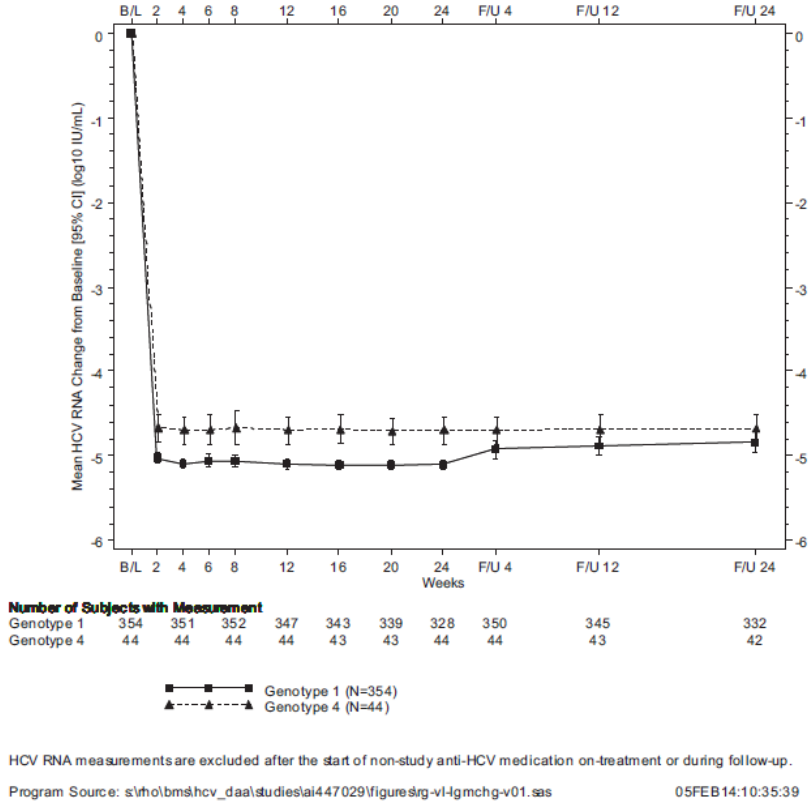


Figure 6: Mean HCV RNA Change from Baseline for Study AI447029 (Observed Values for Treated Subjects) (Source: the CSR Figure 7.3.6-1)

3.2.4.2 Study AI447026 Primary Efficacy Results

- **Primary Efficacy Analysis Results**

The pre-specified primary efficacy endpoint for this study was SVR24. SVR12 and SVR24 results were nearly identical; there was only one less subject in the numerator for SVR24 in the TN_IN cohort (Table 11). SVR12 was considered by the FDA to be the primary efficacy endpoint for consistency purposes. Also, LLOQ was 15 IU/mL in the study.

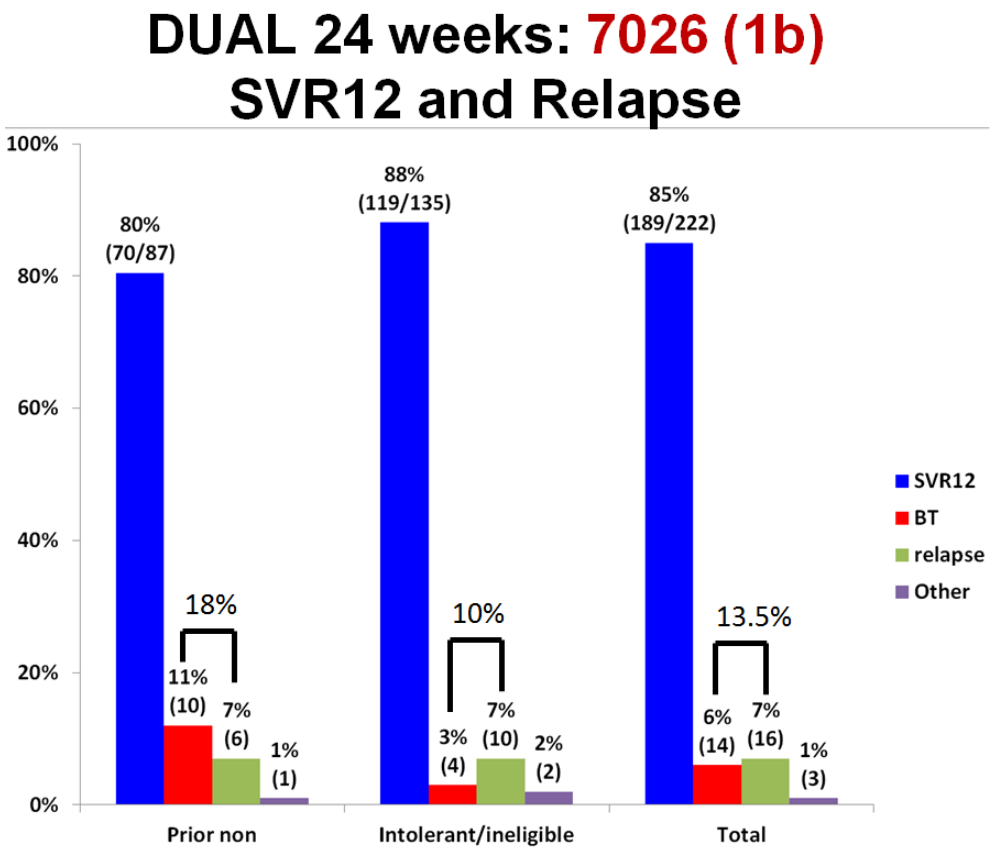
Overall SVR12 rates ranged from 80%-88%, which were almost the same as the applicant's rates (Table 10 and Figure 7). Relapse rates in both cohorts were 8% while virologic breakthrough rates ranged from 3% in TN_IN subjects to 11% in prior non-responder subjects.

Also, there was one subject whose SVR12 was not consistent with the virologic classification in vfail.xpt file; subject 20035 had SVR12 as success and virologic category as relapse because the subject missed the follow-up Week 24 visit, and relapse was calculated using data at follow-up Week 24 visit as well as end-of-treatment (EOT). In these cases, SVR12 took the first priority over virologic classification for summarizing Table 10. Please see Table 19 in the Appendix for details.

Table 10: SVR12 (using <LOQ) and Virologic Failure Rates for Study AI447026 (Treated Subjects)

Cohort	Prior N=87	TN_IN N=135	Total N=222
Responder (SVR12)	**70(80.5%)**	**119(88.1%)**	**189(85.1%)**
95% CI	**(70.6%, 88.2%)**	**(81.5%, 93.1%)**	**(79.8%, 89.2%)**
Reasons of Virologic Failure	17(19.5%)	16(11.9%)	33(14.9%)
VIROLOGIC BREAKTHROUGH	10(11.5%)	4(3.0%)	14(6.3%)
RELAPSE*	6	10	16
DETECTABLE HCV at EOT	1(1.1%)	2(1.5%)	3(1.4%)
Relapse rate**	**6/76(7.9%)**	**10/129(7.8%)**	**16/205(7.8%)**

*: Notes that there was no % for the relapse row. Please see the last row for the relapse rates.
**: Relapse rates were calculated with a denominator of subjects with undetectable HCV RNA at the end of treatment (EOT). Please see Table 11 below for the source of denominators (that is undetectable at EOT using LOD).



Prior non: prior non-responders including Null/partial responders, BT: Breakthrough.
NB: Relapse percentage in figures is total number of relapses / total number of treated subjects in the cohort. This is not the relapse rate defined in the table.

Figure 7: Study AI447026 SVR12, Relapse, Breakthrough, and Other Reasons for Discontinuation (Treated Subjects)

➢ **Secondary Efficacy Analysis Results**

Results of some secondary efficacy endpoints are listed in Table 11 below.

Table 11: Secondary Efficacy Results for Study AI447026 (Treated Subjects)

Parameters analyzed n(%) (95% CI)	Prior Non-responders (N=87)	IFN Ineligible- Naïve/Intolerant (N=135)	Total (N=222)
SVR24	**70 (80.5%)** **(70.6%, 88.2%)**	**118 (87.4%)** **(80.6%, 92.5)**	**188 (84.7%)** **(79.3%, 89.2%)**
SVR12	70 (80.5%) (70.6%, 88.2%)	**119 (88.1%)** **(81.5%, 93.1%)**	189 (85.1%) (79.8%, 89.5%)
EOT	76 (87.4%) (78.5%, 93.5%)	129 (95.6%) (90.6%, 98.4%)	205 (92.3%) (88.0%, 95.5%)
RVR at WK 4	53 (60.9%) (49.9%, 71.2%)	114 (84.4%) (77.2%, 90.1%)	167 (75.2%) (69.0%, 80.8%)
cEVR at WK 12	77 (88.5%) (80.0%, 94.4%)	125 (92.6%) (86.8%, 96.4%)	202 (91.0%) (86.4%, 94.4%)
eRVR	48 (55.2%) (44.1%, 65.9%)	106 (78.5%) (70.1%, 85.1%)	154 (69.4%) (62.9%, 75.4%)

3.2.4.3 Study AI447028 Primary Efficacy Results

Overall, the statistical reviewer obtained the same SVR12 (<LOQ) results as the applicant.

The efficacy analysis was based on the mITT population which included subjects who were randomized and had at least one dose of randomized study drug. The applicant also referred to the mITT population as treated subjects.

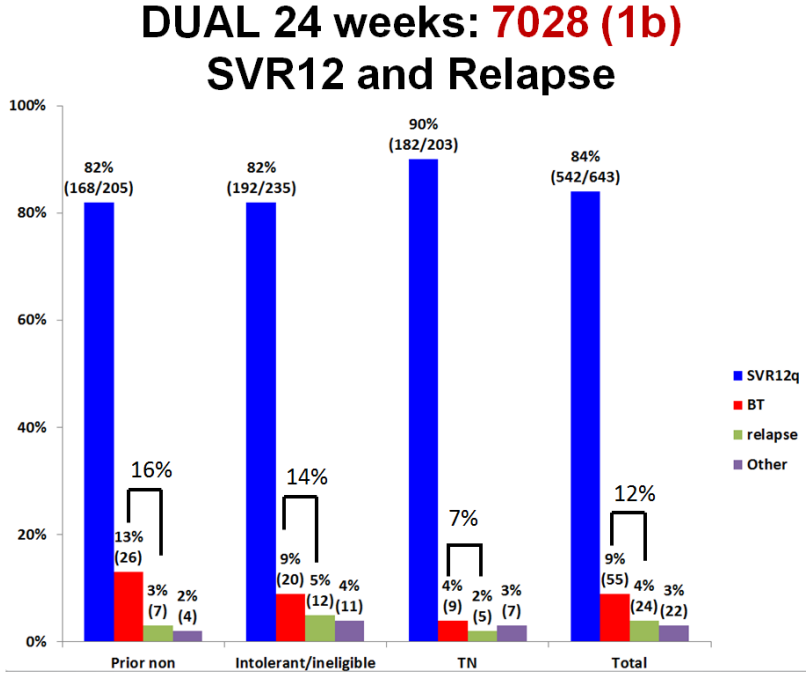
➢ **Primary Efficacy Analysis Results**

Overall SVR12 (<LOQ) rates ranged from 82%-90%, which were the same as the applicant's rates (Table 12 and Figure 8). Virologic Failure rates ranged from 10% in TN subjects to 18% in prior non-responders and TN_IN subjects. Virologic Breakthrough accounted for most of the virologic failures, followed by relapse. Virologic breakthrough rates ranged from 4% in TN subjects to 13% in prior non-responder subjects while relapse rates ranged from 3-6%.

Table 12: SVR12 (using <LOQ) and Virologic Failure Rates for Study AI447028 (Treated Subjects)

	Prior N=205	TN_IN N=235	TN N=203	Total N=643
Responder (SVR12)	**168(82.0%)**	**192(81.7%)**	**182(89.7%)**	**542(84.3%)**
95% CI	**(76.0%, 87.0%)**	**(76.2%, 86.4%)**	**(84.6%, 93.4%)**	**(81.3%, 87.0%)**
Virologic Failure	37(18.0%)	43(18.3%)	21(10.3%)	101(15.7%)
Reasons of Virologic Failure				
RELAPSE*	7	12	5	24
MISSING FU WEEK 12 VISIT	1(0.5%)	3(1.3%)	4(2.0%)	8(1.2%)
VIROLOGIC BREAKTHROUGH	26(12.7%)	20(8.5%)	9(4.4%)	55(8.6%)
DETECTABLE HCV RNA AT EOT	3(1.5%)	7(3.0%)	3(1.5%)	13(2.0%)
CONFIRMED HCV RNA>=LOQ AT WK8	.(. %)	1(0.4%)	.(. %)	1(0.2%)
Relapse rate**	**7/174 (4%)**	**12/204 (6%)**	**5/189 (3%)**	

*: Notes that there was no % for the relapse row. Please see the last row for the relapse rates.
**: Relapse rates were calculated with a denominator of subjects with undetectable HCV RNA at the end of treatment (EOT). Please see Table 13 below for the source of denominators (that is undetectable at EOT using LOD).



Prior non: prior non-responders including Null/partial responders, BT: Breakthrough.
NB: Relapse percentage in figures is total number of relapses / total number of treated subjects in the cohort. This is not the relapse rate defined in the table.

Figure 8: Study AI447028 SVR12, Relapse, Breakthrough, and Other Reasons for Discontinuation (Treated Subjects)

Note that the FDA snapshot approach was used to generate the SVR12 rate results here. If the first available HCV RNA measurement after the post-treatment Week 12 window was used to impute the SVR12 status for subjects with missing post-treatment Week 12 HCV RNA data, five subjects in total became successes. Please see Table 8 above for details. These results were not listed in the reviewer's table (Table 12) because of two reasons:

- If so, the numbers under the "Reasons of Virologic Failure" will be changed;
- The difference is very minor.

Also, there were total of 15 subjects whose SVR12 (using <LOQ) were not consistent with the virologic classification in vfail.xpt file. In these cases, SVR12 was given priority over virologic classification for summarizing Table 12. Please see Table 20 in the Appendix for details.

➢ **Secondary Efficacy Analysis Results**

Results of some secondary efficacy endpoints are listed in Table 13 below.

SVR24 (<LOQ) rates were approximately 10% lower than corresponding SVR12 rates. Since the post-treatment follow-up is ongoing in this study and SVR24 was only observed in 88.6% of evaluable subjects treated with DCV/ASV according to the CSR on page 16, an observed value approach was used for the analysis of the SVR at post-treatment Week 24 (SVR24) counting the unobserved subjects as non-responders.

The CSR stated that there was 99.8% concordance between SVR24 and SVR12 rates. This was not an accurate statement since the estimated concordance only used subjects who had both SVR12 and SVR24 observed; therefore this was not a complete analysis.

Table 13: Secondary Efficacy Results for Study AI447028 (Treated Subjects)

Parameters analyzed n(%) (95% CI)	Prior Non-responders (N=205)	IFN Ineligible-Naïve/Intolerant (N=235)	Treatment-Naïve (randomized) (N=203)	Total (N=643)
SVR24 (LOD)	150 (73.2) (66.6, 79.1)	167 (71.1) (64.8, 76.8)	154 (75.9) (69.4, 81.6)	471 (73.3) (69.7, 76.6)
SVR24 (LOQ)	152 (74.2) (67.6, 80.0)	168 (71.5) (65.3, 77.2)	155 (76.4) (70.0, 82.0)	475 (73.9) (70.3, 77.2)
SVR12 (LOD)	166 (81.0) (74.9, 86.1)	**185 (78.7) (72.9, 83.8)**	180 (88.7) (83.5, 92.7)	531 (82.6) (79.4, 85.4)
SVR12 (LOQ)	**168 (82.0) (76.0, 87.0)**	**192 (81.7) (76.2, 86.4)**	**182 (89.7) (84.6, 93.5)**	**542 (84.3) (81.3, 87.0)**
<LOD was used to generate the following endpoints				
EOT	174 (84.9) (79.2, 89.5)	204 (86.8) (81.8, 90.9)	189 (93.1) (88.7, 96.2)	567 (88.2) (85.4, 90.6)
RVR at WK 4	150 (73.2) (66.6, 79.1)	159 (67.7) (61.3, 73.6)	168 (82.8) (76.9, 87.7)	477 (74.2) (70.6, 77.5)
cEVR at WK 12	182 (88.8) (83.6, 92.8)	205 (87.2) (82.3, 91.2)	191 (94.1) (89.9, 96.9)	578 (89.9) (87.3, 92.1)
eRVR	140 (68.3) (61.5, 74.6)	149 (63.4) (56.9, 69.6)	163 (80.3) (74.2, 85.5)	452 (70.3) (66.6, 73.8)

3.2.4.4 Study AI447029 Efficacy Results

Overall, the statistical reviewer obtained the same SVR12 (<LOQ) results as the applicant.

- **Primary Efficacy Analysis Results**

Overall SVR12 rates ranged from 87% in genotype 1a subjects to 99% in genotype 1b subjects. Relapse rates were 5% in genotype 1a subjects while there were no relapses in genotype 1b and 4 subjects. Virologic breakthrough rates ranged from 0% in genotype 4 subjects to 6% in genotype 1a subjects. The relapse rate in HCV-1a cohort was 5%, and 0% for other two cohorts.

Virologic Failure rates ranged from 1% in genotype 1b subjects to 13% in genotype 1a subjects. Virologic Breakthrough accounted for most of the virologic failures, followed by relapse.

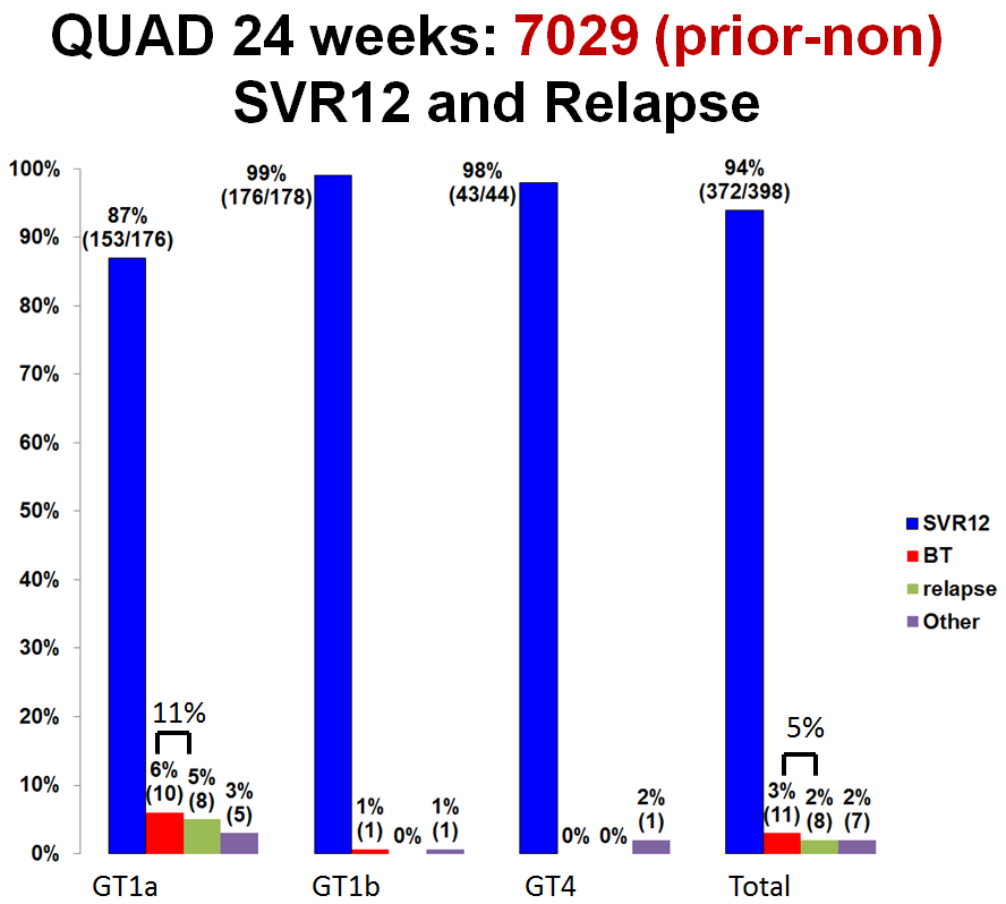
Note that the FDA snapshot approach was used to generate the SVR12 rate results here. If using the first available HCV RNA measurement after the post-treatment Week 12 window to impute the SVR12 status for subjects with missing post-treatment Week 12 HCV RNA data, two subjects in total became successes. Please see Table 9 above for details.

Also, there were total of 14 subjects whose SVR12 (using <LOQ) were not consistent with the virologic classification in vfail.xpt file. In these cases, SVR12 took the first priority over virologic classification for summarizing Table 14. Please see Table 21 in the Appendix for details.

Table 14: SVR12 (using <LOQ) and Virologic Failure Rates for Study AI447029 (Treated Subjects)

	GT1a N=176	GT1b N=178	GT4 N=44	Total N=398
Responder (SVR12)	**153(86.9%)**	**176(98.9%)**	**43(97.7%)**	**372(93.5%)**
95% CI	**(81.0%, 91.5%)**	**(96.0%, 99.9%)**	**(88.0%, 99.9%)**	**(90.6%, 95.7%)**
Virologic Failure	23(13.1%)	2(1.1%)	1(2.3%)	26(6.5%)
Reasons of Virologic Failure				
VIROLOGIC BREAKTHROUGH	10(5.7%)	1(0.6%)	.(. %)	11(2.8%)
DETECTABLE HCV RNA AT EOT	2(1.1%)	.(. %)	.(. %)	2(0.5%)
RELAPSE(CONFIRMED)	8	.	.	8
NOT A VIROLOGIC FAILURE	3(1.7%)	1(0.6%)	1(2.3%)	5(1.3%)
Relapse rate**	**8/162(4.9%)**	**0/175(0%)**	**0/43(0%)**	

*: Notes that there was no % for the relapse row. Please see the last row for the relapse rates.
**: Relapse rates were calculated with a denominator of subjects with undetectable HCV RNA at the end of treatment (EOT). Please see Table 13 below for the source of denominators (that is undetectable at EOT using LOD).



NB: Relapse percentage in figures is total number of relapses / total number of treated subjects in the cohort. This is not the relapse rate defined in the table.

Figure 9: Study AI447029 SVR12, Relapse, Breakthrough, and Other Reasons for Discontinuation (Treated Subjects)

- **Secondary Efficacy Analysis Results**

Results of some secondary efficacy endpoints are listed in Table 15 below.

Table 15: Secondary Efficacy Results for Study AI447029 (Treated Subjects)

Parameters analyzed n(%) (95% CI)	GT1a (N=176)	GT1b (N=178)	GT4 (N=44)	Total (N=398)
SVR24 (LOD)	**139 (79.0) (72.2, 84.8)**	**173 (97.2) (93.6, 99.1)**	**41 (93.2) (81.3, 98.6)**	**353 (88.7) (85.2, 91.6)**
SVR24 (LOQ)	**140 (79.6) (72.8, 85.2)**	**173 (97.2) (93.6, 99.1)**	**42 (95.5) (84.5, 99.4)**	**355 (89.2) (85.7, 92.1)**
SVR12 (LOD)	151 (85.8) (79.8, 90.6)	173 (97.2) (93.6, 99.1)	43 (97.7) (88.0, 99.9)	367 (92.2) (89.1, 94.7)
SVR12 (LOQ)	**153 (86.9) (81.0, 91.5)**	**176 (98.9) (96.0, 99.9)**	**43 (97.7) (88.0, 99.9)**	**372 (93.5) (90.6, 95.7)**
<LOD was used to generate the following endpoints				
EOT	162 (92.1) (87.0, 95.6)	175 (98.3) (95.2, 99.7)	43 (97.7) (88.0, 99.9)	380 (95.50) (93.0, 97.3)
RVR at WK 4	141 (80.1) (73.4, 85.7)	151 (84.8) (78.7, 89.8)	36 (81.8) (67.3, 91.8)	328 (82.4) (78.3, 86.0)
cEVR at WK 12	164 (93.2) (88.4, 96.4)	173 (97.2) (93.6, 99.1)	44 (100) (92.0, 100)	381 (95.7) (93.3, 97.5)
eRVR	136 (77.3) (70.4, 83.2)	148 (83.2) (76.8, 88.3)	36 (81.8) (67.3, 91.8)	320 (80.4) (76.2, 84.2)

3.3 Evaluation of Safety

See the clinical review for the evaluation of safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Note that subgroup analyses need to be interpreted with caution because they were post-hoc (with the exception of gender, race, age and geographic region), with no multiple comparison adjustments, there were inconsistent trends between trials, the limitation of small sample sizes within subgroups and the lack of active-controls.

For HCV-1b subjects, the baseline NS5A polymorphisms of L31 F/I/M/V or Y93H had a significant impact on the SVR12 efficacy results. No other baseline factors had statistically significant effects on the SVR12 efficacy results that were replicated in more than one study. In order to better present this, subgroup analyses based on the baseline polymorphism of HCV-1b subjects in DUAL studies, AI447026 and AI447028, are presented first.

4.1 Baseline NS5A Polymorphism of L31 F/I/M/V or Y93H in HCV-1b in DUAL Studies (AI447026 and AI447028)

❖ **Study AI447026**

Out of 222 subjects enrolled in the study, 8 subjects did not have baseline polymorphism information. As shown in Figure 10, the SVR12 rates for two cohorts for 214 subjects who did have baseline polymorphism are similar to overall SVR12 rates for two cohorts. The SVR12

rates for those 8 subjects are not different from overall SVR12 rates. Please see Table 22 in the Appendix for detailed numbers.

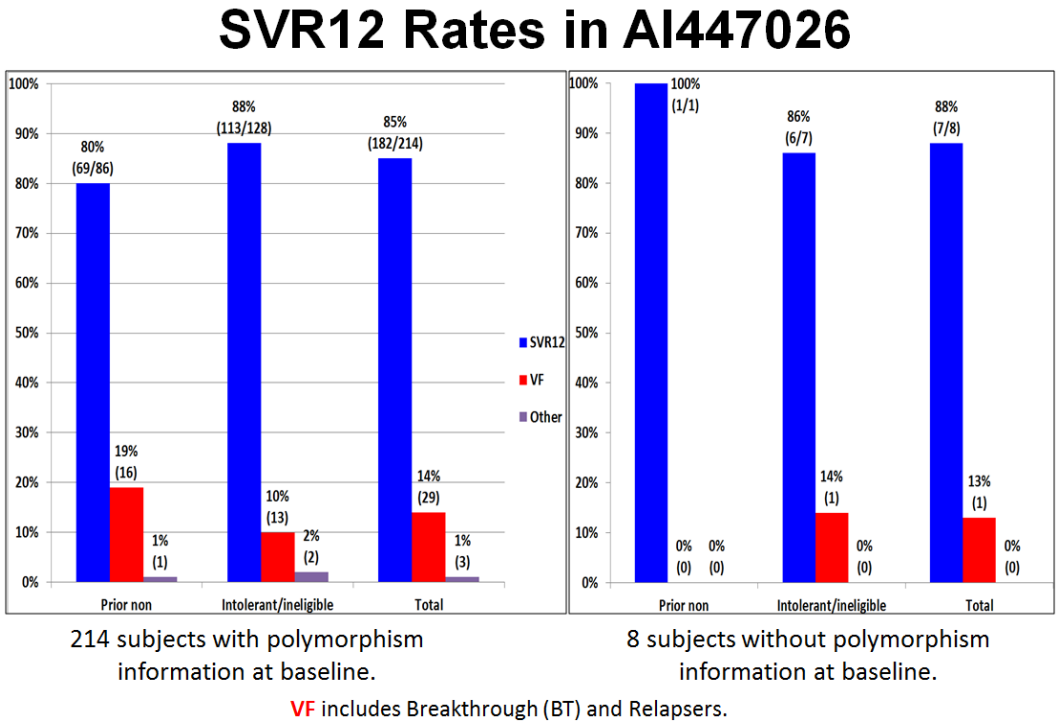


Figure 10: Study AI447026 SVR12, Relapse, Breakthrough, and Other Reasons by Baseline Polymorphism Information Present or Absent (Treated Subjects)

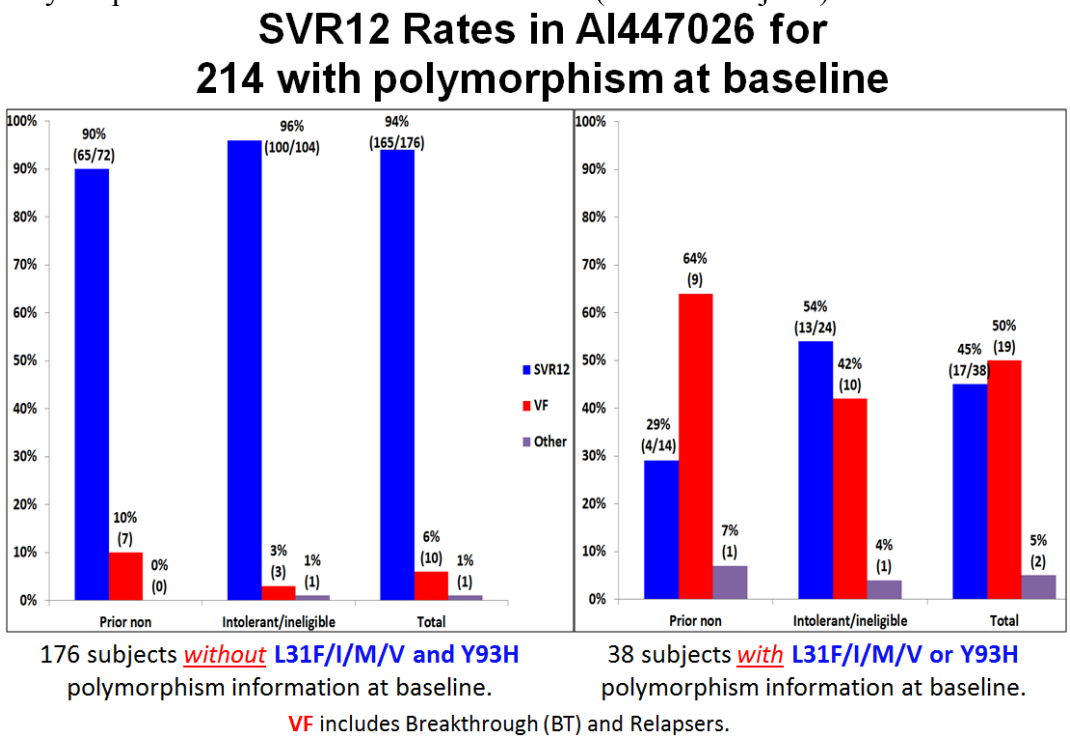


Figure 11: Study AI447026 SVR12, Relapse, Breakthrough, and Other Reasons by Baseline L31F/I/M/V or Y93H Polymorphism Present or Absent (Treated Subjects)

Out of 214 subjects with baseline polymorphism information, 176 subjects did not have baseline **L31F/I/M/V or Y93H** polymorphism; and only 38 subjects had **L31F/I/M/V or Y93H** polymorphism at baseline. As shown in Figure 11, much lower SVR12 rates and much higher VF rates were observed for 38 subjects with L31 F/I/M/V or Y93 polymorphisms at baseline compared to 176 subjects without them. Please see Table 23 in the Appendix for detailed numbers.

❖ **Study AI447028**

Out of 643 subjects enrolled in the study, 46 subjects did not have baseline polymorphism information. As shown in Figure 12, the SVR12 rates for the three cohorts of total 597 subjects who had baseline polymorphism information were similar to SVR12 rates for those 46 subjects who did not have baseline polymorphism information. Please see Table 24 in the Appendix for detailed numbers.

Out of 597 subjects with baseline polymorphism information, 525 subjects did not have baseline **L31F/I/M/V or Y93H** polymorphism; and only 72 subjects had **L31F/I/M/V or Y93H** polymorphism at baseline.

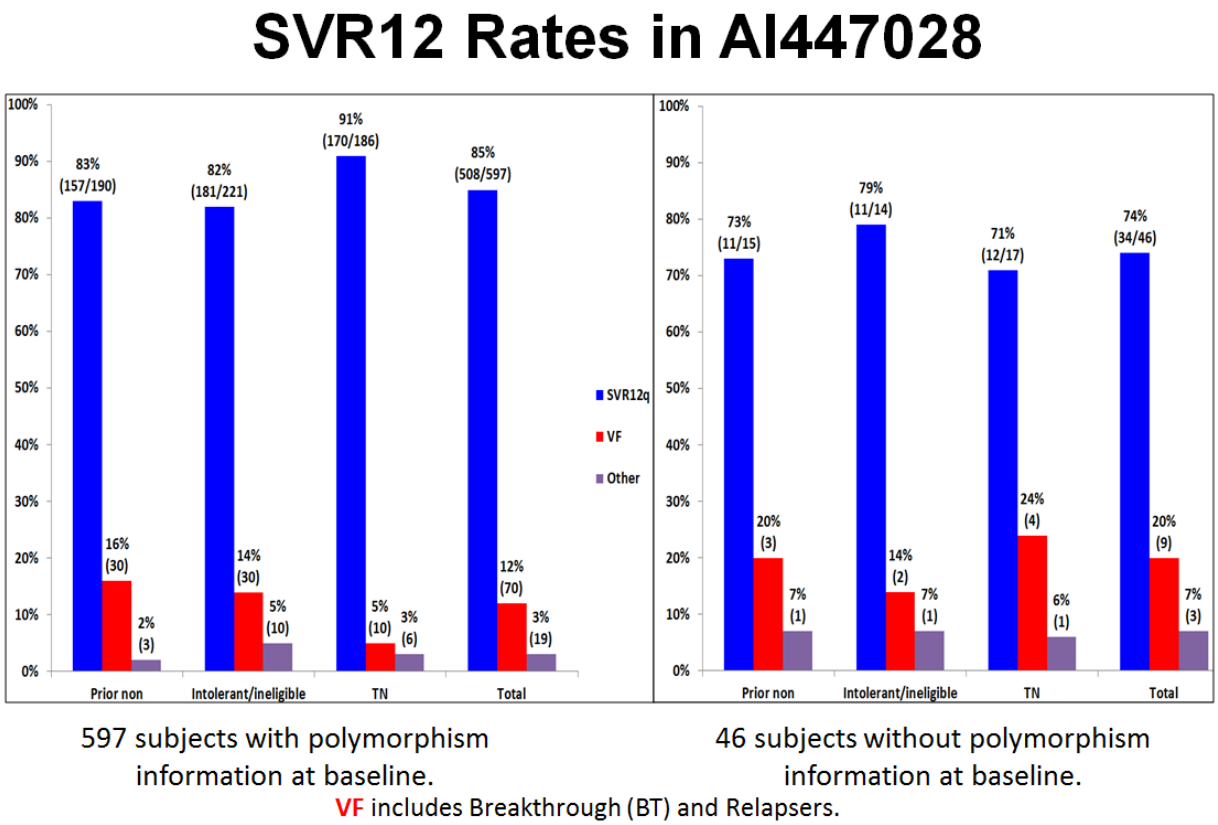


Figure 12: Study AI447028 SVR12, Relapse, Breakthrough, and Other Reasons by Baseline Polymorphism Information Present or Absent (Treated Subjects)

As shown in Figure 13, much lower SVR12 rates and much higher VF rates were observed for 72 subjects with L31 F/I/M/V or Y93 polymorphisms at baseline compared to the 525 subjects without them. Please see Table 25 in the Appendix for detailed numbers.

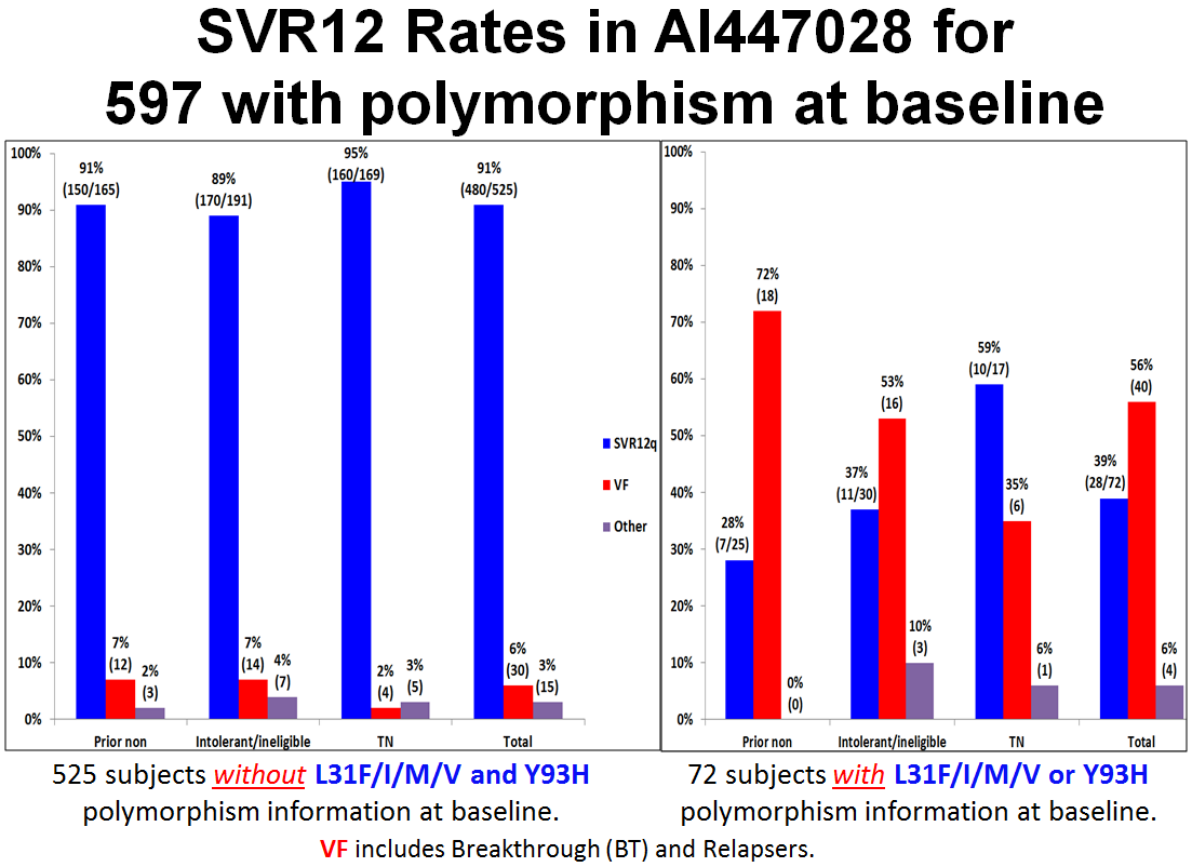


Figure 13: Study AI447028 SVR12, Relapse, Breakthrough, and Other Reasons by Baseline L31F/I/M/V or Y93H Polymorphism Present or Absent (Treated Subjects)

Note that the baseline R30Q and L28M polymorphism were also examined and they did not seem to have as much of an impact on the SVR12. Please see Table 26 and 27 in the Appendix for details.

Please see microbiology review for more information in terms of baseline polymorphism. Note that the microbiology analyses excluded subjects who did not achieve SVR for reasons unrelated to virologic failure. As a result, their numbers may differ from what we presented here.

4.2 Gender, Race, Age, and Geographic Region

For study AI447026 and AI447028, subgroup analyses based on both the all treated subject set and only subjects without L31 F/I/M/V or Y93H polymorphisms at baseline were conducted. For study AI447029 subgroup analyses were conducted based on all treated subjects only.

❖ **Study AI447026**

Among 176 subjects without L31 F/I/M/V or Y93H polymorphisms at baseline, there were no statistically significant gender differences in SVR rates, but there was a higher percentage of subjects over age 65 with an SVR (100% for subjects who were 65 years of age and older compared to 90% for subjects who were younger than age 65, $p<0.007$). However SVR12 rates in subjects age 65 and older and in subjects who were younger than age 65 were similar in Studies AI447028 and AI447029; i.e., this observation is not consistent among studies and there is no statistical or biologic explanation for this age-related finding. Please see Table 28 in the Appendix for details.

Among 222 treated subjects, only age group (>=65 years old vs. <65 years old) had some numeric impact on SVR12. Please see Table 29 in the Appendix for details.

❖ **Study AI447028**

Among 525 subjects without L31 F/I/M/V or Y93H polymorphisms at baseline, none of the age group, gender, race and geographic region prognostic factors had a significant impact on the SVR12. Please see Table 31 in the Appendix for details.

Similar cases observed for all treated subjects. Please see Table 32 in the Appendix for details.

❖ **Study AI447029**

None of the age, gender, race and geographic region prognostic factors had significant impact on the SVR12. Please see Table 34 in the Appendix for details.

4.3 Other Special/Subgroup Populations

The subgroup analysis for other baseline covariates will be presented below for the three studies separately. For study AI447026 and AI447028, subgroup analyses based on both all treated subject set and only subjects without L31 F/I/M/V or Y93H polymorphisms at baseline were conducted. For study AI447029 subgroup analyses were conducted based on all treated subjects only.

4.2.1 Other Baseline Covariates

❖ **Study AI447026**

Among 176 subjects without L31 F/I/M/V or Y93H polymorphisms at baseline, other than the depression finding that was observed for a small subset of subjects who were ineligible for P/R, there were no statistically significant differences in SVR rates for other baseline factors. HCV

RNA viral load at baseline had some numeric impact on SVR12 (the higher SVR12 rates observed in the subjects with lower HCV RNA at baseline and the difference vary depending on the cut-off values). However the effect of baseline HCV RNA on SVR12 was not close to reaching statistical significance at the 0.05 level. Please see Table 28 in the Appendix for details.

Similar trends were observed for SVR12 subgroup analyses observed among all of the 222 treated subjects. Please see Table 29 in the Appendix for details.

Another analysis conducted was the subgroup analysis on the rate of combination of virologic failure plus relapse, which was called virologic failure (VF) rate here (Table 30 in the Appendix). Similar to the SVR12 subgroup analyses, age group had some numeric impact on the VF rates, but the reason for higher SVR12 rates in the 65 and older age group could not be explained clinically.

❖ **Study AI447028**

Among 525 subjects without L31 F/I/M/V or Y93H polymorphisms at baseline, compared to subjects with high baseline viral loads, there appeared to be higher SVR12 rates in subjects with low baseline viral loads although whether or not the difference was statistically significant depended on cutoff values. There were no statistically significant differences in SVR rates for other baseline factors. Please see Table 31 in the Appendix for details.

Similar trends were observed for all of the 643 treated subjects. Please see Table 32 in the Appendix for details.

Another analysis conducted was the subgroup analysis on the rate of combination of virologic failure plus relapse, which was called VF rate here (Table 33 in the Appendix). Again HCV RNA viral load at baseline had some numeric impact on the VF rates depending on the cut-off value. For example, compared to subjects with lower baseline viral loads, there appeared to be statistically significantly higher VF rates in subjects with very high baseline viral loads ≥8 million IU/mL.

❖ **Study AI447029**

There were no statistically significant differences in SVR12 rates between any of the baseline characteristics in study AI447029 although HCV RNA viral load at baseline had some numeric impact on SVR12 (as in study AI447028 higher SVR12 rates were observed in the subjects with lower HCV RNA at baseline). Please see Table 34 in the Appendix for details.

Another analysis conducted was the subgroup analysis on the rate of combination of virologic failure plus relapse, which was called VF rate here (Table 35 in the Appendix). Again HCV RNA viral load at baseline had some numeric impact on the VF rates, but the differences were not statistically significant.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Both NDAs shared the same three phase 3 studies, AI447028 and AI447026 for DCV+ASV, and AI447029 for DCV+ASV+Pegylated Interferons+Ribavirin (P/R), for their efficacy claim.

The primary objective of study AI447028 was to evaluate the efficacy of DCV+ASV for 24 weeks for the treatment of chronic HCV genotype 1b infection using SVR12, defined as HCV RNA<limit of quantitation (LOQ) [target detected (TD) or target not detected (TND)] at post-treatment Week 12.

Study AI447028 was a global study that enrolled subjects from 18 countries; only 19% of subjects were from US sites. The overall SVR12 was 84% (542/643) with 95% confidence interval (CI) of (81%, 87%). The SVR12 rates for treatment-naïve (TN), prior non-responders, and Intolerant/Ineligible cohorts were 90% (182/203) with 95% CI of (85%, 94%), 82% (168/205) with 95% CI of (76%, 87%), and 82% (192/235) with 95% CI of (76%, 86%) respectively.

The primary endpoint for Study AI447028 was the SVR12 rates for subjects who were prior null or partial responders to P/R or were treatment-naive. As defined in the protocol, for the treatment naive cohort: "to determine whether the SVR12 rate in subjects treated with Dual therapy (DCV+ASV) is similar to the historical SVR rate for Telaprevir (TVR) in combination with P/R in previously untreated, genotype 1b, HCV patients, where similar efficacy is defined as the lower bound of the 95% confidence interval for the SVR12 rate being greater than 68%." The benchmark set for the HCV-1b prior non-responders cohort was the lower bound of the 95% CI of SVR12 had to be greater than 59%, and had to be greater than 30% for intolerant/ineligible-naïve HCV-1b cohort. These benchmarks were determined by using Telaprevir ADVANCE trial results and were accepted by the DAVP before the enrollment of the study.

The primary objective of study AI447026 was to evaluate the efficacy of DCV+ASV for 24 weeks for the treatment of chronic HCV genotype 1b infection using SVR24, defined as HCV RNA below lower limit of quantitation (LLOQ of 15 IU/mL target detected or not detected) at Week 24 of post treatment follow-up. Since SVR12 was almost identical to SVR24 in the study, SVR12 was used here in order to be consistent with the other two studies.

Study AI447026 was a Japanese study, and all subjects were from Japan. The overall SVR12 rate was 85% (189/222) with 95% confidence interval (CI) of (80%, 90%). The SVR12 rates for prior non-responders and Intolerant/Ineligible cohorts were 80% (70/87) with 95% CI of (71%, 88%) and 81% (119/135) with 95% CI of (81%, 93%) respectively. This study protocol was not reviewed by the DAVP since it was not under the IND.

For study AI447026, the benchmark set for the HCV-1b prior non-responders cohort was the lower bound of the 95% CI of the SVR12 had to be greater than 45%, and had to be greater than 30% for the intolerant/ineligible-naïve HCV-1b cohort.

The primary objective of study AI447029 was to evaluate the efficacy of DCV+ASV+P/R for 24 weeks for the treatment of chronic HCV genotype 1 and genotype 4 prior non-responders using SVR12.

Study AI447029 was a global study that enrolled subjects from 15 countries; only 29% of subjects were from US sites. The overall SVR12 was 93% (372/398) with 95% CI of (91%, 96%) for these prior non-responders. The SVR12 rates for HCV-1a, HCV-1b, and HCV-4 were 87% (153/176) with 95% CI of (81%, 92%), 99% (176/178) with 95% CI of (96%, 100%), and 98% (43/44) with 95% CI of (88%, 100%) respectively.

There were no other statistical issues identified.

5.2 Conclusions and Recommendations

Studies AI447028 and AI447026 demonstrated the efficacy of DCV+ASV in HCV-1b infected subjects with the exception of subjects with L31F/I/M/CV or Y93H polymorphisms at baseline who had much lower SVR rates and much higher virologic failure rates than other subjects. After excluding these subjects, there were no other baseline factors that appeared to have a statistically significant impact on SVR or virologic failure rates with the possible exception of baseline HCV RNA in study AI447028. (This statistically significant finding depended on which cutoffs were used.)

Note that subgroup analyses need to be interpreted with caution because they were post-hoc (with the exception of age, gender, race and geographic region), with no multiple comparison adjustments, inconsistent trends between trials, the limitation of small sample sizes within subgroups and the lack of active-controls.

Study AI447029 demonstrated the efficacy of DCV+ASV+P/R in HCV-1 and HCV-4 infected subjects. Efficacy for HCV-1b subjects was much higher in study AI447029 than in the other DUAL studies but the tradeoff was that higher efficacy required the use of P/R for 24 weeks.

5.3 Labeling Recommendations

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

While the indication for DCV in its label is still in discussion. It could be as broad as the applicant proposed as following:

<TRADENAME-DCV> (daclatasvir) is indicated in combination with other agents for the treatment of chronic HCV infection in adults (b) (4)

Or it could be as narrow as the label text for ASV above.

There will have some limitations of use associated with the indication. Please see the clinical review for details.

APPENDICES

Table 16: Demographics and Baseline Characteristics for Study AI447026

	Prior	TN IN	Total
As Treated			
N	87	135	222
Gender			
FEMALE	48(55.2%)	97(71.9%)	145(65.3%)
MALE	39(44.8%)	38(28.1%)	77(34.7%)
Race			
JAPANESE	87(100.0%)	135(100.0%)	222(100.0%)
Age (Year)			
Mean (SE)	59.72 (0.857)	61.19 (0.998)	60.62 (0.694)
Median	60.00	64.00	62.50
Range	(42.00, 74.00)	(24.00, 75.00)	(24.00, 75.00)
STD	7.989	11.59	10.34
Age Category			
< 65	60(69.0%)	73(54.1%)	133(59.9%)
>= 65	27(31.0%)	62(45.9%)	89(40.1%)
Baseline HCV RNA log10 (IU/mL)			
Mean (SE)	6.76 (0.051)	6.56 (0.050)	6.64 (0.037)
Median	6.90	6.70	6.80
Range	(5.30, 7.70)	(4.90, 7.60)	(4.90, 7.70)
STD	0.474	0.576	0.545
Baseline HCV RNA Category 1 (IU/mL)			
<800,000	7(8.0%)	26(19.3%)	33(14.9%)
>=800,000	80(92.0%)	109(80.7%)	189(85.1%)
Baseline HCV RNA Category 3 (IU/mL)			
<2,000K	14(16.1%)	39(28.9%)	53(23.9%)
>=2,000K, <4,000K	15(17.2%)	27(20.0%)	42(18.9%)
>=4,000K, <6,000K	7(8.0%)	8(5.9%)	15(6.8%)
>=6,000K, <8,000K	14(16.1%)	18(13.3%)	32(14.4%)
>=10,000K,<12,000K	12(13.8%)	16(11.9%)	28(12.6%)
>=12,000K	25(28.7%)	27(20.0%)	52(23.4%)
Baseline Genotype			
1B	87(100.0%)	135(100.0%)	222(100.0%)
Baseline BMI (kg/m^2)			
Mean (SE)	22.56 (0.278)	22.55 (0.301)	22.56 (0.213)
Median	22.30	21.80	22.10
Range	(16.90, 31.00)	(16.10, 34.90)	(16.10, 34.90)
STD	2.592	3.497	3.167
Baseline BMI Category (Kg/m^2)			
<=25	74(85.1%)	105(77.8%)	179(80.6%)
25<=, <30	11(12.6%)	24(17.8%)	35(15.8%)
>=30	2(2.3%)	6(4.4%)	8(3.6%)

Baseline Cirrhosis Status			
NO	76(87.4%)	124(91.9%)	200(90.1%)
YES	11(12.6%)	11(8.1%)	22(9.9%)
Drug Compliance %			
Mean (SE)	99.53 (0.116)	99.32 (0.155)	99.40 (0.105)
Median	100.0	100.0	100.0
Range	(93.91, 100.0)	(83.82, 100.0)	(83.82, 100.0)
STD	1.084	1.798	1.558
Drug Compliance % Category -1 (>95%)			
Y	73(83.9%)	120(88.9%)	193(86.9%)
N	14(16.1%)	15(11.1%)	29(13.1%)
Drug Compliance % Category -2 (>90%)			
Y	75(86.2%)	121(89.6%)	196(88.3%)
N	12(13.8%)	14(10.4%)	26(11.7%)
Drug Compliance % Category -3 (>85%)			
Y	77(88.5%)	121(89.6%)	198(89.2%)
N	10(11.5%)	14(10.4%)	24(10.8%)
Drug Compliance % Category -3 (>80%)			
Y	77(88.5%)	121(89.6%)	198(89.2%)
N	10(11.5%)	14(10.4%)	24(10.8%)
Duration of Treatment Compliance %			
Mean (SE)	92.66 (2.067)	93.26 (1.715)	93.03 (1.318)
Median	100.0	100.0	100.0
Range	(16.67, 100.0)	(9.52, 100.0)	(9.52, 100.0)
STD	19.28	19.92	19.63
Duration of Treatment Compliance % Category (95%)			
>=95	74(85.1%)	121(89.6%)	195(87.8%)
<95	13(14.9%)	14(10.4%)	27(12.2%)
IL28B genotype			
CC	16(18.4%)	94(69.6%)	110(49.5%)
CT	66(75.9%)	40(29.6%)	106(47.7%)
TT	5(5.7%)	1(0.7%)	6(2.7%)
Ineligibility Reason for PR			
		35(25.9%)	.
ADVANCED AGE	.(. %)	12(8.9%)	.
ANEMIA	.(. %)	12(8.9%)	.
DEPRESSION	.(. %)	10(7.4%)	.
NEUTROPENIA	.(. %)	4(3.0%)	.
OTHER COMPLICATIONS REQUIRING MEDICATION	.(. %)	34(25.2%)	.
THROMBOCYTOPENIA	.(. %)	28(20.7%)	.
Prior Response Category			
NULL RESPONDER	48(55.2%)	.(. %)	.
PARTIAL RESPONDER	36(41.4%)	.(. %)	.
OTHER	3(3.4%)	.(. %)	.

Table 17: Demographics and Baseline Characteristics for Study AI447028

	Prior	TN_IN	TN	Total
As Treated				
N	205	235	203	643
Gender				
FEMALE	94(45.9%)	137(58.3%)	104(51.2%)	335(52.1%)
MALE	111(54.1%)	98(41.7%)	99(48.8%)	308(47.9%)
Race				
WHITE	148(72.2%)	169(71.9%)	133(65.5%)	450(70.0%)
CHINESE	22(10.7%)	25(10.6%)	26(12.8%)	73(11.4%)
KOREAN	21(10.2%)	23(9.8%)	21(10.3%)	65(10.1%)
ASIAN INDIAN	.(. %)	1(0.4%)	1(0.5%)	2(0.3%)
JAPANESE	.(. %)	2(0.9%)	.(. %)	2(0.3%)
ASIAN OTHER	2(1.0%)	5(2.1%)	4(2.0%)	11(1.7%)
BLACK/AFRICAN AMERICAN	10(4.9%)	10(4.3%)	14(6.9%)	34(5.3%)
NATIVE HAWAIIAN/OTHER PACIFIC	.(. %)	.(. %)	2(1.0%)	2(0.3%)
OTHER	2(1.0%)	.(. %)	2(1.0%)	4(0.6%)
Ethnicity				
HISPANIC/LATINO	7(3.4%)	7(3.0%)	9(4.4%)	23(3.6%)
NOT HISPANIC/LATINO	179(87.3%)	213(90.6%)	184(90.6%)	576(89.6%)
NOT REPORTED	19(9.3%)	15(6.4%)	10(4.9%)	44(6.8%)
Age (Year)				
Mean (SE)	56.1 (0.73)	58.0 (0.65)	53.1 (0.82)	55.8 (0.43)
Median	58	60	55	57
Range	(23, 77)	(24, 77)	(20, 79)	(20, 79)
STD	10.5	9.9	11.7	10.8
Age Category				
< 65	161(78.5%)	175(74.5%)	174(85.7%)	510(79.3%)
>= 65	44(21.5%)	60(25.5%)	29(14.3%)	133(20.7%)
Baseline HCV RNA log10 (IU/mL)				
Mean (SE)	6.51(0.04)	6.35(0.04)	6.24(0.05)	6.36(0.03)
Median	6.57	6.40	6.41	6.48
Range	(3.63, 7.48)	(2.78, 7.54)	(2.38, 7.53)	(2.38, 7.54)
STD	0.53	0.65	0.77	0.67
Baseline HCV RNA Category 1 (IU/mL)				
<800,000	27(13.2%)	48(20.4%)	53(26.1%)	128(19.9%)
>=800,000	178(86.8%)	187(79.6%)	150(73.9%)	515(80.1%)
Baseline HCV RNA Category 2 (IU/mL)				
<600,000	13(6.3%)	36(15.3%)	45(22.2%)	94(14.6%)
>=600,000	192(93.7%)	199(84.7%)	158(77.8%)	549(85.4%)
Baseline Genotype				

1B	205(100.0%)	235(100.0%)	203(100.0%)	643(100.0%)
Baseline BMI (kg/m^2)				
Mean (SE)	25.87 (0.275)	26.33 (0.260)	25.55 (0.27)	25.94 (0.155)
Median	25.60	25.90	24.80	25.50
Range	(18.00, 35.50)	(19.00, 36.50)	(18.10,36.70)	(18.00, 36.70)
STD	3.93	3.98	3.84	3.93
Baseline BMI Category (kg/m2)				
<=25	92(44.9%)	101(43.0%)	107(52.7%)	300(46.7%)
25<=, <30	81(39.5%)	91(38.7%)	67(33.0%)	239(37.2%)
>=30	32(15.6%)	43(18.3%)	29(14.3%)	104(16.2%)
Baseline Cirrhosis Status				
NO	142(69.3%)	124(52.8%)	171(84.2%)	437(68.0%)
YES	63(30.7%)	111(47.2%)	32(15.8%)	206(32.0%)
IL28B genotype				
CC	29(14.4%)	82(36.4%)	76(37.4%)	187(29.7%)
CT	123(60.9%)	102(45.3%)	99(48.8%)	324(51.4%)
TT	50(24.8%)	41(18.2%)	28(13.8%)	119(18.9%)
Prior Response Category				
NULL RESPONDER	119(58.0%)	.(. %)	.(. %)	.
PARTIAL RESPONDER	84(41.0%)	.(. %)	.(. %)	.
RELAPSER	2(1.0%)	.(. %)	.(. %)	.
Reason for Intolerant/Ineligible				
ANEMIA OR NEUTROPENIA	.(. %)	87(37.0%)	.(. %)	.
COMPENSATED ADVANCED FIBROSIS/CIRRHOSIS (F3 OR F4) WITH THROMBOCYTOPENIA	.(. %)	77(32.8%)	.(. %)	.
DEPRESSION	.(. %)	71(30.2%)	.(. %)	.
Baseline HCV RNA Category 3 (IU/mL)				
<2M	59(28.8%)	99(42.1%)	90(44.3%)	248(38.6%)
>=2M <4M	51(24.9%)	47(20.0%)	37(18.2%)	135(21.0%)
>=4M <6M	27(13.2%)	26(11.1%)	30(14.8%)	83(12.9%)
>=6M <8M	21(10.2%)	21(8.9%)	14(6.9%)	56(8.7%)
>=8M <10M	16(7.8%)	10(4.3%)	9(4.4%)	35(5.4%)
>=10M <12M	11(5.4%)	8(3.4%)	5(2.5%)	24(3.7%)
>=12M	20(9.8%)	24(10.2%)	18(8.9%)	62(9.6%)
Region				
ASIA	43(21.0%)	47(20.0%)	52(25.6%)	142(22.1%)
AUSTRALIA	15(7.3%)	23(9.8%)	20(9.9%)	58(9.0%)
EUROPE	102(49.8%)	112(47.7%)	63(31.0%)	277(43.1%)
NORTH AMERICA	44(21.5%)	48(20.4%)	62(30.5%)	154(24.0%)
SOUTH AMERICA	1(0.5%)	5(2.1%)	6(3.0%)	12(1.9%)
Country				
ARGEN	1(0.5%)	5(2.1%)	6(3.0%)	12(1.9%)
AUS	15(7.3%)	2(0.9%)	8(3.9%)	25(3.9%)
AUSTL	15(7.3%)	23(9.8%)	20(9.9%)	58(9.0%)

CAN	9(4.4%)	4(1.7%)	22(10.8%)	35(5.4%)
FRA	36(17.6%)	35(14.9%)	12(5.9%)	83(12.9%)
GER	15(7.3%)	30(12.8%)	9(4.4%)	54(8.4%)
IRE	1(0.5%)	.(. %)	5(2.5%)	6(0.9%)
ISR	3(1.5%)	9(3.8%)	.(. %)	12(1.9%)
ITALY	4(2.0%)	8(3.4%)	5(2.5%)	17(2.6%)
KOREA	21(10.2%)	23(9.8%)	22(10.8%)	66(10.3%)
NETH	4(2.0%)	2(0.9%)	6(3.0%)	12(1.9%)
NZEAL	.(. %)	.(. %)	5(2.5%)	5(0.8%)
POL	.(. %)	.(. %)	5(2.5%)	5(0.8%)
RUSS	15(7.3%)	17(7.2%)	.(. %)	32(5.0%)
SPAIN	5(2.4%)	6(2.6%)	5(2.5%)	16(2.5%)
TAIW	22(10.7%)	24(10.2%)	25(12.3%)	71(11.0%)
UK	4(2.0%)	3(1.3%)	8(3.9%)	15(2.3%)
USA	35(17.1%)	44(18.7%)	40(19.7%)	119(18.5%)

Table 18: Demographics and Baseline Characteristics for Study AI447029

	GT1a	GT1b	GT4	Total
As Treated				
N	176	178	44	398
Gender				
FEMALE	46(26.1%)	68(38.2%)	11(25.0%)	125(31.4%)
MALE	130(73.9%)	110(61.8%)	33(75.0%)	273(68.6%)
Race				
WHITE	149(84.7%)	122(68.5%)	33(75.0%)	304(76.4%)
BLACK/AFRICAN AMEERICAN	23(13.1%)	10(5.6%)	4(9.1%)	37(9.3%)
AMERICAN INDIAN/ALASKA NATIVE	1(0.6%)	.(. %)	1(2.3%)	2(0.5%)
ASIAN INDIAN	.(. %)	1(0.6%)	.(. %)	1(0.3%)
ASIAN OTHER	2(1.1%)	3(1.7%)	1(2.3%)	6(1.5%)
CHINESE	.(. %)	13(7.3%)	.(. %)	13(3.3%)
JAPANESE	.(. %)	1(0.6%)	.(. %)	1(0.3%)
KOREAN	.(. %)	27(15.2%)	.(. %)	27(6.8%)
NATIVE HAWAIIAN/OTHER PACIFIC	.(. %)	1(0.6%)	.(. %)	1(0.3%)
OTHER	1(0.6%)	.(. %)	5(11.4%)	6(1.5%)
Age (Year)				
Mean (SE)	52.5 (0.61)	53.2 (0.83)	50.8 (1.40)	52.7 (0.49)
Median	53	54	51	53
Range	(21, 68)	(19, 76)	(20, 71)	(19, 76)
STD	8.12	11.09	9.31	9.69
Age Category				
< 65	168(95.5%)	152(85.4%)	41(93.2%)	361(90.7%)
>= 65	8(4.5%)	26(14.6%)	3(6.8%)	37(9.3%)

Baseline HCV RNA log10 (IU/mL)				
Mean (SE)	6.6 (0.04)	6.4 (0.04)	6.1 (0.08)	6.5 (0.03)
Median	6.6	6.5	6.3	6.5
Range	(5.0, 7.4)	(3.9, 7.5)	(4.0, 7.0)	(3.9, 7.5)
STD	0.50	0.55	0.55	0.55
Baseline HCV RNA Category 1 (IU/mL)				
<800,000	16(9.1%)	31(17.4%)	15(34.1%)	62(15.6%)
>=800,000	160(90.9%)	147(82.6%)	29(65.9%)	336(84.4%)
Baseline HCV RNA Category 2 (IU/mL)				
<600,000	14(8.0%)	21(11.8%)	12(27.3%)	47(11.8%)
>=600,000	162(92.0%)	157(88.2%)	32(72.7%)	351(88.2%)
Baseline HCV RNA Category 3 (IU/mL)				
<2M	50(28.4%)	62(34.8%)	24(54.5%)	136(34.2%)
>=2M <4M	41(23.3%)	40(22.5%)	17(38.6%)	98(24.6%)
>=4M <6	15(8.5%)	24(13.5%)	.(. %)	39(9.8%)
>=6M <8M	20(11.4%)	19(10.7%)	1(2.3%)	40(10.1%)
>=8M <10M	12(6.8%)	7(3.9%)	1(2.3%)	20(5.0%)
>=10M <12M	10(5.7%)	5(2.8%)	1(2.3%)	16(4.0%)
>=12M	28(15.9%)	21(11.8%)	.(. %)	49(12.3%)
Baseline BMI (kg/m^2)				
Mean (SE)	26.4 (0.31)	26.5 (0.29)	26.0 (0.49)	26.4 (0.20)
Median	26.0	26.3	25.4	26.1
Range	(18.7, 39.1)	(17.7, 35.3)	(19.8, 33.2)	(17.7, 39.1)
STD	4.11	3.84	3.25	3.90
Baseline BMI Category (kg/m2)				
<=25	67(38.1%)	68(38.2%)	19(43.2%)	154(38.7%)
25<=, <30	75(42.6%)	72(40.4%)	20(45.5%)	167(42.0%)
>=30	34(19.3%)	38(21.3%)	5(11.4%)	77(19.3%)
Baseline Cirrhosis Status				
NO	132(75.0%)	149(83.7%)	24(54.5%)	305(76.6%)
YES	44(25.0%)	29(16.3%)	20(45.5%)	93(23.4%)
IL28B genotype				
CC	13(7.4%)	20(11.2%)	3(6.8%)	36(9.0%)
CT	115(65.3%)	116(65.2%)	31(70.5%)	262(65.8%)
TT	48(27.3%)	42(23.6%)	10(22.7%)	100(25.1%)
Prior Response Category				
NULL RESPONDER	118(67.0%)	116(65.2%)	34(77.3%)	268(67.3%)
PARTIAL RESPONDER	58(33.0%)	62(34.8%)	10(22.7%)	130(32.7%)
Ethnicity				
HISPANIC/LATINO	17(9.7%)	16(9.0%)	2(4.5%)	35(8.8%)
NOT HISPANIC/LATINO	159(90.3%)	162(91.0%)	42(95.5%)	363(91.2%)

Region				
ASIA	.(. %)	42(23.6%)	.(. %)	42(10.6%)
EUROPE	80(45.5%)	95(53.4%)	29(65.9%)	204(51.3%)
NORTH AMERICA	91(51.7%)	35(19.7%)	15(34.1%)	141(35.4%)
SOUTH AMERICA	5(2.8%)	6(3.4%)	.(. %)	11(2.8%)
Country				
ARGEN	5(2.8%)	6(3.4%)	.(. %)	11(2.8%)
CAN	9(5.1%)	1(0.6%)	10(22.7%)	20(5.0%)
DEN	3(1.7%)	3(1.7%)	1(2.3%)	7(1.8%)
FRA	32(18.2%)	17(9.6%)	22(50.0%)	71(17.8%)
GER	22(12.5%)	17(9.6%)	5(11.4%)	44(11.1%)
ITALY	5(2.8%)	13(7.3%)	.(. %)	18(4.5%)
KOREA	.(. %)	27(15.2%)	.(. %)	27(6.8%)
MEX	1(0.6%)	5(2.8%)	.(. %)	6(1.5%)
NETH	6(3.4%)	2(1.1%)	.(. %)	8(2.0%)
RUSS	.(. %)	21(11.8%)	.(. %)	21(5.3%)
SPAIN	4(2.3%)	18(10.1%)	.(. %)	22(5.5%)
SWE	7(4.0%)	.(. %)	1(2.3%)	8(2.0%)
SWITZ	1(0.6%)	4(2.2%)	.(. %)	5(1.3%)
TAIW	.(. %)	15(8.4%)	.(. %)	15(3.8%)
USA	81(46.0%)	29(16.3%)	5(11.4%)	115(28.9%)

Table 19: The Discrepancy between SVR12 and Virologic Classification for Study AI446026

Cohort	Vrologic Failure Category / SVR12	Not vriologic failure (VFN=0)	V Break Through (VFN=1)	Treatment futility (>=LOQ at Week 8) (VFN=2)	Detectable at EOT with LOD=0 (VFN=5)	Relapse (confirmed) LOQ=1 after EOT (VFN=6)	Relapse LOQ=1 after EOT (VFN=6.1)	Total
Prior	Filure		10		1	6		17
	Responder	70						70
TN_IN	Filure		4		2	10		16
	Responder	118				1 (20035) missing FW24 visit SVR12=1		119

Table 20: The Discrepancy between SVR12 and Virologic Classification for Study AI446028

Cohort	Vrologic Failure Category / SVR12q	Not vriologic failure (VFN=0)	V Break Through (VFN=1)	Treatment futility (>=LOQ at Week 8) (VFN=2)	Detectable at EOT with LOD=0 (VFN=5)	Relapse (confirmed) LOQ=1 after EOT (VFN=6)	Relapse LOQ=1 after EOT (VFN=6.1)	Total
Prior	0	1 (80180) missed FW12 FW4=1 & FW24=1	26		3	7		37
	1	165			2 (80223, 80138) EOT=0, EOTq=1		1 (80492) Two FW12 data 14MAY13 VRLOD=0, VRLOQ=1, 11JUN13 VRLOD=VRLOQ=1	168
	total	166	26		5	7	1	205
TN_IN	0	3 (80584, 80872, 80228) missed FW12 FW4=1 & FW24=1	20	1	37	12		43

	1	189			2 (80512, 80072) EOT=0, EOTq=1	1		192
	total	192	20	1	9	13	1	235
TN	0	4 (80804, 80748, 80154) missed FW12, wtih FW4=1 & FW24=1 (80788) missed FW12, FW24 with FW4=1 only	926		3	5		21
	1	181			1 (80629) EOT=0, EOTq=1			182
	total	185	9		4	5	1	203

Table 21: The Discrepancy between SVR12 and Virologic Classification for Study AI446029

Cohort	Vrologic Failure Category	Not vriologic failure (VFN=0)	V Break Through (VFN=1)	Treatment futility (>=LOQ at Week 8) (VFN=2)	Detectable at EOT with LOD=0 (VFN=5)	Relapse (confirmed) LOQ=1 after EOT (VFN=6)	Relapse LOQ=1 after EOT (VFN=6.1)	Total
	SVR12q							
Gt1a	0	3 (90189, 90056) missed FW12, with FW4=1 (90295) only had WK20 (LOD=1) data and no further data.	10		2	8		23
	1	147			2 (90123, 90225) EOT=0, EOTq=1	3 (90222, 90132) SVR12q=1 while SVR24q=0 (90257) SVR12q=1, SVR12=0, while SVR24q=0	1 (90099) SVR24q=0, while SVR12q=1 and SVR36q=1	153
	total	150	10		4	11	1	176
Gt1b	0	1 (90445) WK24 LOD=1, no further data	1					2
	1	174			2 (90058) discontinuted at WK24 due to AE (WK24 LOD=1) should be counted as failure as BT. (90297) EOT=0 with EOTq=1			176
	total	175	1		2			178
GT4	0	1 (90057) missing SVR12, while SVR4q=1 and SVR24q=1 – should be success.						1
	1	42			1 (90130) EOT=0, EOTq=1			43
	total	43			1			44

Table 22: SVR12 (using <LOQ) and Virologic Failure Rates for Study AI447026 by Subjects with or without Baseline Polymorphism Information (Treated Subjects)

Subgroup	Prior	TN_IN	Total
Number of Subjects without Baseline Polymorphism Information			
N	1	7	8
Responder (SVR12)	1(100.0%)	6(85.7%)	7(87.5%)
Breakthrough or relapse	.(. %)	1(14.3%)	1(12.5%)
Number of Subjects with Baseline Polymorphism Information			
N	86	128	214
Responder (SVR12)	69(80.2%)	113(88.3%)	182(85.0%)
Breakthrough or relapse	16(18.6%)	13(10.2%)	29(13.6%)
Other	1(1.2%)	2(1.6%)	3(1.4%)

Table 23: SVR12 (using <LOQ) and Virologic Failure Rates for Study AI447026 by Subjects with or without Baseline L31F/I/M/V or Y93H Polymorphism (Treated Subjects)

Subgroup	Prior	TN_IN	Total
Number of Subjects with Baseline L31F/I/M/V or Y93H Polymorphism			
N	14	24	38
Responder (SVR12)	4(28.6%)	13(54.2%)	17(44.7%)
Breakthrough or relapse	9(64.3%)	10(41.7%)	19(50.0%)
Other	1(7.1%)	1(4.2%)	2(5.3%)
Number of Subjects without Baseline L31F/I/M/V or Y93H Polymorphism			
N	72	104	176
Responder (SVR12)	65(90.3%)	100(96.2%)	165(93.8%)
Breakthrough or relapse	7(9.7%)	3(2.9%)	10(5.7%)
Other	.(. %)	1(1.0%)	1(0.6%)

Table 24: SVR12 (using <LOQ) and Virologic Failure Rates for Study AI447028 by Subjects with or without Baseline Polymorphism Information (Treated Subjects)

Subgroup	Prior	TN_IN	TN	Total
Number of Subjects without Baseline Polymorphism Information				
N	15	14	17	46
Responder (SVR12)	11(73.3%)	11(78.6%)	12(70.6%)	34(73.9%)
Breakthrough or relapse	3(20.0%)	2(14.3%)	4(23.5%)	9(19.6%)
Other	1(6.7%)	1(7.1%)	1(5.9%)	3(6.5%)
Number of Subjects with Baseline Polymorphism Information				
N	190	221	186	597
Responder (SVR12)	157(82.6%)	181(81.9%)	170(91.4%)	508(85.1%)
Breakthrough or relapse	30(15.8%)	30(13.6%)	10(5.4%)	70(11.7%)
Other	3(1.6%)	10(4.5%)	6(3.2%)	19(3.2%)

Table 25: SVR12 (using <LOQ) and Virologic Failure Rates for Study AI447028 by Subjects with or without Baseline L31F/I/M/V or Y93H Polymorphism (Treated Subjects)

Subgroup	Prior	TN_IN	TN	Total
Number of Subjects with Baseline L31F/I/M/V or Y93H Polymorphism				
N	25	30	17	72
Responder (SVR12)	7(28.0%)	11(36.7%)	10(58.8%)	28(38.9%)
Breakthrough or relapse	18(72.0%)	16(53.3%)	6(35.3%)	40(55.6%)
Other	.(. %)	3(10.0%)	1(5.9%)	4(5.6%)
Number of Subjects without Baseline L31F/I/M/V or Y93H Polymorphism				
N	165	191	169	525
Responder (SVR12)	150(90.9%)	170(89.0%)	160(94.7%)	480(91.4%)
Breakthrough or relapse	12(7.3%)	14(7.3%)	4(2.4%)	30(5.7%)
Other	3(1.8%)	7(3.7%)	5(3.0%)	15(2.9%)

Table 26: SVR12 (using <LOQ) and Virologic Failure Rates for Study AI447028 by Subjects with or without Baseline R30Q Polymorphism (Treated Subjects)

Subgroup	Prior	TN_IN	TN	Total
Number of Subjects with Baseline R30Q Polymorphism				
N	9	22	11	42
Responder (SVR12)	5(55.6%)	15(68.2%)	10(90.9%)	30(71.4%)
Breakthrough or relapse	4(44.4%)	5(22.7%)	1(9.1%)	10(23.8%)
Other	.(. %)	2(9.1%)	.(. %)	2(4.8%)
Number of Subjects without Baseline R30Q Polymorphism				
N	181	199	175	555
Responder (SVR12)	152(84.0%)	166(83.4%)	160(91.4%)	478(86.1%)
Breakthrough or relapse	26(14.4%)	25(12.6%)	9(5.1%)	60(10.8%)
Other	3(1.7%)	8(4.0%)	6(3.4%)	17(3.1%)

Table 27: SVR12 (using <LOQ) and Virologic Failure Rates for Study AI447028 by Subjects with or without Baseline L28M Polymorphism (Treated Subjects)

Subgroup	Prior	TN_IN	TN	Total
Number of Subjects with Baseline L28M Polymorphism				
N	4	6	3	13
Responder (SVR12)	2(50.0%)	4(66.7%)	1(33.3%)	7(53.8%)
Breakthrough or relapse	2(50.0%)	2(33.3%)	2(66.7%)	6(46.2%)
Number of Subjects without Baseline L28M Polymorphism				
N	186	215	183	584
Responder (SVR12)	155(83.3%)	177(82.3%)	169(92.3%)	501(85.8%)
Breakthrough or relapse	28(15.1%)	28(13.0%)	8(4.4%)	64(11.0%)
Other	3(1.6%)	10(4.7%)	6(3.3%)	19(3.3%)

Table 28: The Summary Subgroup Analyses of SVR12 for Study AI447026 (176 Subjects without Baseline L31F/I/M/V or Y93H Polymorphism)

Efficacy Parameter	Prior	TN_IN	Total
176 Subjects who had baseline polymorphism information but not L31F/I/M/V or Y93H			
N	72	104	176
Overall SVR12	65/ 72(90.3)	100/104(96.2)	165/176(93.8)
Gender			
FEMALE	36 / 41 (87.8)	71 / 74 (95.9)	107 /115 (93.0)
MALE	29 / 31 (93.5)	29 / 30 (96.7)	58 / 61 (95.1)
P-value	0.6910	1.000	0.7499
Race			
JAPANESE	65 / 72 (90.3)	100 /104 (96.2)	165 /176 (93.8)
Age Group -1			
< 65	44 / 51 (86.3)	54 / 58 (93.1)	98 /109 (89.9)
>= 65	**21 / 21 (100)**	**46 / 46 (100)**	**67 / 67 (100)**
P-value	**0.0982**	**0.1278**	**0.0073**
HCV RNA BSL <600K			
<600,000	5 / 5 (100)	13 / 14 (92.9)	18 / 19 (94.7)
>=600,000	60 / 67 (89.6)	87 / 90 (96.7)	147 /157 (93.6)
HCV RNA BSL <800K			
<800,000	5 / 6 (83.3)	23 / 24 (95.8)	28 / 30 (93.3)
>=800,000	60 / 66 (90.9)	77 / 80 (96.3)	137 /146 (93.8)
HCV RNA BSL <1M			
<1M	5 / 6 (83.3)	23 / 24 (95.8)	28 / 30 (93.3)
>=1M	60 / 66 (90.9)	77 / 80 (96.3)	137 /146 (93.8)
P-value	0.4713	1.000	1.000
HCV RNA BSL <2M			
<2M	11 / 12 (91.7)	33 / 34 (97.1)	44 / 46 (95.7)
>=2M	54 / 60 (90.0)	67 / 70 (95.7)	121 /130 (93.1)
HCV RNA BSL <3M			
<3M	15 / 17 (88.2)	40 / 42 (95.2)	55 / 59 (93.2)
>=3M	50 / 55 (90.9)	60 / 62 (96.8)	110 /117 (94.0)
HCV RNA BSL <4M			
<4M	**24 / 27 (88.9)**	**55 / 59 (93.2)**	**79 / 86 (91.9)**
>=4M	**41 / 45 (91.1)**	**45 / 45 (100)**	**86 / 90 (95.6)**
HCV RNA BSL <5M			
<5M	24 / 27 (88.9)	55 / 59 (93.2)	79 / 86 (91.9)
>=5M	41 / 45 (91.1)	45 / 45 (100)	86 / 90 (95.6)
HCV RNA BSL <6M			
<6M	27 / 31 (87.1)	62 / 66 (93.9)	89 / 97 (91.8)
>=6M	38 / 41 (92.7)	38 / 38 (100)	76 / 79 (96.2)

HCV RNA BSL <7M			
<7M	33 / 37 (89.2)	66 / 70 (94.3)	99 /107 (92.5)
>=7M	32 / 35 (91.4)	34 / 34 (100)	66 / 69 (95.7)
HCV RNA BSL <8M			
<8M	39 / 43 (90.7)	77 / 81 (95.1)	116 /124 (93.5)
>=8M	26 / 29 (89.7)	23 / 23 (100)	49 / 52 (94.2)
P-value	1.000	0.5732	1.000
HCV RNA BSL <9M			
<9M	39 / 43 (90.7)	77 / 81 (95.1)	116 /124 (93.5)
>=9M	26 / 29 (89.7)	23 / 23 (100)	49 / 52 (94.2)
HCV RNA BSL <10M			
<10M	39 / 43 (90.7)	77 / 81 (95.1)	116 /124 (93.5)
>=10M	26 / 29 (89.7)	23 / 23 (100)	49 / 52 (94.2)
HCV RNA BSL <11M			
<11M	**49 / 53 (92.5)**	**85 / 89 (95.5)**	**134 /142 (94.4)**
>=11M	**16 / 19 (84.2)**	**15 / 15 (100)**	**31 / 34 (91.2)**
P-value	0.3708	1.000	0.4464
HCV RNA BSL <12M			
<12M	49 / 53 (92.5)	85 / 89 (95.5)	134 /142 (94.4)
>=12M	16 / 19 (84.2)	15 / 15 (100)	31 / 34 (91.2)
BMI category			
25<=, <30	6 / 7 (85.7)	16 / 16 (100)	22 / 23 (95.7)
<=25	57 / 63 (90.5)	80 / 84 (95.2)	137 /147 (93.2)
>=30	2 / 2 (100)	4 / 4 (100)	6 / 6 (100)
<30 vs. >=30 P-value	1.000	1.000	1.000
Baseline Cirrhosis Category			
NO	55 / 62 (88.7)	92 / 96 (95.8)	147 /158 (93.0)
YES	10 / 10 (100)	8 / 8 (100)	18 / 18 (100)
P-value	0.5827	1.000	0.6066
IL28B Genotype			
CC	11 / 11 (100)	64 / 68 (94.1)	75 / 79 (94.9)
CT	51 / 57 (89.5)	35 / 35 (100)	86 / 92 (93.5)
TT	3 / 4 (75.0)	1 / 1 (100)	4 / 5 (80.0)
CC vs. Non-CC P-value	0.5854	0.2955	0.7564
Reason of Ineligible for PR			
ADVANCED AGE	. / . (.)	10 / 10 (100)	10 / 10 (100)
ANEMIA	. / . (.)	12 / 12 (100)	12 / 12 (100)
DEPRESSION	**. / . (.)**	**5 / 7 (71.4)**	**5 / 7 (71.4)**
NEUTROPENIA	. / . (.)	3 / 3 (100)	3 / 3 (100)
OTHER COMPLICATION REQUIRING MEDICATION			
	. / . (.)	22 / 24 (91.7)	22 / 24 (91.7)
THROMBOCYTOPENI	. / . (.)	21 / 21 (100)	21 / 21 (100)
Depression vs. Other P-value		0.0220	0.0220
Prior Response Category			

NULL RESPONDER	36 / 41 (87.8)	. / . (.)	36 / 41 (87.8)
PARTIAL RESPOND	26 / 28 (92.9)	. / . (.)	26 / 28 (92.9)
OTHER	3 / 3 (100)	27 / 27 (100)	30 / 30 (100)
Partial vs. Null P-value	0.6925		0.6925

Table 29: The Summary Subgroup Analyses of SVR12 for Study AI447026 (Treated Subjects)

Efficacy Parameter	Prior	TN_IN	Total
Treated	70/ 87(80.5)	119/135(88.1)	189/222(85.1)
Gender			
FEMALE	38 / 48 (79.2)	86 / 97 (88.7)	124 /145 (85.5)
MALE	32 / 39 (82.1)	33 / 38 (86.8)	65 / 77 (84.4)
Age Group			
< 65	47 / 60 (78.3)	61 / 73 (83.6)	108 /133 (81.2)
>= 65	**23 / 27 (85.2)**	**58 / 62 (93.5)**	**81 / 89 (91.0)**
HCV RNA BSL <600K			
<600,000	5 / 5 (100)	14 / 15 (93.3)	19 / 20 (95.0)
>=600,000	65 / 82 (79.3)	105 /120 (87.5)	170 /202 (84.2)
HCV RNA BSL <800K			
<800,000	6 / 7 (85.7)	25 / 26 (96.2)	31 / 33 (93.9)
>=800,000	64 / 80 (80.0)	94 /109 (86.2)	158 /189 (83.6)
HCV RNA BSL <1M			
<1M	6 / 7 (85.7)	25 / 26 (96.2)	31 / 33 (93.9)
>=1M	64 / 80 (80.0)	94 /109 (86.2)	158 /189 (83.6)
HCV RNA BSL <2M			
<2M	13 / 14 (92.9)	37 / 39 (94.9)	50 / 53 (94.3)
>=2M	57 / 73 (78.1)	82 / 96 (85.4)	139 /169 (82.2)
HCV RNA BSL <3M			
<3M	17 / 19 (89.5)	44 / 47 (93.6)	61 / 66 (92.4)
>=3M	53 / 68 (77.9)	75 / 88 (85.2)	128 /156 (82.1)
HCV RNA BSL <4M			
<4M	26 / 29 (89.7)	60 / 66 (90.9)	86 / 95 (90.5)
>=4M	44 / 58 (75.9)	59 / 69 (85.5)	103 /127 (81.1)
HCV RNA BSL <5M			
<5M	**26 / 29 (89.7)**	**60 / 66 (90.9)**	**86 / 95 (90.5)**
>=5M	44 / 58 (75.9)	59 / 69 (85.5)	103 /127 (81.1)
HCV RNA BSL <6M			
<6M	29 / 36 (80.6)	67 / 74 (90.5)	96 /110 (87.3)
>=6M	41 / 51 (80.4)	52 / 61 (85.2)	93 /112 (83.0)

HCV RNA BSL <7M			
<7M	35 / 43 (81.4)	71 / 78 (91.0)	106 /121 (87.6)
>=7M	35 / 44 (79.5)	48 / 57 (84.2)	83 /101 (82.2)
HCV RNA BSL <8M			
<8M	42 / 50 (84.0)	84 / 92 (91.3)	126 /142 (88.7)
>=8M	28 / 37 (75.7)	35 / 43 (81.4)	63 / 80 (78.8)
HCV RNA BSL <9M			
<9M	42 / 50 (84.0)	84 / 92 (91.3)	126 /142 (88.7)
>=9M	28 / 37 (75.7)	35 / 43 (81.4)	63 / 80 (78.8)
HCV RNA BSL <10M			
<10M	**42 / 50 (84.0)**	**84 / 92 (91.3)**	**126 /142 (88.7)**
>=10M	28 / 37 (75.7)	35 / 43 (81.4)	63 / 80 (78.8)
HCV RNA BSL <11M			
<11M	52 / 62 (83.9)	96 /108 (88.9)	148 /170 (87.1)
>=11M	18 / 25 (72.0)	23 / 27 (85.2)	41 / 52 (78.8)
HCV RNA BSL <12M			
<12M	52 / 62 (83.9)	96 /108 (88.9)	148 /170 (87.1)
>=12M	18 / 25 (72.0)	23 / 27 (85.2)	41 / 52 (78.8)
BMI category			
<=25	**60 / 74 (81.1)**	**92 /105 (87.6)**	**152 /179 (84.9)**
25<=, <30	8 / 11 (72.7)	22 / 24 (91.7)	30 / 35 (85.7)
>=30	2 / 2 (100)	5 / 6 (83.3)	7 / 8 (87.5)
IL28B Genotype			
CC	14 / 16 (87.5)	80 / 94 (85.1)	94 /110 (85.5)
CT	52 / 66 (78.8)	38 / 40 (95.0)	90 /106 (84.9)
TT	4 / 5 (80.0)	1 / 1 (100)	5 / 6 (83.3)
Baseline Cirrhosis Category			
NO	60 / 76 (78.9)	109 /124 (87.9)	169 /200 (84.5)
YES	**10 / 11 (90.9)**	**10 / 11 (90.9)**	**20 / 22 (90.9)**
Prior Response Category			
NULL RESPONDER	39 / 48 (81.3)	.	.
PARTIAL RESPONDER	28 / 36 (77.8)	.	.
OTHER	3 / 3 (100)	.	.
Reason of Ineligible for PR			
ADVANCED AGE	. / . (.)	11 / 12 (91.7)	.
ANEMIA	. / . (.)	12 / 12 (100)	.
DEPRESSION	. / . (.)	6 / 10 (60.0)	.
NEUTROPENIA	. / . (.)	3 / 4 (75.0)	.
OTHER COMPLICATION REQUIRING MEDICATION	. / . (.)	28 / 34 (82.4)	.
THROMBOCYTOPENI	. / . (.)	26 / 28 (92.9)	.

Table 30: Baseline Covariates Subgroup Analyses of Virologic Failures for Study AI447026 (176 Subjects without Baseline L31F/I/M/V or Y93H Polymorphism)

Efficacy Parameter	Prior	TN_IN	Total
176 Subjects who had baseline polymorphism information but not L31F/I/M/V or Y93H			
N	7/ 72(9.72)	3/104(2.88)	10/176(5.68)
Gender			
FEMALE	5 / 41 (12.2)	3 / 74 (4.05)	8 /115 (6.96)
MALE	2 / 31 (6.45)	. / 30 (0.00)	2 / 61 (3.28)
P-value	0.6910	1.000	0.7499
Race			
JAPANESE	7 / 72 (9.72)	3 /104 (2.88)	10 /176 (5.68)
Age Group			
< 65	7 / 51 (13.7)	3 / 58 (5.17)	10 /109 (9.17)
>= 65	. / 21 (0.00)	. / 46 (0.00)	. / 67 (0.00)
P-value	0.0982	0.1278	0.0073
HCV RNA BSL <600K			
<600,000	. / 5 (0.00)	. / 14 (0.00)	. / 19 (0.00)
>=600,000	7 / 67 (10.4)	3 / 90 (3.33)	10 /157 (6.37)
HCV RNA BSL <800K			
<800,000	1 / 6 (16.7)	. / 24 (0.00)	1 / 30 (3.33)
>=800,000	6 / 66 (9.09)	3 / 80 (3.75)	9 /146 (6.16)
HCV RNA BSL <1M			
<1M	1 / 6 (16.7)	. / 24 (0.00)	1 / 30 (3.33)
>=1M	6 / 66 (9.09)	3 / 80 (3.75)	9 /146 (6.16)
P-value	0.4713	1.000	1.000
HCV RNA BSL <2M			
<2M	1 / 12 (8.33)	. / 34 (0.00)	1 / 46 (2.17)
>=2M	6 / 60 (10.0)	3 / 70 (4.29)	9 /130 (6.92)
HCV RNA BSL <3M			
<3M	2 / 17 (11.8)	1 / 42 (2.38)	3 / 59 (5.08)
>=3M	5 / 55 (9.09)	2 / 62 (3.23)	7 /117 (5.98)
HCV RNA BSL <4M			
<4M	3 / 27 (11.1)	3 / 59 (5.08)	6 / 86 (6.98)
>=4M	4 / 45 (8.89)	. / 45 (0.00)	4 / 90 (4.44)
HCV RNA BSL <5M			
<5M	3 / 27 (11.1)	3 / 59 (5.08)	6 / 86 (6.98)
>=5M	4 / 45 (8.89)	. / 45 (0.00)	4 / 90 (4.44)
HCV RNA BSL <6M			
<6M	4 / 31 (12.9)	3 / 66 (4.55)	7 / 97 (7.22)
>=6M	3 / 41 (7.32)	. / 38 (0.00)	3 / 79 (3.80)
HCV RNA BSL <7M			

<7M	4 / 37 (10.8)	3 / 70 (4.29)	7 /107 (6.54)
>=7M	3 / 35 (8.57)	. / 34 (0.00)	3 / 69 (4.35)
HCV RNA BSL <8M			
<8M	4 / 43 (9.30)	3 / 81 (3.70)	7 /124 (5.65)
>=8M	3 / 29 (10.3)	. / 23 (0.00)	3 / 52 (5.77)
P-value	1.000	0.5732	1.000
HCV RNA BSL <9M			
<9M	4 / 43 (9.30)	3 / 81 (3.70)	7 /124 (5.65)
>=9M	3 / 29 (10.3)	. / 23 (0.00)	3 / 52 (5.77)
HCV RNA BSL <10M			
<10M	4 / 43 (9.30)	3 / 81 (3.70)	7 /124 (5.65)
>=10M	3 / 29 (10.3)	. / 23 (0.00)	3 / 52 (5.77)
HCV RNA BSL <11M			
<11M	4 / 53 (7.55)	3 / 89 (3.37)	7 /142 (4.93)
>=11M	3 / 19 (15.8)	. / 15 (0.00)	3 / 34 (8.82)
P-value	0.3708	1.000	0.4464
HCV RNA BSL <12M			
<12M	4 / 53 (7.55)	3 / 89 (3.37)	7 /142 (4.93)
>=12M	3 / 19 (15.8)	. / 15 (0.00)	3 / 34 (8.82)
BMI category			
25<=, <30	1 / 7 (14.3)	. / 16 (0.00)	1 / 23 (4.35)
<=25	6 / 63 (9.52)	3 / 84 (3.57)	9 /147 (6.12)
>=30	. / 2 (0.00)	. / 4 (0.00)	. / . (.)
<30 vs. >=30 P-value	1.000	1.000	1.000
Baseline Cirrhosis Category			
NO	7 / 62 (11.3)	3 / 96 (3.13)	10 /158 (6.33)
YES	. / 10 (0.00)	. / 8 (0.00)	. / . (.)
P-value	0.5827	1.000	0.6066
IL28B Genotype			
CC	. / 11 (0.00)	3 / 68 (4.41)	3 / 79 (3.80)
CT	6 / 57 (10.5)	. / 35 (0.00)	6 / 92 (6.52)
TT	1 / 4 (25.0)	. / 1 (0.00)	1 / 5 (20.0)
CC vs. Non-CC P-value	0.5854	0.2955	0.7564
Reason of Ineligible for PR			
ADVANCED AGE	. / . (.)	. / 10 (0.00)	
ANEMIA	. / . (.)	. / 12 (0.00)	
DEPRESSION	**. / . (.)**	**2 / 7 (28.6)**	
NEUTROPENIA	. / . (.)	. / 3 (0.00)	
OTHER COMPLICATION REQUIRING MEDICATION	. / . (.)	1 / 24 (4.17)	
THROMBOCYTOPENI	. / . (.)	. / 21 (0.00)	
Depression vs. Other P-value		0.0220	
Prior Response Category			
NULL RESPONDER	5 / 41 (12.2)	. / . (.)	
PARTIAL RESPOND	2 / 28 (7.14)	. / . (.)	

OTHER	. / 3 (0.00)	. / . (.)		
Partial vs. Null P-value	0.6925			0.6925

*: Virologic Failures here includes breakthrough and relapse.

Table 31: The Summary Subgroup Analyses of SVR12 for Study AI447028 (525 Subjects without Baseline L31F/I/M/V or Y93H Polymorphism)

Efficacy Parameter	Prior	TN_IN	TN	Total
525 subjects who had baseline polymorphism but not L31F/I/M/V or Y93H (SVR12q)				
N	150/165(90.9)	170/191(89.0)	160/169(94.7)	480/525(91.4)
Gender				
FEMALE	63 / 69(91.3)	94 /107(87.9)	81/86(94.2)	238/262(90.8)
MALE	87 / 96(90.6)	76 / 84(90.5)	79/83(95.2)	242/263(92.0)
Race				
WHITE	108 /117(92.3)	125/140(89.3)	106/113(93.8)	339/370(91.6)
CHINESE	16 / 20(80.0)	20/ 20(100)	15/ 16(93.8)	51/ 56(91.1)
KOREAN	16 / 16(100)	14/ 18(77.8)	19/ 20(95.0)	49/ 54(90.7)
ASIAN INDIAN	. / .(.)	1/ 1(100)	1/ 1(100)	2/ 2(100)
JAPANESE	. / .(.)	1/ 2(50.0)	./ . (.)	1/ 2(50.0)
ASIAN OTHER	1 / 2(50.0)	2/ 2(100)	3/ 3(100)	6/ 7(85.7)
BLACK/AFRICAN AMERICAN	8 / 8(100)	7/ 8(87.5)	13/ 13(100)	28/ 29(96.6)
NATIVE HAWAIIAN	. / .(.)	./ .(.)	1/ 1(100)	1/ 1(100)
OTHER	1 / 2(50.0)	./ .(.)	2/ 2(100)	3/ 4(75.0)
Ethnicity				
HISPANIC/LATINO	4 / 4(100)	4/ 5(80.0)	6/ 8(75.0)	14/ 17(82.4)
NOT HISPANIC/LATINO	135 /148(91.2)	157/177(88.7)	145/152(95.4)	437/477(91.6)
	11 / 13(84.6)	9/ 9(100)	9/ 9(100)	29/ 31(93.5)
Age Group				
< 65	120 /133(90.2)	124/142(87.3)	137/146(93.8)	381/421(90.5)
>= 65	30 / 32(93.8)	46/ 49(93.9)	23/ 23(100)	99/104(95.2)
HCV RNA BSL <600K				
<600,000	11 / 11(100)	28/ 32(87.5)	39/ 39(100)	78/ 82(95.1)
>=600,000	139 /154(90.3)	142/159(89.3)	121/130(93.1)	402/443(90.7)
HCV RNA BSL <800K				
<800,000	22 / 22(100)	36/ 40(90.0)	46/ 47(97.9)	104/109(95.4)
>=800,000	128 /143(89.5)	134/151(88.7)	114/122(93.4)	376/416(90.4)
HCV RNA BSL <1M				
<1M	**25 / 25(100)**	**47/ 51(92.2)**	**53/ 54(98.1)**	**125/130(96.2)**
>=1M	**125 /140(89.3)**	**123/140(87.9)**	**107/115(93.0)**	**355/395(89.9)**
P-value	**0.1303**	**0.6013**	**0.2745**	**0.0291**

HCV RNA BSL <2M				
<2M	50 / 51(98.0)	77/ 86(89.5)	73/ 75(97.3)	200/212(94.3)
>=2M	100 /114(87.7)	93/105(88.6)	87/ 94(92.6)	280/313(89.5)
HCV RNA BSL <3M				
<3M	70 / 73(95.9)	101/111(91.0)	90/ 93(96.8)	261/277(94.2)
>=3M	80 / 92(87.0)	69/ 80(86.3)	70/ 76(92.1)	219/248(88.3)
HCV RNA BSL <4M				
<4M	87 / 92(94.6)	118/128(92.2)	102/106(96.2)	307/326(94.2)
>=4M	63 / 73(86.3)	52/ 63(82.5)	58/ 63(92.1)	173/199(86.9)
HCV RNA BSL <5M				
<5M	98 /103(95.1)	125/138(90.6)	113/121(93.4)	336/362(92.8)
>=5M	52 / 62(83.9)	45/ 53(84.9)	47/ 48(97.9)	144/163(88.3)
HCV RNA BSL <6M				
<6M	109 /116(94.0)	131/145(90.3)	125/133(94.0)	365/394(92.6)
>=6M	41 / 49(83.7)	39/ 46(84.8)	35/ 36(97.2)	115/131(87.8)
HCV RNA BSL <7M				
<7M	118 /126(93.7)	140/155(90.3)	133/141(94.3)	391/422(92.7)
>=7M	32 / 39(82.1)	30/ 36(83.3)	27/ 28(96.4)	89/103(86.4)
HCV RNA BSL <8M				
<8M	**124 /133(93.2)**	**145/160(90.6)**	**137/145(94.5)**	**406/438(92.7)**
>=8M	**26 / 32(81.3)**	**25/ 31(80.6)**	**23/ 24(95.8)**	**74/ 87(85.1)**
P-value	0.0786	0.1185	1.000	0.0333
HCV RNA BSL <9M				
<9M	130 /140(92.9)	145/161(90.1)	142/150(94.7)	417/451(92.5)
>=9M	20 / 25(80.0)	25/ 30(83.3)	18/ 19(94.7)	63/ 74(85.1)
HCV RNA BSL <10M				
<10M	135 /146(92.5)	151/169(89.3)	145/153(94.8)	431/468(92.1)
>=10M	15 / 19(78.9)	19/ 22(86.4)	15/ 16(93.8)	49/ 57(86.0)
HCV RNA BSL <11M				
<11M	138 /150(92.0)	153/171(89.5)	147/155(94.8)	438/476(92.0)
>=11M	12 / 15(80.0)	17/ 20(85.0)	13/ 14(92.9)	42/ 49(85.7)
HCV RNA BSL <12M				
<12M	141 /154(91.6)	156/174(89.7)	149/157(94.9)	446/485(92.0)
>=12M	9 / 11(81.8)	14/ 17(82.4)	11/ 12(91.7)	34/ 40(85.0)
BMI category				
<=25	67 / 72(93.1)	71/ 81(87.7)	87/ 91(95.6)	225/244(92.2)
25<=, <30	60 / 67(89.6)	65/ 71(91.5)	50/ 55(90.9)	175/193(90.7)
>=30	23 / 26(88.5)	34/ 39(87.2)	23/ 23(100)	80/ 88(90.9)
<30 vs.>=30 P-value	0.7086	0.7740	0.6117	0.8353
Baseline Cirrhosis Category				
NO	100 /112(89.3)	92/100(92.0)	137/144(95.1)	329/356(92.4)
YES	50 / 53(94.3)	78/ 91(85.7)	23/ 25(92.0)	151/169(89.3)
P-value	0.3909	0.1748	0.6231	0.2464

IL28B Genotype				
CC	18 / 19(94.7)	56/ 63(88.9)	54/ 57(94.7)	128/139(92.1)
CT	90 /101(89.1)	76/ 84(90.5)	82/ 87(94.3)	248/272(91.2)
TT	41 / 44(93.2)	31/ 35(88.6)	24/ 25(96.0)	96/104(92.3)
CC vs. Non-CC P-value	1.000	1.000	1.000	0.8605
Reason for Intolerant/Ineligible				
ANEMIA OR NEUTROPENIA				
	./ .(.)	73/ 76(96.1)	./ .(.)	
COMPENSATED ADVANCED FIBROSIS/CIRRHOSIS (F3 OR F4) WITH THROMBOCYTOPENIA				
	./ .(.)	47/ 60(78.3)	./ .(.)	
DEPRESSION	./ .(.)	50/ 55(90.9)	./ .(.)	
Prior Response Category				
NULL RESPONDER	87 / 97(89.7)	./ .(.)	./ .(.)	
PARTIAL RESPOND	61 / 66(92.4)	./ .(.)	./ .(.)	
RELAPSER	2 / 2(100)	./ .(.)	./ .(.)	
Region				
ASIA	32 / 36(88.9)	33/ 37(89.2)	39/ 41(95.1)	104/114(91.2)
AUSTRALIA	14 / 15(93.3)	18/ 19(94.7)	15/ 16(93.8)	47/ 50(94.0)
EUROPE	70 / 78(89.7)	79/ 88(89.8)	45/ 49(91.8)	194/215(90.2)
NORTH AMERICA	33 / 35(94.3)	36/ 43(83.7)	57/ 58(98.3)	126/136(92.6)
SOUTH AMERICA	1 / 1(100)	4/ 4(100)	4/ 5(80.0)	9/ 10(90.0)
Country				
ARGEN	1 / 1(100)	4/ 4(100)	4/ 5(80.0)	9/ 10(90.0)
AUS	7 / 10(70.0)	1/ 1(100)	6/ 6(100)	14/ 17(82.4)
AUSTL	14 / 15(93.3)	18/ 19(94.7)	15/ 16(93.8)	47/ 50(94.0)
CAN	7 / 7(100)	4/ 4(100)	21/ 21(100)	32/ 32(100)
FRA	25 / 29(86.2)	26/ 26(100)	6/ 7(85.7)	57/ 62(91.9)
GER	13 / 13(100)	22/ 23(95.7)	7/ 7(100)	42/ 43(97.7)
IRE	1 / 1(100)	./ .(.)	5/ 5(100)	6/ 6(100)
ISR	1 / 1(100)	6/ 8(75.0)	./ .(.)	7/ 9(77.8)
ITALY	2 / 2(100)	5/ 7(71.4)	3/ 4(75.0)	10/ 13(76.9)
KOREA	16 / 16(100)	14/ 18(77.8)	20/ 21(95.2)	50/ 55(90.9)
NETH	1 / 2(50.0)	1/ 1(100)	5/ 5(100)	7/ 8(87.5)
NZEAL	./ .(.)	./ .(.)	5/ 5(100)	5/ 5(100)
POL	./ .(.)	./ .(.)	4/ 5(80.0)	4/ 5(80.0)
RUSS	12 / 12(100)	12/ 15(80.0)	./ .(.)	24/ 27(88.9)
SPAIN	4 / 4(100)	4/ 5(80.0)	3/ 3(100)	11/ 12(91.7)
TAIW	16 / 20(80.0)	19/ 19(100)	14/ 15(93.3)	49/ 54(90.7)
UK	4 / 4(100)	2/ 2(100)	6/ 7(85.7)	12/ 13(92.3)
USA	26 / 28(92.9)	32/ 39(82.1)	36/ 37(97.3)	94/104(90.4)

Table 32: The Summary Subgroup Analyses of SVR12 for Study AI447028 (Treated Subjects)

Efficacy Parameter	Prior	TN_IN	TN	Total
As Randomized and Dosed (Treated)				
N	168/205(82.0)	192/235(81.7)	182/203(89.7)	542/643(84.3)
Gender				
FEMALE	76/ 94(80.9)	111/137(81.0)	93/104(89.4)	280/335(83.6)
MALE	92/111(82.9)	81/ 98(82.7)	89/ 99(89.9)	262/308(85.1)
Race				
WHITE	121/148(81.8)	140/169(82.8)	118/133(88.7)	379/450(84.2)
CHINESE	17/ 22(77.3)	23/ 25(92.0)	23/ 26(88.5)	63/ 73(86.3)
KOREAN	18/ 21(85.7)	16/ 23(69.6)	20/ 21(95.2)	54/ 65(83.1)
ASIAN INDIAN	./ .(.)	1/ 1(100)	1/ 1(100)	2/ 2(100)
JAPANESE	./ .(.)	1/ 2(50.0)	./ .(.)	1/ 2(50.0)
ASIAN OTHER	1/ 2(50.0)	3/ 5(60.0)	4/ 4(100)	8/ 11(72.7)
BLACK/AFRICAN AMERICAN	10/ 10(100)	8/ 10(80.0)	13/ 14(92.9)	31/ 34(91.2)
NATIVE HAWAIIAN	./ .(.)	./ .(.)	1/ 2(50.0)	1/ 2(50.0)
OTHER	1/ 2(50.0)	./ .(.)	2/ 2(100)	3/ 4(75.0)
Ethnicity				
HISPANIC/LATINO	4/ 7(57.1)	4/ 7(57.1)	7/ 9(77.8)	15/ 23(65.2)
NOT HISPANIC/LATINO	150/179(83.8)	175/213(82.2)	165/184(89.7)	490/576(85.1)
	14/ 19(73.7)	13/ 15(86.7)	10/ 10(100)	37/ 44(84.1)
Age Group				
< 65	134/161(83.2)	138/175(78.9)	153/174(87.9)	425/510(83.3)
>= 65	34/ 44(77.3)	54/ 60(90.0)	29/ 29(100)	117/133(88.0)
HCV RNA BSL <600K				
<600,000	12/ 13(92.3)	31/ 36(86.1)	44/ 45(97.8)	87/ 94(92.6)
>=600,000	156/192(81.3)	161/199(80.9)	138/158(87.3)	455/549(82.9)
HCV RNA BSL <800K				
<800,000	25/ 27(92.6)	42/ 48(87.5)	51/ 53(96.2)	118/128(92.2)
>=800,000	143/178(80.3)	150/187(80.2)	131/150(87.3)	424/515(82.3)
HCV RNA BSL <1,000K				
<1,000K	29/ 31(93.5)	55/ 61(90.2)	59/ 62(95.2)	143/154(92.9)
>=1,000K	139/174(79.9)	137/174(78.7)	123/141(87.2)	399/489(81.6)
HCV RNA BSL <2,000K				
<2,000K	56/ 59(94.9)	85/ 99(85.9)	83/ 90(92.2)	224/248(90.3)
>=2,000K	112/146(76.7)	107/136(78.7)	99/113(87.6)	318/395(80.5)
HCV RNA BSL <3,000K				
<3,000K	76/ 83(91.6)	111/127(87.4)	103/111(92.8)	290/321(90.3)
>=3,000K	92/122(75.4)	81/108(75.0)	79/ 92(85.9)	252/322(78.3)
HCV RNA BSL <4,000K				
<4,000K	97/110(88.2)	128/146(87.7)	117/127(92.1)	342/383(89.3)
>=4,000K	71/ 95(74.7)	64/ 89(71.9)	65/ 76(85.5)	200/260(76.9)

HCV RNA BSL <5,000K				
<5,000K	108/123(87.8)	136/161(84.5)	129/143(90.2)	373/427(87.4)
>=5,000K	60/ 82(73.2)	56/ 74(75.7)	53/ 60(88.3)	169/216(78.2)
HCV RNA BSL <6,000K				
<6,000K	119/137(86.9)	145/172(84.3)	143/157(91.1)	407/466(87.3)
>=6,000K	49/ 68(72.1)	47/ 63(74.6)	39/ 46(84.8)	135/177(76.3)
HCV RNA BSL <7,000K				
<7,000K	129/149(86.6)	157/185(84.9)	153/167(91.6)	439/501(87.6)
>=7,000K	39/ 56(69.6)	35/ 50(70.0)	29/ 36(80.6)	103/142(72.5)
HCV RNA BSL <8,000K				
<8,000K	136/158(86.1)	164/193(85.0)	157/171(91.8)	457/522(87.5)
>=8,000K	32/ 47(68.1)	28/ 42(66.7)	25/ 32(78.1)	85/121(70.2)
HCV RNA BSL <9,000K				
<9,000K	143/167(85.6)	164/194(84.5)	162/176(92.0)	469/537(87.3)
>=9,000K	25/ 38(65.8)	28/ 41(68.3)	20/ 27(74.1)	73/106(68.9)
HCV RNA BSL <10,000K				
<10,000K	148/174(85.1)	170/203(83.7)	166/180(92.2)	484/557(86.9)
>=10,000K	20/ 31(64.5)	22/ 32(68.8)	16/ 23(69.6)	58/ 86(67.4)
HCV RNA BSL <11,000K				
<11,000K	153/181(84.5)	173/208(83.2)	169/183(92.3)	495/572(86.5)
>=11,000K	15/ 24(62.5)	19/ 27(70.4)	13/ 20(65.0)	47/ 71(66.2)
HCV RNA BSL <12,000K				
<12,000K	156/185(84.3)	176/211(83.4)	171/185(92.4)	503/581(86.6)
>=12,000K	12/ 20(60.0)	16/ 24(66.7)	11/ 18(61.1)	39/ 62(62.9)
BMI category				
<=25	75/ 92(81.5)	82/101(81.2)	98/107(91.6)	255/300(85.0)
25<=, <30	65/ 81(80.2)	74/ 91(81.3)	60/ 67(89.6)	199/239(83.3)
>=30	28/ 32(87.5)	36/ 43(83.7)	24/ 29(82.8)	88/104(84.6)
Baseline Cirrhosis Category				
NO	113/142(79.6)	104/124(83.9)	153/171(89.5)	370/437(84.7)
YES	55/ 63(87.3)	88/111(79.3)	29/ 32(90.6)	172/206(83.5)
IL28B Genotype				
CC	22/ 29(75.9)	66/ 82(80.5)	68/ 76(89.5)	156/187(83.4)
CT	100/123(81.3)	83/102(81.4)	87/ 99(87.9)	270/324(83.3)
TT	43/ 50(86.0)	36/ 41(87.8)	27/ 28(96.4)	106/119(89.1)
Reason for Intolerant/Ineligible				
ANEMIA OR NEUTROPENIA				
	./ .(.)	79/ 87(90.8)	./ .(.)	
COMPENSATED ADVANCED FIBROSIS/CIRRHOSIS (F3 OR F4) WITH THROMBOCYTOPENIA				
	./ .(.)	56/ 77(72.7)	./ .(.)	
DEPRESSION	./ .(.)	57/ 71(80.3)	./ .(.)	
Prior Response Category				

NULL RESPONDER	98/119(82.4)	./ .(.)	./ .(.)	
PARTIAL RESPOND	68/ 84(81.0)	./ .(.)	./ .(.)	
RELAPSER	2/ 2(100)	./ .(.)	./ .(.)	
Region				
ASIA	35/ 43(81.4)	38/ 47(80.9)	48/ 52(92.3)	121/142(85.2)
AUSTRALIA	14/ 15(93.3)	21/ 23(91.3)	16/ 20(80.0)	51/ 58(87.9)
EUROPE	82/102(80.4)	91/112(81.3)	55/ 63(87.3)	228/277(82.3)
NORTH AMERICA	36/ 44(81.8)	38/ 48(79.2)	58/ 62(93.5)	132/154(85.7)
SOUTH AMERICA	1/ 1(100)	4/ 5(80.0)	5/ 6(83.3)	10/ 12(83.3)
Country				
ARGEN	1/ 1(100)	4/ 5(80.0)	5/ 6(83.3)	10/ 12(83.3)
AUS	12/ 15(80.0)	2/ 2(100)	8/ 8(100)	22/ 25(88.0)
AUSTL	14/ 15(93.3)	21/ 23(91.3)	16/ 20(80.0)	51/ 58(87.9)
CAN	7/ 9(77.8)	4/ 4(100)	21/ 22(95.5)	32/ 35(91.4)
FRA	29/ 36(80.6)	31/ 35(88.6)	9/ 12(75.0)	69/ 83(83.1)
GER	13/ 15(86.7)	26/ 30(86.7)	8/ 9(88.9)	47/ 54(87.0)
IRE	1/ 1(100)	./ .(.)	5/ 5(100)	6/ 6(100)
ISR	3/ 3(100)	6/ 9(66.7)	./ .(.)	9/ 12(75.0)
ITALY	2/ 4(50.0)	5/ 8(62.5)	4/ 5(80.0)	11/ 17(64.7)
KOREA	18/ 21(85.7)	16/ 23(69.6)	21/ 22(95.5)	55/ 66(83.3)
NETH	1/ 4(25.0)	1/ 2(50.0)	6/ 6(100)	8/ 12(66.7)
NZEAL	./ .(.)	./ .(.)	5/ 5(100)	5/ 5(100)
POL	./ .(.)	./ .(.)	4/ 5(80.0)	4/ 5(80.0)
RUSS	12/ 15(80.0)	13/ 17(76.5)	./ .(.)	25/ 32(78.1)
SPAIN	5/ 5(100)	4/ 6(66.7)	4/ 5(80.0)	13/ 16(81.3)
TAIW	17/ 22(77.3)	22/ 24(91.7)	22/ 25(88.0)	61/ 71(85.9)
UK	4/ 4(100)	3/ 3(100)	7/ 8(87.5)	14/ 15(93.3)
USA	29/ 35(82.9)	34/ 44(77.3)	37/ 40(92.5)	100/119(84.0)

Table 33: Baseline Covariates Subgroup Analyses of Virologic Failures for Study AI447028 (525 Subjects without Baseline L31F/I/M/V or Y93H Polymorphism)

Efficacy Parameter	Prior	TN_IN	TN	Total
525 subjects who had baseline polymorphism but not L31F/I/M/V or Y93H (BT or Relapser)				
N	12/165(7.27)	14/191(7.33)	4/169(2.37)	30/525(5.71)
Gender				
FEMALE	6/ 69(8.70)	8/107(7.48)	1/ 86(1.16)	15/262(5.73)
MALE	6/ 96(6.25)	6/ 84(7.14)	3/ 83(3.61)	15/263(5.70)
Race				
WHITE	6/117(5.13)	10/140(7.14)	4/113(3.54)	20/370(5.41)
CHINESE	4/ 20(20.0)	./ 20(0.00)	./ 16(0.00)	4/ 56(7.14)
KOREAN	./ 16(0.00)	3/ 18(16.7)	./ 20(0.00)	3/ 54(5.56)
ASIAN INDIAN	./ .(.)	./ 1(0.00)	./ 1(0.00)	./ .(.)
ASIAN OTHER	1/ 2(50.0)	./ 2(0.00)	./ 3(0.00)	1/ 7(14.3)
JAPANESE	./ .(.)	1/ 2(50.0)	./ .(.)	1/ 2(50.0)
BLACK/AFRICAN AMERICAN				

	./ 8(0.00)	./ 8(0.00)	./ 13(0.00)	./ .(.)
NATIVE HAWAIIAN	./ .(.)	./ .(.)	./ 1(0.00)	./ .(.)
OTHER	1/ 2(50.0)	./ .(.)	./ 2(0.00)	1/ 4(25.0)
Ethnicity				
HISPANIC/LATINO	./ 4(0.00)	1/ 5(20.0)	1/ 8(12.5)	2/ 17(11.8)
NOT HISPANIC/LATINO				
	10/148(6.76)	13/177(7.34)	3/152(1.97)	26/477(5.45)
	2/ 13(15.4)	./ 9(0.00)	./ 9(0.00)	2/ 31(6.45)
Age Group				
< 65	10/133(7.52)	13/142(9.15)	4/146(2.74)	27/421(6.41)
>= 65	2/ 32(6.25)	1/ 49(2.04)	./ 23(0.00)	3/104(2.88)
HCV RNA BSL <600K				
<600,000	./ 11(0.00)	3/ 32(9.38)	./ 39(0.00)	3/ 82(3.66)
>=600,000	12/154(7.79)	11/159(6.92)	4/130(3.08)	27/443(6.09)
HCV RNA BSL <800K				
<800,000	./ 22(0.00)	3/ 40(7.50)	./ 47(0.00)	3/109(2.75)
>=800,000	12/143(8.39)	11/151(7.28)	4/122(3.28)	27/416(6.49)
HCV RNA BSL <1M				
<1M	**./ 25(0.00)**	**3/ 51(5.88)**	**./ 54(0.00)**	**3/130(2.31)**
>=1M	**12/140(8.57)**	**11/140(7.86)**	**4/115(3.48)**	**27/395(6.84)**
P-value	0.2163	0.7632	0.3074	0.0783
HCV RNA BSL <2M				
<2M	1/ 51(1.96)	7/ 86(8.14)	./ 75(0.00)	8/212(3.77)
>=2M	11/114(9.65)	7/105(6.67)	4/ 94(4.26)	22/313(7.03)
HCV RNA BSL <3M				
<3M	2/ 73(2.74)	8/111(7.21)	./ 93(0.00)	10/277(3.61)
>=3M	10/ 92(10.9)	6/ 80(7.50)	4/ 76(5.26)	20/248(8.06)
HCV RNA BSL <4M				
<4M	3/ 92(3.26)	8/128(6.25)	1/106(0.94)	12/326(3.68)
>=4M	9/ 73(12.3)	6/ 63(9.52)	3/ 63(4.76)	18/199(9.05)
HCV RNA BSL <5M				
<5M	3/103(2.91)	8/138(5.80)	4/121(3.31)	15/362(4.14)
>=5M	9/ 62(14.5)	6/ 53(11.3)	./ 48(0.00)	15/163(9.20)
HCV RNA BSL <6M				
<6M	5/116(4.31)	8/145(5.52)	4/133(3.01)	17/394(4.31)
>=6M	7/ 49(14.3)	6/ 46(13.0)	./ 36(0.00)	13/131(9.92)
HCV RNA BSL <7M				
<7M	6/126(4.76)	8/155(5.16)	4/141(2.84)	18/422(4.27)
>=7M	6/ 39(15.4)	6/ 36(16.7)	./ 28(0.00)	12/103(11.7)
HCV RNA BSL <8M				
<8M	**7/133(5.26)**	**8/160(5.00)**	**4/145(2.76)**	**19/438 (4.34)**
>=8M	**5/ 32(15.6)**	**6/ 31(19.4)**	**./ 24(0.00)**	**11/ 87(12.6)**
P-value	0.0576	0.0132	1.000	0.0050

HCV RNA BSL <9M				
<9M	8/140(5.71)	9/161(5.59)	4/150(2.67)	21/451(4.66)
>=9M	4/ 25(16.0)	5/ 30(16.7)	./ 19(0.00)	9/ 74(12.2)
HCV RNA BSL <10M				
<10M	8/146(5.48)	11/169(6.51)	4/153(2.61)	23/468(4.91)
>=10M	4/ 19(21.1)	3/ 22(13.6)	./ 16(0.00)	7/ 57(12.3)
HCV RNA BSL <11M				
<11M	9 /150(6.00)	11/171(6.43)	4/155(2.58)	24/476(5.04)
>=11M	3 / 15(20.0)	3/ 20(15.0)	./ 14(0.00)	6/ 49(12.2)
HCV RNA BSL <12M				
<12M	10/154(6.49)	11/174(6.32)	4/157(2.55)	25/485(5.15)
>=12M	2/ 11(18.2)	3/ 17(17.6)	./ 12(0.00)	5/ 40(12.5)
BMI category				
25<=, <30	4/ 67(5.97)	4/ 71(5.63)	2/ 55(3.64)	10/193(5.18)
<=25	5/ 72(6.94)	6/ 81(7.41)	2/ 91(2.20)	13/244(5.33)
>=30	3/ 26(11.5)	4/ 39(10.3)	./ 23(0.00)	7/ 88(7.95)
<30 vs. >=30 P-value	0.4055	0.4899	1.000	0.3164
Baseline Cirrhosis Category				
NO	10/112(8.93)	7/100(7.00)	3/144(2.08)	20/356(5.62)
YES	2/ 53(3.77)	7/ 91(7.69)	1/ 25(4.00)	10/169(5.92)
P-value	0.3410	1.000	0.4762	1.000
IL28B Genotype				
CC	1/ 19(5.26)	4/ 63(6.35)	1/ 57(1.75)	6/139(4.32)
CT	9/101(8.91)	7/ 84(8.33)	3/ 87(3.45)	19/272(6.99)
TT	2/ 44(4.55)	1/ 35(2.86)	./ 25(0.00)	3/104(2.88)
CC vs. Non-CC P-value	1.000	1.000	1.000	0.5244
Reason for Intolerant/Ineligible				
ANEMIA OR NEUTROPENIA	./ .(.)	3/ 76(3.95)	./ .(.)	3/ 76(3.95)
COMPENSATED ADVANCED FIBROSIS/CIRRHOSIS (F3 OR F4) WITH THROMBOCYTOPENIA	./ .(.)	7/ 60(11.7)	./ .(.)	7/ 60(11.7)
DEPRESSION	./ .(.)	4/ 55(7.27)	./ .(.)	4/ 55(7.27)
Prior Response Category				
NULL RESPONDER	8/ 97(8.25)	./ .(.)	./ .(.)	8/ 97(8.25)
PARTIAL RESPOND	4/ 66(6.06)	./ .(.)	./ .(.)	4/ 66(6.06)
RELAPSER	./ 2(0.00)	./ .(.)	./ .(.)	./ .(.)
RAND	./ .(.)	./ .(.)	4/169(2.37)	4/169(2.37)
Region				
ASIA	4/ 36(11.1)	3/ 37(8.11)	./ 41(0.00)	7/114(6.14)
AUSTRALIA	1/ 15(6.67)	./ 19(0.00)	1/ 16(6.25)	2/ 50(4.00)
EUROPE	7/ 78(8.97)	5/ 88(5.68)	2/ 49(4.08)	14/215(6.51)
NORTH AMERICA	./ 35(0.00)	6/ 43(14.0)	./ 58(0.00)	6/136(4.41)
SOUTH AMERICA	./ 1(0.00)	./ 4(0.00)	1/ 5(20.0)	1/ 10(10.0)
Country				
ARGEN	./ 1(0.00)	./ 4(0.00)	1/ 5(20.0)	1/ 10(10.0)

AUS	2/ 10(20.0)	./ 1(0.00)	./ 6(0.00)	2/ 17(11.8)
AUSTL	1/ 15(6.67)	./ 19(0.00)	1/ 16(6.25)	2/ 50(4.00)
CAN	./ 7(0.00)	./ 4(0.00)	./ 21(0.00)	./ .(.)
FRA	4/ 29(13.8)	./ 26(0.00)	./ 7(0.00)	4/ 62(6.45)
GER	./ 13(0.00)	./ 23(0.00)	./ 7(0.00)	./ .(.)
IRE	./ 1(0.00)	./ .(.)	./ 5(0.00)	./ .(.)
ISR	./ 1(0.00)	2/ 8(25.0)	./ .(.)	2/ 9(22.2)
ITALY	./ 2(0.00)	1/ 7(14.3)	1/ 4(25.0)	2/ 13(15.4)
KOREA	./ 16(0.00)	3/ 18(16.7)	./ 21(0.00)	3/ 55(5.45)
NETH	1/ 2(50.0)	./ 1(0.00)	./ 5(0.00)	1/ 8(12.5)
NZEAL	/ .(.)	./ .(.)	./ 5(0.00)	./ .(.)
POL	./ .(.)	./ .(.)	./ 5(0.00)	./ .(.)
RUSS	./ 12(0.00)	2/ 15(13.3)	./ .(.)	2/ 27(7.41)
SPAIN	./ 4(0.00)	./ 5(0.00)	./ 3(0.00)	./ .(.)
TAIW	4/ 20(20.0)	./ 19(0.00)	./ 15(0.00)	4/ 54(7.41)
UK	./ 4(0.00)	./ 2(0.00)	1/ 7(14.3)	1/ 13(7.69)
USA	./ 28(0.00)	6/ 39(15.4)	./ 37(0.00)	6/104(5.77)

*: Virologic Failures here includes breakthrough and relapse.

Table 34: The Summary Subgroup Analyses of SVR12 for Study AI447029 (Treated Subjects)

Efficacy Parameter	GT1a	GT1b	GT4	Total
As Dosed (Treated)				
N	53/176(86.9)	176/178(98.9)	43/44(97.7)	372/398(93.5)
Gender				
FEMALE	39/ 46(84.8)	67/ 68(98.5)	11/ 11(100)	117/125(93.6)
MALE	114/130(87.7)	109/110(99.1)	32/ 33(97.0)	255/273(93.4)
Race				
WHITE	130/149(87.2)	121/122(99.2)	32/ 33(97.0)	283/304(93.1)
BLACK/AFRICAN AMERICAN	19/ 23(82.6)	10/ 10(100)	4/ 4(100)	33/ 37(89.2)
AMERICAN INDIAN/ALASKA NATIVE	1/ 1(100)	./ .(.)	1/ 1(100)	2/ 2(100)
KOREAN	./ .(.)	26/ 27(96.3)	./ .(.)	26/ 27(96.3)
CHINESE	./ .(.)	13/ 13(100)	./ .(.)	13/ 13(100)
ASIAN INDIAN	./ .(.)	1/ 1(100)	./ .(.)	1/ 1(100)
ASIAN OTHER	2/ 2(100)	3/ 3(100)	1/ 1(100)	6/ 6(100)
JAPANESE	./ .(.)	1/ 1(100)	./ .(.)	1/ 1(100)
NATIVE HAWAIIAN/OTHER PACIFIC	./ .(.)	1/ 1(100)	./ .(.)	1/ 1(100)
OTHER	1/ 1(100)	./ .(.)	5/ 5(100)	6/ 6(100)
Ethnicity				
HISPANIC/LATINO	15/ 17(88.2)	16/ 16(100)	2/ 2(100)	33/ 35(94.3)
NOT HISPANIC/LATINO	138/159(86.8)	160/162(98.8)	41/ 42(97.6)	339/363(93.4)

Age Group				
< 65	147/168(87.5)	150/152(98.7)	40/ 41(97.6)	337/361(93.4)
>= 65	6/ 8(75.0)	26/ 26(100)	3/ 3(100)	35/ 37(94.6)
P-value	0.2808			
HCV RNA BSL <600K				
<600,000	13/ 14(92.9)	21/ 21(100)	12/ 12(100)	46/ 47(97.9)
>=600,000	140/162(86.4)	155/157(98.7)	31/ 32(96.9)	326/351(92.9)
HCV RNA BSL <800K				
<800,000	15/ 16(93.8)	31/ 31(100)	15/ 15(100)	61/ 62(98.4)
>=800,000	138/160(86.3)	145/147(98.6)	28/ 29(96.6)	311/336(92.6)
P-value	0.6982			
HCV RNA BSL <1M				
<1M	19/ 21(90.5)	33/ 33(100)	16/ 16(100)	68/ 70(97.1)
>=1M	134/155(86.5)	143/145(98.6)	27/ 28(96.4)	304/328(92.7)
HCV RNA BSL <2M				
<2M	46/ 50(92.0)	62/ 62(100)	24/ 24(100)	132/136(97.1)
>=2M	107/126(84.9)	114/116(98.3)	19/ 20(95.0)	240/262(91.6)
HCV RNA BSL <3M				
<3M	61/ 68(89.7)	82/ 83(98.8)	37/ 38(97.4)	180/189(95.2)
>=3M	92/108(85.2)	94/ 95(98.9)	6/ 6(100)	192/209(91.9)
HCV RNA BSL <4M				
<4M	82/ 91(90.1)	101/102(99.0)	40/ 41(97.6)	223/234(95.3)
>=4M	71/ 85(83.5)	75/ 76(98.7)	3/ 3(100)	149/164(90.9)
HCV RNA BSL <5M				
<5M	88/ 97(90.7)	115/116(99.1)	40/ 41(97.6)	243/254(95.7)
>=5M	65/ 79(82.3)	61/ 62(98.4)	3/ 3(100)	129/144(89.6)
HCV RNA BSL <6M				
<6M	96/106(90.6)	125/126(99.2)	40/ 41(97.6)	261/273(95.6)
>=6M	57/ 70(81.4)	51/ 52(98.1)	3/ 3(100)	111/125(88.8)
HCV RNA BSL <7M				
<7M	105/116(90.5)	136/137(99.3)	40/ 41(97.6)	281/294(95.6)
>=7M	48/ 60(80.0)	40/ 41(97.6)	3/ 3(100)	91/104(87.5)
HCV RNA BSL <8M				
<8M	113/126(89.7)	144/145(99.3)	41/ 42(97.6)	298/313(95.2)
>=8M	40/ 50(80.0)	32/ 33(97.0)	2/ 2(100)	74/ 85(87.1)
P-value	0.1342			
HCV RNA BSL <9M				
<9M	117/132(88.6)	149/150(99.3)	42/ 43(97.7)	308/325(94.8)
>=9M	36/ 44(81.8)	27/ 28(96.4)	1/ 1(100)	64/ 73(87.7)
HCV RNA BSL <10M				
<10M	122/138(88.4)	151/152(99.3)	42/ 43(97.7)	315/333(94.6)
>=10M	31/ 38(81.6)	25/ 26(96.2)	1/ 1(100)	57/ 65(87.7)
P-value	0.2821			

HCV RNA BSL <11M				
<11M	125/143(87.4)	154/155(99.4)	43/ 44(97.7)	322/342(94.2)
>=11M	28/ 33(84.8)	22/ 23(95.7)	./ .(.)	50/ 56(89.3)
HCV RNA BSL <12M				
<12M	130/148(87.8)	156/157(99.4)	43/ 44(97.7)	329/349(94.3)
>=12M	23/ 28(82.1)	20/ 21(95.2)	./ .(.)	43/ 49(87.8)
BMI category				
<=25	61/ 67(91.0)	66/ 68(97.1)	18/ 19(94.7)	145/154(94.2)
25<=, <30	59/ 75(78.7)	72/ 72(100)	20/ 20(100)	151/167(90.4)
>=30	33/ 34(97.1)	38/ 38(100)	5/ 5(100)	76/ 77(98.7)
<30 vs. >=30 P-value	0.0516			
Baseline Cirrhosis Category				
NO	115/132(87.1)	148/149(99.3)	24/ 24(100)	287/305(94.1)
YES	38/ 44(86.4)	28/ 29(96.6)	19/ 20(95.0)	85/ 93(91.4)
CC vs. Non-CC P-value	1.000			
IL28B Genotype				
CC	11/ 13(84.6)	20/ 20(100)	3/ 3(100)	34/ 36(94.4)
CT	98/115(85.2)	115/116(99.1)	30/ 31(96.8)	243/262(92.7)
TT	44/ 48(91.7)	41/ 42(97.6)	10/ 10(100)	95/100(95.0)
CC vs. Non-CC P-value	0.6799			
Previous Response Category				
NULL RESPONDER	104/118(88.1)	115/116(99.1)	33/ 34(97.1)	252/268(94.0)
PARTIAL RESPONDER	49/ 58(84.5)	61/ 62(98.4)	10/ 10(100)	120/130(92.3)
Partial vs. Null P-value	0.4865			
Region				
ASIA	./ .(.)	41/ 42(97.6)	./ .(.)	41/ 42(97.6)
EUROPE	67/ 80(83.8)	94/ 95(98.9)	28/ 29(96.6)	189/204(92.6)
NORTH AMERICA	82/ 91(90.1)	35/ 35(100)	15/ 15(100)	132/141(93.6)
SOUTH AMERICA	4/ 5(80.0)	6/ 6(100)	./ .(.)	10/ 11(90.9)
Europe vs. North America P-value	0.2560			
Country				
ARGEN	4/ 5(80.0)	6/ 6(100)	./ .(.)	10/ 11(90.9)
CAN	8/ 9(88.9)	1/ 1(100)	10/ 10(100)	19/ 20(95.0)
DEN	3/ 3(100)	3/ 3(100)	1/ 1(100)	7/ 7(100)
FRA	25/ 32(78.1)	16/ 17(94.1)	21/ 22(95.5)	62/ 71(87.3)
GER	17/ 22(77.3)	17/ 17(100)	5/ 5(100)	39/ 44(88.6)
ITALY	5/ 5(100)	13/ 13(100)	./ .(.)	18/ 18(100)
KOREA	./ .(.)	26/ 27(96.3)	./ .(.)	26/ 27(96.3)
MEX	1/ 1(100)	5/ 5(100)	./ .(.)	6/ 6(100)
NETH	6/ 6(100)	2/ 2(100)	./ .(.)	8/ 8(100)
RUSS	./ .(.)	21/ 21(100)	./ .(.)	21/ 21(100)
SPAIN	3/ 4(75.0)	18/ 18(100)	./ .(.)	21/ 22(95.5)
SWE	7/ 7(100)	./ .(.)	1/ 1(100)	8/ 8(100)
SWITZ	1/ 1(100)	4/ 4(100)	./ .(.)	5/ 5(100)
TAIW	./ .(.)	15/ 15(100)	./ .(.)	15/ 15(100)
USA	73/ 81(90.1)	29/ 29(100)	5/ 5(100)	107/115(93.0)

Table 35: Baseline Covariates Subgroup Analyses of Virologic Failures for Study AI447029 (Treated Subjects)*

Efficacy Parameter	GT1a	GT1b	GT4	Total
As Dosed (Treated)				
N	18/176(10.2)	1/178(0.56)	0/ 44(0.00)	19/398(4.77)
Gender				
FEMALE	5/ 46(10.9)	./ 68(0.00)	./ 11(0.00)	5/125(4.00)
MALE	13/130(10.0)	1/110(0.91)	./ 33(0.00)	14/273(5.13)
Race				
WHITE	15/149(10.1)	1/122(0.82)	./ 33(0.00)	16/304(5.26)
BLACK/AFRICAN AMERICAN	3/ 23(13.0)	./ 10(0.00)	./ 4(0.00)	3/ 37(8.11)
AMERICAN INDIAN/ALASKA NATIVE	./ 1(0.00)	./ .(.)	./ 1(0.00)	./ .(.)
KOREAN	./ .(.)	./ 27(0.00)	./ .(.)	./ .(.)
CHINESE	./ .(.)	./ 13(0.00)	./ .(.)	./ .(.)
ASIAN INDIAN	./ .(.)	./ 1(0.00)	./ .(.)	./ .(.)
JAPANESE	./ .(.)	./ 1(0.00)	./ .(.)	./ .(.)
ASIAN OTHER	./ 2(0.00)	./ 3(0.00)	./ 1(0.00)	./ .(.)
NATIVE HAWAIIAN/OTHER PACIFIC	./ .(.)	./ 1(0.00)	./ .(.)	./ .(.)
OTHER	./ 1(0.00)	./ .(.)	./ 5(0.00)	./ .(.)
Ethnicity				
HISPANIC/LATINO	2/ 17(11.8)	./ 16(0.00)	./ 2(0.00)	2/ 35(5.71)
NOT HISPANIC/LATINO	16/159(10.1)	1/162(0.62)	./ 42(0.00)	17/363(4.68)
Age Group				
< 65	17/168(10.1)	1/152(0.66)	./ 41(0.00)	18/361(4.99)
>= 65	1/ 8(12.5)	./ 26(0.00)	./ 3(0.00)	1/ 37(2.70)
HCV RNA BSL <600K				
<600,000	1/ 14(7.14)	./ 21(0.00)	./ 12(0.00)	1/ 47(2.13)
>=600,000	17/162(10.5)	1/157(0.64)	./ 32(0.00)	18/351(5.13)
HCV RNA BSL <800K				
<800,000	1/ 16(6.25)	./ 31(0.00)	./ 15(0.00)	1/ 62(1.61)
>=800,000	17/160(10.6)	1/147(0.68)	./ 29(0.00)	18/336(5.36)
P-value	1.000			
HCV RNA BSL <1M				
<1M	2/ 21(9.52)	./ 33(0.00)	./ 16(0.00)	2/ 70(2.86)
>=1M	16/155(10.3)	1/145(0.69)	./ 28(0.00)	17/328(5.18)
HCV RNA BSL <2M				
<2M	4/ 50(8.00)	./ 62(0.00)	./ 24(0.00)	4/136(2.94)
>=2M	14/126(11.1)	1/116(0.86)	./ 20(0.00)	15/262(5.73)
HCV RNA BSL <3M				
<3M	5/ 68(7.35)	./ 83(0.00)	./ 38(0.00)	5/189(2.65)

>=3M	13/108(12.0)	1/ 95(1.05)	./ 6(0.00)	14/209(6.70)
HCV RNA BSL <4M				
<4M	6/ 91(6.59)	./102(0.00)	./ 41(0.00)	6/234(2.56)
>=4M	12/ 85(14.1)	1/ 76(1.32)	./ 3(0.00)	13/164(7.93)
HCV RNA BSL <5M				
<5M	6/ 97(6.19)	./116(0.00)	./ 41(0.00)	6/254(2.36)
>=5M	12/ 79(15.2)	1/ 62(1.61)	./ 3(0.00)	13/144(9.03)
HCV RNA BSL <6M				
<6M	7/106(6.60)	./126(0.00)	./ 41(0.00)	7/273(2.56)
>=6M	11/ 70(15.7)	1/ 52(1.92)	./ 3(0.00)	12/125(9.60)
HCV RNA BSL <7M				
<7M	7/116(6.03)	./137(0.00)	./ 41(0.00)	7/294(2.38)
>=7M	11/ 60(18.3)	1/ 41(2.44)	./ 3(0.00)	12/104(11.5)
HCV RNA BSL <8M				
<8M	9/126(7.14)	./145(0.00)	./ 42(0.00)	9/313(2.88)
>=8M	9/ 50(18.0)	1/ 33(3.03)	./ 2(0.00)	10/ 85(11.8)
P-value	0.0503			
HCV RNA BSL <9M				
<9M	11/132(8.33)	./150(0.00)	./ 43(0.00)	11/325(3.38)
>=9M	7/ 44(15.9)	1/ 28(3.57)	./ 1(0.00)	8/ 73(11.0)
HCV RNA BSL <10M				
<10M	12/138(8.70)	./152(0.00)	./ 43(0.00)	12/333(3.60)
>=10M	6/ 38(15.8)	1/ 26(3.85)	./ 1(0.00)	7/ 65(10.8)
P-value	0.2278			
HCV RNA BSL <11M				
<11M	14/143(9.79)	./155(0.00)	./ 44(0.00)	14/342(4.09)
>=11M	4/ 33(12.1)	1/ 23(4.35)	./ .(.)	5/ 56(8.93)
HCV RNA BSL <12M				
<12M	14/148(9.46)	./157(0.00)	./ 44(0.00)	14/349(4.01)
>=12M	4/ 28(14.3)	1/ 21(4.76)	./ .(.)	5/ 49(10.2)
BMI category				
25<=, <30	14/ 75(18.7)	./ 72(0.00)	./ 20(0.00)	14/167(8.38)
<=25	3/ 67(4.48)	1/ 68(1.47)	./ 19(0.00)	4/154(2.60)
>=30	1/ 34(2.94)	./ 38(0.00)	./ 5(0.00)	1/ 77(1.30)
<30 vs. >=30 P-value	0.2038			
Baseline Cirrhosis Category				
NO	12/132(9.09)	./149(0.00)	./ 24(0.00)	12/305(3.93)
YES	6/ 44(13.6)	1/ 29(3.45)	./ 20(0.00)	7/ 93(7.53)
P-value	0.3963			
IL28B Genotype				
CC	2/ 13(15.4)	./ 20(0.00)	./ 3(0.00)	2/ 36(5.56)
CT	13/115(11.3)	./116(0.00)	./ 31(0.00)	13/262(4.96)
TT	3/ 48(6.25)	1/ 42(2.38)	./ 10(0.00)	4/100(4.00)
CC vs. Non-CC P-value	0.6262			

Previous Response Category				
NULL RESPONDER	11/118(9.32)	1/116(0.86)	./ 34(0.00)	12/268(4.48)
PARTIAL RESPONDER	7/ 58(12.1)	./ 62(0.00)	./ 10(0.00)	7/130(5.38)
Partial vs. Null P-value		0.6018		
Region				
ASIA	./ .(.)	./ 42(0.00)	./ .(.)	./ .(.)
EUROPE	10/ 80(12.5)	1/ 95(1.05)	./ 29(0.00)	11/204(5.39)
NORTH AMERICA	7/ 91(7.69)	./ 35(0.00)	./ 15(0.00)	7/141(4.96)
SOUTH AMERICA	1/ 5(20.0)	./ 6(0.00)	./ .(.)	1/ 11(9.09)
Europe vs. North America P-value		0.3175		
Country				
ARGEN	1/ 5(20.0)	./ 6(0.00)	./ .(.)	1/ 11(9.09)
CAN	1/ 9(11.1)	./ 1(0.00)	./ 10(0.00)	1/ 20(5.00)
DEN	./ 3(0.00)	./ 3(0.00)	./ 1(0.00)	./ .(.)
FRA	5/ 32(15.6)	1/ 17(5.88)	./ 22(0.00)	6/ 71(8.45)
GER	5/ 22(22.7)	./ 17(0.00)	./ 5(0.00)	5/ 44(11.4)
ITALY	./ 5(0.00)	./ 13(0.00)	./ .(.)	./ .(.)
KOREA	./ .(.)	./ 27(0.00)	./ .(.)	./ .(.)
MEX	./ 1(0.00)	./ 5(0.00)	./ .(.)	./ .(.)
NETH	./ 6(0.00)	./ 2(0.00)	./ .(.)	./ .(.)
RUSS	./ .(.)	./ 21(0.00)	./ .(.)	./ .(.)
SPAIN	./ 4(0.00)	./ 18(0.00)	./ .(.)	./ .(.)
SWE	./ 7(0.00)	./ .(.)	./ 1(0.00)	./ .(.)
SWITZ	./ 1(0.00)	./ 4(0.00)	./ .(.)	./ .(.)
TAIW	./ .(.)	./ 15(0.00)	./ .(.)	./ .(.)
USA	6/ 81(7.41)	./ 29(0.00)	./ 5(0.00)	6/115(5.22)

*: Virologic Failures here includes breakthrough and relapse.

Table 36: Summary of Supportive Phase 2 Trials

Trial	Country	Population	Study Design/Type of Control	Treatment Regimen	Number of Subjects
Phase 2 data supportive of DCV and ASV (DUAL or QUAD)					
AI447011	France; United States	Genotype 1 null responders	Randomized, open-label, parallel group	DCV: 60 mg QD ASV:200 mg BID with or without peg IFN/RBV; 24 weeks	N=122; **N=18** for DUAL and **N=20** (arm B1) for QUAD are included for analyses
AI447017	Japan	Genotype 1 Null responder, IFN therapy ineligible naive/ intolerant	Non-randomized, open-label, 2 parallel groups, 2 parts	ASV: 200, 600 mg BID DCV: 60 mg QD 24 weeks	N=43 **N=33** for DUAL are included for analyses
Phase 2 data supportive of DCV (DCV + pegIFN/RBV; DCV/SOF*)					
AI444010	Australia; Canada;	Genotype 1 and 4	Randomized, double-blind,	DCV: 0, 20, 60 mg	N=395 (GT-1:365;

	Denmark; Egypt; France; Germany; Italy; Mexico; Sweden; United States, including Puerto Rico	Treatment-naive	placebo-controlled, multinational	with pegIFN-2a/RBV 24 or 48 weeks	GT-4:30) **N=158** included for analyses; N=78 PBO
AI444011	Argentina; Australia; Canada; Denmark; France; Germany; Italy; Mexico; Sweden; United States, including Puerto Rico	Genotype 1 Null or partial responders	Randomized, double-blind, placebo-controlled, multinational	DCV: 0, 20, 60 mg with pegIFN-2a/RBV 24 or 48 weeks	N=419 **N=199** included for analyses; N=17 PBO
AI444014	France, United States	Genotype 1 Treatment-naive	Randomized, double-blind, placebo-controlled	DCV: 0, 3, 10, 60 mg with pegIFN-2a/RBV 48 weeks	N=48 **N=12** included for analyses; N=12 PBO
AI444021	Japan	Genotype 1	Randomized, double-blind, placebo-controlled	DCV: 0, 3, 10, 60 mg with pegIFN-2a/RBV 24 or 48 weeks	N=45 **N=19** included for analyses; N=8 PBO
AI444022	Japan	Genotype 1	Randomized, double-blind, placebo-controlled	DCV: 0, 3, 10, 60 mg with pegIFN-2a/RBV 24 or 48 weeks	N=42 **N=17** included for analyses; N=8 PBO
AI444031	Australia; Canada; Denmark; France; Italy; United States	Genotype 2 and 3 Treatment-naive	Randomized, double-blinded, placebo-controlled	DCV: 0, 60 mg with pegIFN-2a/RBV	N=151 **N= 100** included for analyses; N=51 PBO
AI444040*	United States, including Puerto Rico	Genotype 1, 2, and 3 Treatment-naive or telaprevir or boceprevir treatment failure	Randomized, open label, parallel treatment group	DCV: 60 mg QD SOF: 400 mg QD RBV: 200 mg BID	**N=211**
Phase 2 data supportive of ASV (ASV + pegIFN/RBV)					

*AI444040 (DCV/SOF) data are included for safety analyses only; BMS did not provide a right of reference to sofosbuvir (SOF) which is owned by Gilead Sciences
Source: Clinical review Table 7.

References

1. StatXact PROCs User Manual for SAS Users, Version 6, 2004, Cytel.
2. SAS Version 9.3, SAS Inc.

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/s/

WEN ZENG
08/29/2014

FRASER B SMITH
08/29/2014

GUOXING SOON
08/29/2014

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 206-843
Drug Name:	BMS-790052
Applicant:	Sponsor: Bristol-Myers Squibb Company Test Facility: (b) (4)
Documents Reviewed:	Electronic data submitted on December 4, 2013, Also include the sponsor's reports submitted.
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Min Min, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Antiviral Products
Reviewing Pharmacologist:	Myers, Laine (Peyton) Ph.D.
Project Manager:	Sohail Mosaddegh, Pharm.D.
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in rats and one in transgenic mice. These studies were intended to further assess the carcinogenic potential of BMS-790052, an inhibitor of the non-structural protein 3 protease of the hepatitis C virus, in Sprague-Dawley rats (Crl:CD[SD]) and CByB6F1/Tg rasH2 hemizygous (transgenic) mice transgenic mice, when administered daily via oral gavage to transgenic mice for 26 weeks and rats for at least 104 weeks.

Results of this review have been discussed with the reviewing pharmacologist Dr. Myers who suggested doing analysis for rat and transgenic mouse studies.

2. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and two control groups. Three hundred and twenty five Sprague-Dawley rats (Crl:CD[SD]) of each sex were randomly allocated to treated and control groups. There were 65 animals per sex in each of groups. Treated animals each received dose preparations 5, 15, or 50 mg/kg. Eight additional satellite groups, each consisting of 20 rats per sex, received the same doses and were used for toxicokinetic evaluations. Vehicle (also used for the BMS-790052 treatment groups) consisted of 60% polyethylene glycol 400 and 40% Vitamin E-d-α-tocopheryl polyethylene glycol 1000 succinate. Water control rats were given Ultra Pure water only. Dose volume for all groups was 5 ml/kg.
Due to lower survival in Group 1 (water control) and Group 2 (vehicle control) males and Group 2 (vehicle control) females, all surviving rats were euthanized commencing Week 94 and Week 92 for males and females, respectively. Early termination of all groups in this study was considered to have no impact on the assessment of carcinogenic potential because the number of animals evaluated and study duration were sufficient based on FDA guidance.

Male and female Sprague-Dawley rats (Crl:CD[SD]) were assigned to groups, and doses were administered as indicated in the following table. Rats were dosed via oral gavage.

Group No.	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Concentration (mg/mL)	No. of Animals			
				Main Study[a]		Toxicokinetic Study[b]	
				Males	Females	Males	Females
1/ Water Control	0	10	0	1001 to 1065	1501 to 1565	1066 to 1083	1566 to 1583
2/ Vehicle Control	0	10	0	2001 to 2065	2501 to 2565	2066 to 2083	2566 to 2583
3/ BMS-790052	5	10	0.5	3001 to 3065	3501 to 3565	3066 to 3083	3566 to 3583
4/ BMS-790052	15	10	1.5	4001 to 4065	4501 to 4565	4066 to 4083	4566 to 4583
5/ BMS-790052	50	10	5	5001 to 5065	5501 to 5565	5066 to 5083	5566 to 5583
6/ Health Screen[c]	-	-	-	6001 to 6010[d]	6501 to 6510[d]	-	-
7/ Sentinel[d]	-	-	-	7001 to 7025	7501 to 7525	-	-

- = Not applicable.

[a] Male animals were necropsied during Week 94 and female animals were necropsied during Week 92.

[b] Toxicokinetic animals were used for toxicokinetic evaluations only. Data relating to clinical examination and body weight collected from these animals were retained, but not reported.

[c] Health Screen animals were used for health-screen evaluations only

[d] Tests were conducted on sentinel animals only as indicated in Section 14 of the Study Plan/Protocol. Data from these animals were retained on file but not included in the study report.

2.1. Sponsor's analyses

2.1.1. Survival analysis

The effect of the vehicle on mortality was examined by plotting the survival data from the vehicle and water control groups as Kaplan-Meier product-limit curves, separately by sex. For each assessment, differences between the 2 curves were evaluated with a two-sided, life-table test at the 0.05 level of significance. The survival data of the BMS-790052 treated groups and vehicle control groups were displayed as Kaplan-Meier product-limit curves, separately for each sex. Dose-related trends in survival were tested with a two-sided life table test, at the 0.05 level of significance, using the vehicle-control groups.

Sponsor's findings: The survival rates to not scheduled sacrifice (94 (males) and 92 (females)) were 31, 31, 35, 23, and 29% in males and 34, 31, 46, 46, and 37% in females given 0 (two control groups separately: water and vehicle control), 5, 15, or 50 mg/kg/day, respectively. There were no BMS-790052-related effects on survival or on any specific cause of death.

No evidence was seen of a treatment effect of BMS-790052 on mortality or on any specific cause of death. Between 35/65 and 50/65 animals per group were found dead or euthanized for humane reasons during the preterminal phase of this study. As is typical for animals of this species, the most frequent cause of early

death/euthanasia was the presence of spontaneously occurring neoplastic change in the pituitary pars distalis.

Figure 1: Kaplan-Meier plot of Survival in Male Rats

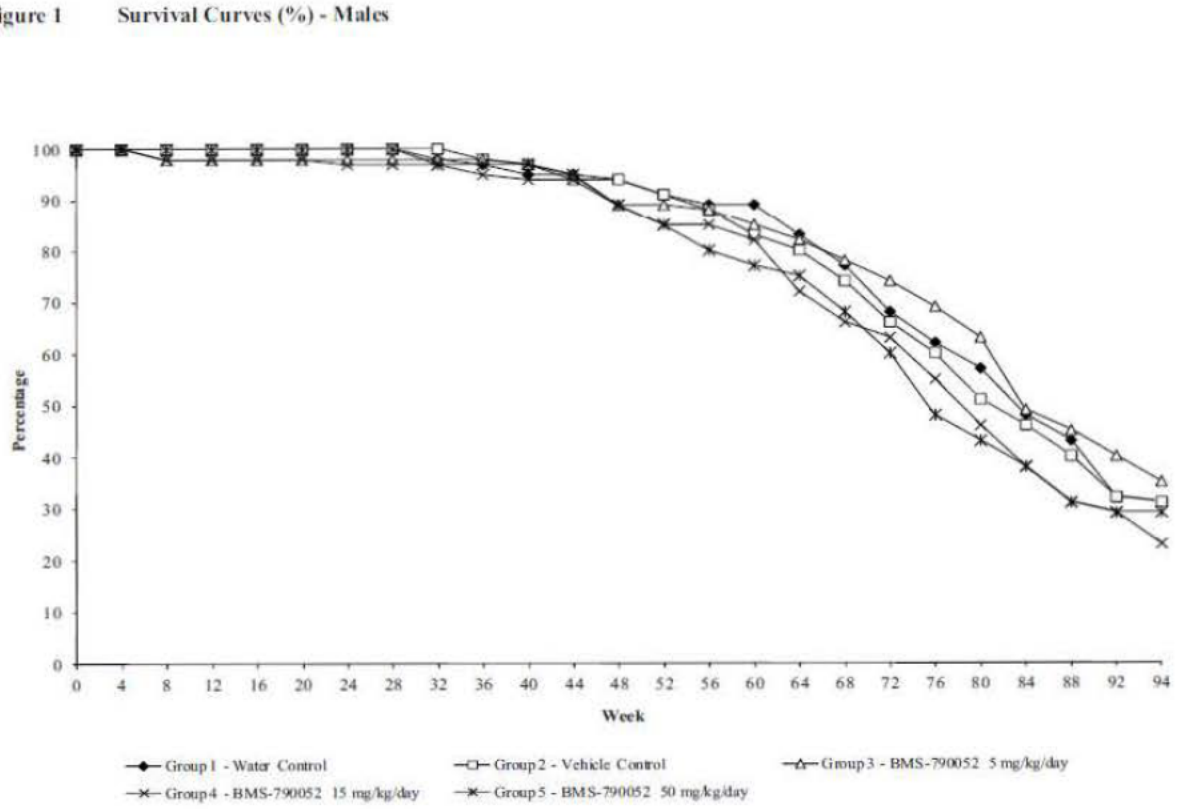
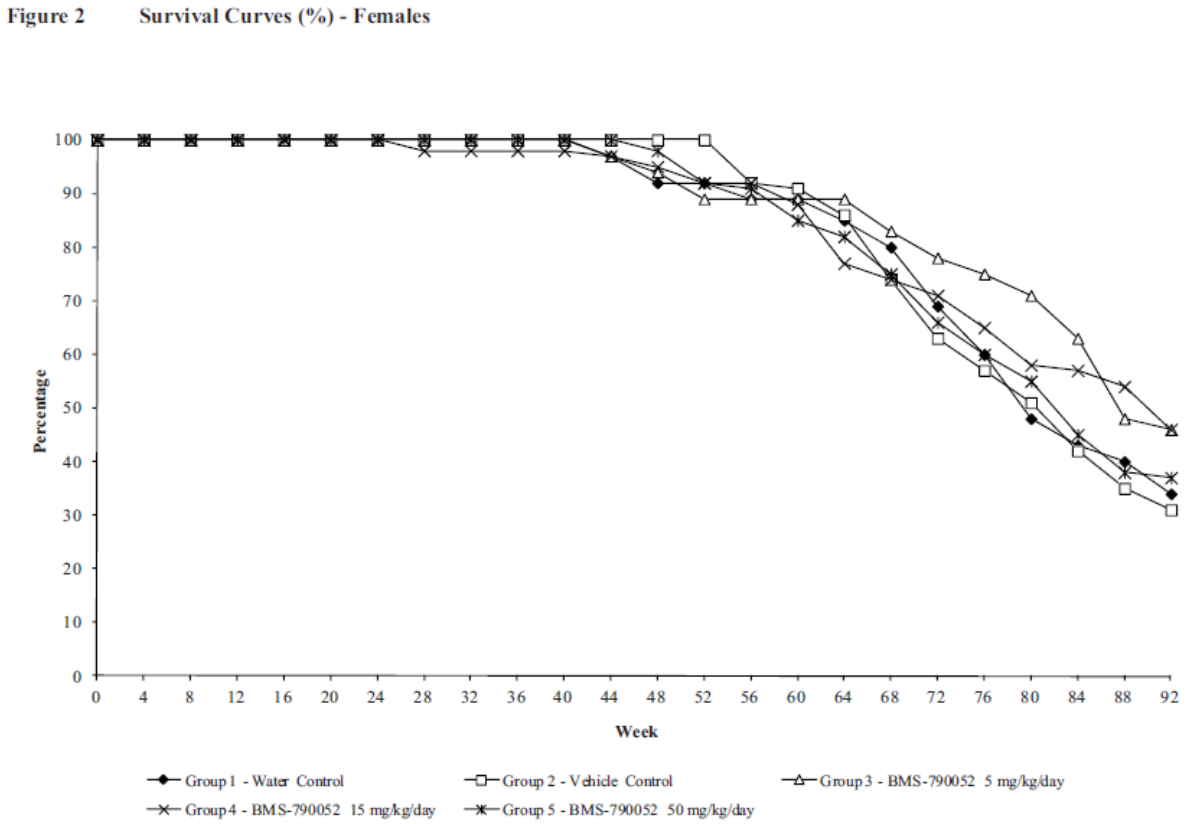


Figure 2: Kaplan-Meier plot of Survival in Female Rats



2.1.2. Tumor data analysis

Tumor data were analyzed using the poly-3 trend test, followed by Fisher Exact tests for each BMS-790052 treated group versus the vehicle-control group, separately by sex. The trend tests and pairwise tests were one-sided (increasing trend with dose and increases over vehicle control). These analyses were applied, as appropriate, to all tumor types found on study plan/protocolspecified tissues as well as to certain categories of combined tumors as decided by the Sponsor. All trend tests were evaluated at a significance level of 0.05 for rare tumors and 0.01 for common tumors. Pairwise comparisons were evaluated at a significance level of 0.05 for rare tumors, and 0.01 for common tumors. The distinction between rare and common tumors was made by the study pathologist.

Sponsor's findings: There were no effects of BMS-790052 on the incidence, distribution or nature of the neoplastic changes seen during the course of this study. No meaningful differences were seen between the tumor incidences in either of the 2 control groups (Group 1 – water, Group 2 – vehicle) and the tumor profile seen in the control groups was entirely within the expected spontaneous incidence range for animals of this species. All neoplastic changes recorded were typical of those commonly observed in animals of this strain and species and were considered to have been spontaneous in origin.
With the exception of tumors with *p*-values very slightly below 0.05 due to a single occurrence of the tumor in the high dose group only, a total of 3 tumors or tumor combinations were statistically significant on trend tests (but not pairwise comparisons) at $p < 0.05$. These included:

1. Benign squamous skin neoplasms (keratoacanthoma and keratoacanthoma combined with squamous papilloma) in males. These were noted at incidences of 2, 0, 1, 4 and 2, 0, 2, 4 for vehicle, 5, 15 and 50 mg/kg/day respectively, with p values of 0.025 and 0.034 for keratoacanthoma alone, and combined with squamous papilloma, respectively. The control incidence of 3% indicates that keratoacanthoma (and by implication its combination with papilloma) represents a common tumor. There was no significant difference between the control and high dose based on pairwise comparison ($p = 0.340$) and the apparent trend from low to high dose was considered most likely a chance occurrence, with the trend influenced by the low incidence in Group 2.

2. Benign granular cell tumors of the cervix in females. These were recorded at an incidence of 0, 0, 0, 2 for vehicle, 5, 15 and 50 mg/kg/day respectively ($p = 0.008$). Granular cell tumors are very common in the female reproductive tract of ageing SD rats (incidences of 3-13% for 2-year studies are described in the literature), and the historical range for this laboratory, cervix and uterus combined, is 0-5%, mean 0.8%. The incidence in the high dose group was therefore within the expected historical range and unlikely to be the result of treatment. Furthermore, the incidence of this tumor in the female reproductive tract as a whole was low in comparison with both historical and published data.

3. Skin/subcutis fibroma and fibrosarcoma combined in females. These were noted at incidences of 3, 2, 2, 6 for vehicle, 5, 15 and 50 mg/kg/day respectively, with a p-value of 0.042 on the trend test and not significant ($p = 0.246$) for pairwise comparison of control and 50 mg/kg/day. The control incidence of approximately 5% indicates that this combination should be regarded as a common tumor. The very marginal significance on the trend test was considered to represent chance variation and not any effect of BMS-790052.

There were no treatment effects on the incidence or distribution of neoplastic changes. Fine vacuolation and/or cytoplasmic rarefaction of adrenal cortical cells were increased relative to control animals at the 50 mg/kg/day dose level. This effect was primarily evident in male animals.

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform the additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically. Survival and tumor analysis for vehicle control and three treat groups were done in the reviewer's analysis.

2.2.1. Survival analysis

The survival distributions of animals in all five treatment groups (three treated groups and two control groups) were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested using the Cox test (Cox, 1972). The inter-current mortality data are given in Tables 1A and 1B in the appendix for five treatment groups in males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for five treatment groups in males and females, respectively. Results for the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for five groups (two controls and three treated goups) and four groups (vehicle control and three treated groups) in males and females, respectively.

Reviewer's findings: The test results showed no statistically significant dose-response mortality and statistically significant difference in mortality in both females and males when compared with vehicle control. Also the test results showed no statistically significant difference in mortality in both females and males when compared

between water and vehicle control groups. There were some differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships and pair-wise comparisons of vehicle control group with each of the treated groups were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for males and females, respectively.

According to pharmacologist request, we have the following tumor combinations in rat and mouse studies:

Organ system	Neoplasms	Combine?
Integumentary system		
Skin	Basal cell neoplasms-all types	yes
	Sq. cell papilloma and sq cell carcinoma	yes
	Sq. cell neoplasms and keratoacanthomas	yes
	Sq. cell neoplasms and adnexal neoplasms	Sometimes
Subcutis	Benign mesenchymal neoplasms- various types	no
	Malignant mesenchymal neoplasms- various types	no
	Fibromas and fibrosarcomas	yes
	Fibromas, fibrosarcomas, and sarcomas, NOS	Usually yes
Mammary gland	Adenomas, adenofibromas, and fibroadenomas	yes
	Carcinomas, various types	yes
	Benign epithelial neoplasms and malignant epithelial neoplasms	Sometimes, when a continuum is observed
Preputial, clitoral, Zymbal	Adenomas, various types,	yes
	Carcinomas, various types	yes
	Adenomas and carcinomas	yes
Respiratory system		
Nasal cavity	Sq. cell papilloma and sq cell carcinoma	Yes
	Sq. cell neoplasms and glandular cell neoplasms	no
	Esthesioneural epithelial neplasms and other neoplasms	no
Lung	a/b adenomas and a/b carcinomas	yes
	Sq. cell neoplasms and a/b neoplasms	no
CV system Vascular endothelium- all tissues	Hemangiomas and hemangiosarcomas	yes
Hematopoietic system Rat	Mononuclear cell leukemias and leukemia-other Types- all sites	yes
	Malignant lymphomas-all types all sites	yes
	Mononuclear cell leukemia and malignant lymphomas-all types	no
	Malignant lymphomas-all types-and histiocytic sarcomas	no

	Histiocytic sarcomas all sites	yes
Mouse	Malignant lymphomas-all types, all sites	yes
	Malignant lymphomas-all types-and histiocytic sarcomas	no
	Malignant lymphornas-all types-and lymphocytic leukemia	yes
	Leukemias all types	no
	Histiocytic sarcomas all sites	yes
Digestive system		yes
Oral cavity, Esophagus, and Forestomach,	Sq. cell papilloma and sq cell carcinoma	
Glandular stomach	Glandular adenomas and adenocarcinomas	yes
Small and large intestines	Adenomatous polyps, adenomas, adenocarcinomas	yes
Small and large intest. Cont.	Benign mesenchymal neoplasms- various types malignant	no
	Malignant mesenchymal neoplasms- various types	no
	Leiomyomas and leiomyosarcomas	yes
Liver	Hepatocellular adenomas and hepatocellular carcinomas	yes
	Bile duct neoplasms and hepatocellular neoplasms	no
	Hepatocellular neoplasms and vascularendothelial neoplasms	no
Exocrine pancreas	Acinar cell adenomas and acinar cell carcinomas	yes
Urinary system		
Kidney	Tubular cell adenomas and tubular cell carcinomas	yes
	Transitional cell adenomas and transitional cell carcinomas	yes
	Tubular cell neoplasms and transitional cell neoplasms	no
	Mesenchymal neoplasms and epithelial neoplasms	no
Urinary bladder	Transitional cell adenomas and transitional cell carcinomas	yes
Endocrine system		
Pituitary gland	Anterior pituitary and pituitary intermedia neoplasms	no
	Anterior pituitaryadenomas and carcinomas	yes
Thyroid gland	F-cell adenomas and F-cell carcinomas	yes
	C-cell adenomas and C-cell carcinomas	yes
	F-cell neoplasms and C-cell neoplasms	no
Pancreatic islets	Adenomas and carcinomas	yes
Adrenal gland	Cortical adenomas and carcinomas	yes
	Cortical neoplasms and subcapsular neoplasms (mouse)	no
	Pheochromocytomas and malignant pheochromocytomas	yes
	Cortical neoplasm and medullary neoplasms	no
	Subcapsular and medulaary neoplasms (mouse)	
Genital system		
Ovary and testicle	Germ cell neoplasm- all types	yes
	Stromal neoplasms-all types	yes
	Leiomyomas and leiomyosarcomas	yes
	Germ cell neoplasm and stromal neoplasms	no
Uterus and cervix	Glandular adenomas and glandular carcinomas	yes
	Stromal polyps and stromal sarcomas	yes
	Stromal neoplasms and glandular neoplasms	no
Vagina	Sq. cell polyps and sq cell carcinomas	yes
Prostate	Adenomas and carcinomas	yes

Nervous system	Gliomas- various types	yes
	Gliomas and astrocytomas	Usually yes
	Glioma and medulloblastomas	no
	Granular cell neoplasms and gliomas	no
	Meningiomas –all types- and other cns neoplasms	no
Skeletal system	Bone neoplasms and cartilage neoplasms	Sometimes, if continuum
White fat	Lipomas and liposarcomas	yes
	Lipomas and liposarcomas (all sites)	Usually yes
Brown fat	Hibernomas (all sites)	Usually yes
Organ system	Neoplasms	Combine?
Integumentary system		
Skin	Basal cell neoplasms-all types	yes
	Sq. cell papilloma and sq cell carcinoma	yes
	Sq. cell neoplasms and keratoacanthomas	yes
	Sq. cell neoplasms and adnexal neoplasms	Sometimes
Subcutis	Benign mesenchymal neoplasms- various types	no
	Malignant mesenchymal neoplasms- various types	no
	Fibromas and fibrosarcomas	yes
	Fibromas, fibrosarcomas, and sarcomas, NOS	Usually yes
Mammary gland	Adenomas, adenofibromas, and fibroadenomas	yes
	Carcinomas, various types	yes
	Benign epithelial neoplasms and malignant epithelial neoplasms	Sometimes, when a continuum is observed
Preputial, clitoral, Zymbal	Adenomas, various types,	yes
	Carcinomas, various types	yes
	Adenomas and carcinomas	yes

Multiple testing adjustment: Adjustment for the multiple dose response relationship testing was done using the criteria developed by Lin and Rahman (1998). The criteria recommend the use of a significance level α=0.025 for rare tumors and α=0.005 for common tumors for a submission with two species, and a significance level α=0.05 for rare tumors and α=0.01 for common tumors for a submission with only one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the spontaneous tumor rate is less than 1%. The adjustment for multiple pair-wise comparisons was done using the criteria developed by Haseman (1983) that recommends the use of significance level α=0.05 for rare tumors and α=0.01 for common tumors, in order to keep the false-positive rate at the nominal level of approximately 10%.
It should be noted that the recommended test levels by Lin and Rahman for the adjustment of multiple testing were originally based on the result of a simulation and an empirical study using the Peto method for dose response relationship analysis. However, some later simulation results by Rahman and Lin (2008) indicate that the criteria apply equally well to the analysis using the poly-3 test.

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 either tests for dose response relationship and/or pair-wise comparisons between vehicle control and each of individual treated groups.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pair-wise Comparison (vehicle control, low, medium and high dose groups)

	Organ Name	Tumor Name	0 mg Cont N=65	5 mg Low N=65	15 mg Med N=65	50 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Male										
	SKIN MISCELLANE									
		Keratoacanthoma	2	0	1	4	0.031	1.000	0.866	0.292
		#EXAMINED ANIMALS	(65)	(65)	(65)	(65)	.	.	.	.
		PERCENTAGE	3.07%	0%	1.54%	6.15%				
		ADJUSTED N	[40]	[42]	[36]	[33]	.	.	.	.
	SKIN_M	SQ_CELL_PAPILLOMA								
		+KERATOACANTHOMA	2	0	2	4	0.036	1.000	0.664	0.292
		#EXAMINED ANIMALS	(65)	(65)	(65)	(65)	.	.	.	.
		PERCENTAGE	3.07%	0%	3.07%	6.15%				
		ADJUSTED N	[40]	[42]	[36]	[33]	.	.	.	.
Female										
	SUBCUTANEOUS_TI	FIBROSARCOMA+FIBROMA	2	2	1	6	0.024	0.738	0.891	0.148
		#EXAMINED ANIMALS	(65)	(65)	(65)	(65)	.	.	.	.
		PERCENTAGE	3.07%	3.07%	1.54%	9.23%				
		ADJUSTED N	[42]	[48]	[46]	[44]	.	.	.	.

Based on the criteria of adjustment for multiple testing of trends proposed by Lin and Rahman, the incidence of none of the above or any other tested tumor types in either sex was considered to have a statistically significant positive dose response relationship. Also based on the same proposed level of significance, none of the pair-wise comparisons of treated groups with the vehicle control was considered to be statistically significant in either sex for increased tumor incidence in the treated group.

3. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and two control groups. One hundred and twenty five CByB6F1/Tg rasH2 hemizygous (transgenic) mice of each sex were randomly allocated to each dose group of 25 animals. BMS-790052 was administered daily by oral gavage at doses of 0 (water or vehicle control), 30, 100, or 300 mg/kg/day to groups of 25 mice per sex for a minimum of 26 consecutive weeks. In this review these dose groups would be referred to as the low, medium, and high dose group, respectively. Male and female CByB6F1/Tg rasH2 hemizygous (transgenic) mice were assigned to groups, and doses were administered as indicated in the following table. Mice were dosed via oral gavage.

Group Number	Dose Route	Daily Dose		Concentration	Number of Animals	
		Dose Level (mg/kg/day)	Volume (mL/kg)	(mg/mL)	Dosing Period (Tg)	Toxicokinetic Period (non-Tg)
1	Oral	0	10	0	25 M, 25 F	-
2	Oral	0	10	0	25 M, 25 F	36 M, 36 F
3	Oral	30	10	3	25 M, 25 F	36 M, 36 F
4	Oral	100	10	10	25 M, 25 F	36 M, 36 F
5	Oral	300	10	30	25 M, 25 F	36 M, 36 F
6	Intraperitoneal Injection[a]	75	10	7.5	15 M, 15 F	-

M = male; F = female.

[a] Single administration on Day 1.

3.1. Sponsor's analyses

3.1.1. Survival analysis

Survival data from the mouse study were analyzed by the sponsor using the same statistical methodologies that were used to analyze the survival data from the rat study. All statistical analysis was performed for males and females separately.

Sponsor's findings: Kaplan-Meier product limit survival curves are presented in Figure 3 (males) and Figure 4 (females). The survival rates to scheduled sacrifice (Week 27 of the dosing phase) were 88, 96, 88, 96, and 92% in males and 96, 96, 100, 100, and 96% in females given 0 (two control groups separately) water control, vehicle control, 30, 100, or 300 mg/kg/day, respectively. There were no statistically significant differences in survival for any of the BMS-790052 groups in either sex relative to controls. There were no BMS-790052-related effects on survival or on any specific cause of death.

Figure 3: Kaplan-Meier plot of Survival in Male Mice

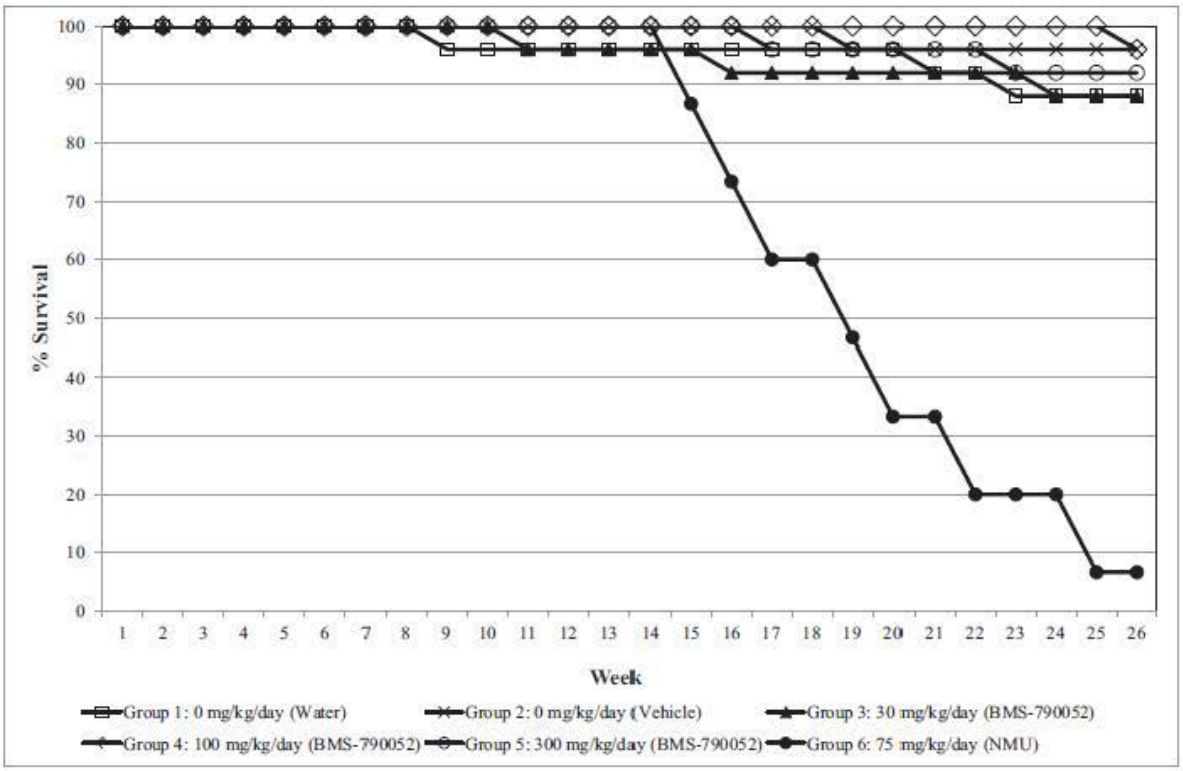
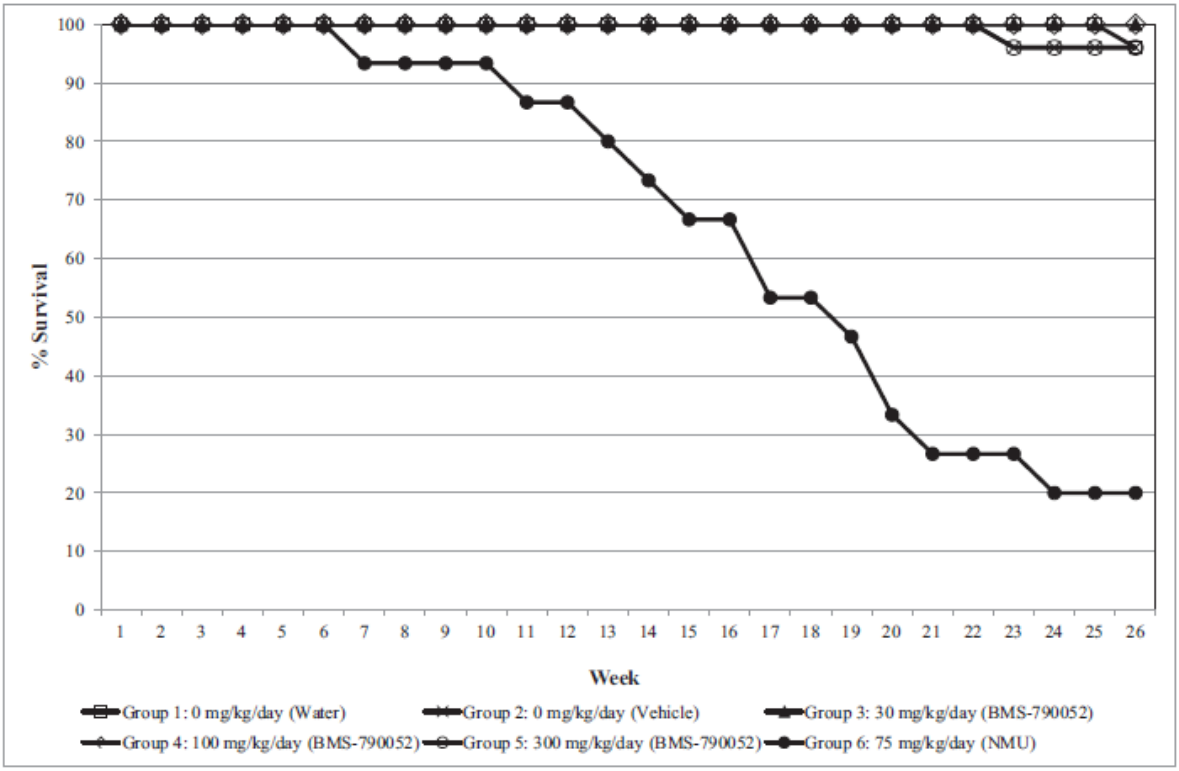


Figure 4: Kaplan-Meier plot of Survival in Female Mice



3.1.2. Tumor data analysis

Tumor data from transgenic mouse study were also analyzed by the sponsor using the same statistical methodologies that were used to analyze the tumor data from the rat study.

Sponsor's findings: As expected, the positive control substance (NMU) produced an increased incidence of systemic lymphomas, as well as, squamous cell carcinoma and/or papilloma in the stomach, skin, vagina, and tongue; papillomas of the transitional epithelium of the prostate gland; and squamous cell papillomas and carcinomas in the skin of the pinna (secondary to wounding and dermal irritation associated with ear tags). These and other findings in this group were similar to those previously reported in NMU-treated (positive control) CByB6F1-Tg (HRAS) 2Jic transgenic mouse bioassays.

In conclusion, BMS-790052 was not carcinogenic in CByB6F1/Tg rasH2 hemizygous mice following daily oral administration for 6 months at doses of $\leq$200 mg/kg/day (mean combined-sex AUC$\leq$1292 μg.h/ml at Week 26). Tumor incidences in the water- and vehicle-control groups were similar and there were no BMS-790052-related neoplastic microscopic findings at any dose.

3.2. Reviewer's analyses

This reviewer independently performed survival and tumor data analyses for mouse study. For the mouse data analyses this reviewer used similar methodologies that she used to analyze the data from the rat study. Data used in

this reviewer's analyses were provided by the sponsor electronically.

3.2.1. Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for five treatment groups in males and females, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the males and females, respectively. Results for the tests for dose response relationship and homogeneity of survivals, are given in Tables 5A and 5B in the appendix for five groups (two controls and three treated groups) and four groups (one vehicle control and three treated groups) in males and females, respectively.

Reviewer's findings: The test results showed no statistically significant dose-response mortality and statistically significant difference in mortality in both females and males when compared separately with vehicle control. Also the test results showed no statistically significant difference in mortality in both females and males when compared between water and vehicle control groups. There were some differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.

3.2.2. Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and pair-wise comparisons of control and treated groups are given in Table 6A and 6B in the appendix for three sets of data in males and females, respectively. As suggested by the reviewing pharmacologist Dr. Myers.

Reviewer's findings: Tests did not show statistically significant positive dose response relationship or increased tumor incidence in the treated groups compared to the vehicle control in any tumor type.

4. Evaluation of validity of the designs of the rat and mouse studies

As having been noted, the tumor data analyses from both rat and transgenic mouse studies including vehicle control with three treated groups showed no statistically significant dose-response relationship in any tested single tumor type. Before drawing any conclusion regarding the carcinogenic or non-carcinogenic potential of the drug in rats and mice, it is important to look into the following two issues, as have been pointed out in the paper by Haseman (1984).

(i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?
(ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?
There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group. The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman (1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3Fl mice conducted at the National Toxicology Program (NTP). It was found that, on the average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics-6, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals or 20 to 30 animals still alive in the high dose group, between weeks 80-90, would be consider as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward (1981), suggested that" to be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of

animals with greater than 50% survival at one-year."

It appears, from these three sources that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the maximum tolerated dose (MTD). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met.

(i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."

(ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."
We will now investigate the validity of the BMS-790052 in rat and transgenic mouse studies, in the light of the above guidelines.

4.1. Rat Study

The following is the summary of survival data of rats in the high dose groups:

Percentage of survival in the high dose group at the end of Weeks 52, 78, and 91

	Percentage of survival		
	End of 52 weeks	End of 78 weeks	End of 91 weeks
Male	85%	48%	29%
Female	94%	59%	37%

Based on the survival criterion Haseman proposed, it could be concluded that there were not enough rats were exposed to the high dose for a sufficient amount of time in both males and females.

The following table shows the percent difference in mean body weight gain from the concurrent combined control, defined as

$$\text{Percent difference} = \frac{(\text{Final BW} - \text{Baseline BW})_{\text{Treated}} - (\text{Final BW} - \text{Baseline BW})_{\text{Control}}}{(\text{Final BW} - \text{Baseline BW})_{\text{Control}}} \times 100$$

Percent Difference in Mean body Weight Gain From Vehicle control

Male			Female		
5mg	15mg	50mg	5mg	15mg	50mg
5.98	3.23	-0.49	11.27	1.7	13.24

Therefore, relative to the vehicle control, there had been at least 1.7% increase in body weight gain in all dosed groups in both females and males except 0.49% decrement in body weight gain in male rats in high dose group.

The mortality rates at the end of the experiment were as follows:

Mortality Rates at the End of the Experiment

	Cont.	Low	Medium	High
Male	32%	37%	23%	29%
Female	31%	46%	46%	37%

This shows that the morality rate of in the high dose group in females is 6% higher than the vehicle control but in males is 3% lower than the vehicle control. Thus, from the body weight gain and mortality data it can be concluded that for both females and males the used high dose level might be considered to be close to the MTD. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

4.2. Transgenic mouse Study

For long term 104 weeks regular rat and mouse studies there are some published statistical criteria to deal with the above mentioned issues. These statistical criteria along with the histopathological findings are generally applied to evaluate negative long term rat and mouse carcinogenicity studies. However, for CB6F1-Tg rasH2 transgenic mouse studies there are no such published statistical criteria. A determination regarding the above issues in this short term CB6F1-Tg rasH2 transgenic mice might be made using the clinical signs and histopathological toxic effects alone.

5. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in transgenic mice. These studies were intended to further assess the carcinogenic potential of BMS-790052 in rats and transgenic mice, when administered daily via oral gavage to rats for at least 104 weeks and to transgenic mice for at least 26 weeks.

Rat Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and two control groups. Three hundred and twenty five Sprague-Dawley rats (Crl:CD[SD]) of each sex were randomly allocated to treated and control groups. There were 65 animals per sex in each of groups. Treated animals each received dose preparations 5, 15, or 50 mg/kg.

The test results showed no statistically significant dose-response mortality and statistically significant difference in mortality in both females and males when compared separately with vehicle control. Also the test results showed no statistically significant difference in mortality in both females and males when compared between water and vehicle control groups. There were some differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.

Based on the criteria of adjustment for multiple testing of trends proposed by Lin and Rahman, the incidence of none of the above or any other tested tumor types in either sex was considered to have a statistically significant positive dose response relationship. Also based on the same proposed level of significance, none of

the pair-wise comparisons of treated groups with the vehicle control was considered to be statistically significant in either sex for increased tumor incidence in the treated group.

From the body weight gain and mortality data it can be concluded that for both females and males the used high dose level might be considered to be close to the MTD. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

Mouse Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and two control groups. One hundred and twenty five CByB6F1/Tg rasH2 hemizygous (transgenic) mice of each sex were randomly allocated to each dose group of 25 animals. BMS-790052 was administered daily by oral gavage at doses of 0 (water or vehicle control), 30, 100, or 300 mg/kg/day to groups of 25 mice per sex for a minimum of 26 consecutive weeks.

The test results showed no statistically significant dose-response mortality and statistically significant difference in mortality in both females and males when compared separately with vehicle control. Also the test results showed no statistically significant difference in mortality in both females and males when compared between water and vehicle control groups. There were some differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.

Based on the criteria of adjustment for multiple testing of trends proposed by Lin and Rahman, the incidence of none of the above or any other tested tumor types in either sex was considered to have a statistically significant positive dose response relationship. Also based on the same proposed level of significance, none of the pair-wise comparisons of treated groups with the vehicle control was considered to be statistically significant in either sex for increased tumor incidence in the treated group.

For long term 104 weeks regular rat and mouse studies there are some published statistical criteria to deal with the above mentioned issues. These statistical criteria along with the histopathological findings are generally applied to evaluate negative long term rat and mouse carcinogenicity studies. However, for CB6F1-Tg rasH2 transgenic mouse studies there are no such published statistical criteria. A determination regarding the above issues in this short term CB6F1-Tg rasH2 transgenic mice might be made using the clinical signs and histopathological toxic effects alone.

Min Min, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D.
Team Leader, Biometrics-6

cc:
Archival NDA 20-6843
Dr. Myers
Dr. Tiwari
Dr. Nevius
Lillian Patrician
Dr. Tsong
Dr. Lin
Dr. Min

6. Appendix

Table 1A: Intercurrent Mortality Rate
Male Rats

Week	WATER CONTROL NO.OF DEATH	PERCENT	VEHICLE CONTROL NO.OF DEATH	PERCENT	LOW NO.OF DEATH	PERCENT	MEDIUM NO.OF DEATH	PERCENT	HIGH NO.OF DEATH	PERCENT
0-52	6	9.2%	6	9.2%	7	10.8%	10	15.4%	10	15.4%
53-78	21	41.5%	24	46.2%	16	35.4%	22	49.2%	24	52.3%
79-93	17	67.7%	14	67.7%	18	63.1%	18	76.9%	12	70.8%
Term. Sac.	21	100.0%	21	100.0%	24	100.0%	15	100.0%	19	100.0%

Table 1B: Intercurrent Mortality Rate
Female Rats

Week	WATER_CONTROL NO.OF DEATH	PERCENT	VEHICLE_CONTROL NO.OF DEATH	PERCENT	LOW NO.OF DEATH	PERCENT	MEDIUM NO.OF DEATH	PERCENT	HIGH NO.OF DEATH	PERCENT
0-52	5	7.7%	.	.	7	10.8%	5	7.7%	4	6.2%
53-78	23	43.1%	32	49.2%	11	27.7%	20	38.5%	23	41.5%
79-91	15	65.2%	13	69.2%	17	53.9%	20	53.9%	14	63.1%
Term. Sac.	22	100.0%	20	100.0%	30	100.0%	30	100.0%	24	100.0%

Table 2A: Intercurrent Mortality Comparison
Male Rats

Test	P-Value (across five groups)	P-Value (water control vs vehicle control)	P-Value (water control vs low)	P-Value (water control vs medium)	P-Value (water control vs high)
Dose Response	0.3129	0.8729	0.6488	0.2858	0.4643
Homogeneity	0.5823	0.7644	0.5637	0.3286	0.4987

Test	P-Value (across four groups)	P-Value (vehicle control vs low)	P-Value (vehicle control vs medium)	P-Value (vehicle control vs high)
Dose Response	0.3690	0.5398	0.3703	0.5414
Homogeneity	0.4580	0.3718	0.4871	0.6699

Table 2B: Intercurrent Mortality Comparison
Female Rats

Test	P-Value (across five groups)	P-Value (water control vs vehicle control)	P-Value (water control vs low)	P-Value (water control vs medium)	P-Value (water control vs high)
Dose Response	0.9646	0.7503	0.2029	0.3604	0.8512
Homogeneity	0.2389	0.6949	0.0694	0.2334	0.8135

Test	P-Value (across four groups)	P-Value (vehicle control vs low)	P-Value (vehicle control vs medium)	P-Value (vehicle control vs high)
Dose Response	0.7673	0.1264	0.2238	0.6720
Homogeneity	0.1883	0.0483	0.1183	0.5981

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Vehicle control, low, medium and high dose goups)

Organ Name	Tumor Name	0 mg Cont N=65	5 mg Low N=65	15 mg Med N=65	50 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ADRENAL		(65)	(64)	(65)	(65)	.	.	.	.
	Benign pheochromocytoma	6	4	1	1	0.968	0.869	0.992	0.992
		[40]	[42]	[35]	[33]	.	.	.	.
	Carcinoma: cortical	1	0	0	0	1.000	1.000	1.000	1.000
		[39]	[42]	[35]	[33]	.	.	.	.
	Ganglioneuroma	0	0	0	1	0.222	.	.	0.475
		[39]	[42]	[35]	[33]	.	.	.	.
	Malignant pheochromocytoma	2	5	1	3	0.429	0.256	0.870	0.464
		[39]	[42]	[36]	[34]	.	.	.	.
ADRENAL_GLAND		(65)	(65)	(65)	(65)	.	.	.	.
	CORTICAL_ADENOMA+CARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[39]	[42]	[35]	[33]	.	.	.	.
	M+B_PHEOCHROMOCYTOMA	7	9	2	4	0.833	0.450	0.981	0.870
		[40]	[43]	[36]	[34]	.	.	.	.
ALL_SITES		(65)	(65)	(65)	(65)	.	.	.	.
	HEMANGIOMA+HEMANGIOSARCOMA	0	2	1	0	0.688	0.265	0.488	.
		[39]	[42]	[35]	[33]	.	.	.	.
BRAIN		(65)	(65)	(65)	(65)	.	.	.	.
	Malignant astrocytoma	1	1	0	0	0.933	0.770	1.000	1.000
		[39]	[42]	[35]	[33]	.	.	.	.
	Malignant oligodendroglioma	1	0	0	0	1.000	1.000	1.000	1.000
		[40]	[42]	[35]	[33]	.	.	.	.
CAVITY NASAL/SI		(65)	(65)	(65)	(65)	.	.	.	.
	Carcinoma: squamous cell	0	1	0	0	0.738	0.517	.	.
		[39]	[42]	[35]	[33]	.	.	.	.
DIGESTIVE_SYSTE		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA	6	6	9	1	0.958	0.669	0.236	0.991
		[40]	[43]	[37]	[33]	.	.	.	.
	SQ_CELL_CARCINOMA+PAPILLOMA	0	2	3	1	0.416	0.265	0.116	0.482
		[39]	[42]	[37]	[33]	.	.	.	.
HEMOLYM. TISSUE		(65)	(65)	(65)	(65)	.	.	.	.
	Histiocytic sarcoma	2	1	0	0	0.982	0.888	1.000	1.000
		[40]	[42]	[35]	[33]	.	.	.	.
	Malignant lymphoma	2	0	1	2	0.243	1.000	0.866	0.654
		[40]	[42]	[36]	[34]	.	.	.	.
KIDNEY		(65)	(65)	(65)	(65)	.	.	.	.
	Liposarcoma	0	0	0	1	0.222	.	.	0.482
		[39]	[42]	[35]	[33]	.	.	.	.

Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Vehicle control, low, medium and high dose goups)

Organ Name	Tumor Name	0 mg Cont N=65	5 mg Low N=65	15 mg Med N=65	50 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
L.NODE MESENTER		(65)	(65)	(63)	(65)	.	.	.	.
	Hemangioma	0	0	1	0	0.456	.	0.488	.
		[39]	[42]	[35]	[33]	.	.	.	.
LIVER		(65)	(65)	(65)	(65)	.	.	.	.
	Adenoma: hepatocellular	1	0	2	0	0.630	1.000	0.473	1.000
		[40]	[42]	[36]	[33]	.	.	.	.
	Carcinoma: hepatocellular	2	0	0	1	0.531	1.000	1.000	0.865
		[39]	[42]	[35]	[33]	.	.	.	.
	Cholangiocarcinoma	1	0	0	0	1.000	1.000	1.000	1.000
		[39]	[42]	[35]	[33]	.	.	.	.
	HEPA_ADENOMA+CARCINOMA	3	0	2	1	0.625	1.000	0.797	0.929
		[40]	[42]	[36]	[33]	.	.	.	.
	Hemangiosarcoma	0	2	0	0	0.784	0.265	.	.
		[39]	[42]	[35]	[33]	.	.	.	.
LUNG		(65)	(65)	(65)	(65)	.	.	.	.
	Adenoma: alveolar/bronchiolar	1	0	0	0	1.000	1.000	1.000	1.000
		[40]	[42]	[35]	[33]	.	.	.	.
MAMMARY GLAND		(64)	(63)	(63)	(64)	.	.	.	.
	Adenocarcinoma	0	1	0	0	0.738	0.523	.	.
		[39]	[42]	[35]	[33]	.	.	.	.
	Fibroadenoma	0	2	0	2	0.155	0.265	.	0.229
		[39]	[42]	[35]	[34]	.	.	.	.
PANCREAS		(65)	(65)	(65)	(65)	.	.	.	.
	Adenoma: acinar cell	1	1	0	1	0.482	0.764	1.000	0.728
		[40]	[42]	[35]	[33]	.	.	.	.
	Adenoma: islet cell	5	6	7	1	0.944	0.548	0.344	0.981
		[40]	[43]	[36]	[33]	.	.	.	.
	Carcinoma: acinar cell	2	0	0	0	1.000	1.000	1.000	1.000
		[40]	[42]	[35]	[33]	.	.	.	.
	Carcinoma: islet cell	2	2	2	4	0.097	0.709	0.654	0.292
		[40]	[42]	[35]	[33]	.	.	.	.
	ISLET_CELL_ADENOMA+CARCINOMA	7	8	9	5	0.646	0.558	0.332	0.774
		[40]	[43]	[37]	[33]	.	.	.	.
PARATHYROID GLA		(63)	(58)	(60)	(62)	.	.	.	.
	Adenoma	0	2	0	0	0.784	0.270	.	.
		[39]	[42]	[35]	[33]	.	.	.	.
PITUITARY		(65)	(65)	(65)	(65)	.	.	.	.
	Adenoma: pars distalis	46	51	46	40	0.629	0.209	0.438	0.703
		[54]	[55]	[50]	[46]	.	.	.	.

Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Vehicle control, low, medium and high dose goups)

Organ Name	Tumor Name	0 mg Cont N=65	5 mg Low N=65	15 mg Med N=65	50 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
	Carcinoma: pars distalis	0	1	0	0	0.738	0.517	.	.
		[39]	[42]	[35]	[33]	.	.	.	.
PITUITARY_GLAND		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA+CARCINOMA	46	52	46	40	0.680	0.138	0.438	0.703
		[54]	[55]	[50]	[46]	.	.	.	.
PROSTATE		(65)	(65)	(65)	(65)	.	.	.	.
	Adenocarcinoma	0	0	1	0	0.456	.	0.482	.
		[39]	[42]	[35]	[33]	.	.	.	.
SKIN MISCELLANE		(65)	(65)	(65)	(65)	.	.	.	.
	Adenoma: sebaceous	0	1	0	0	0.738	0.517	.	.
		[39]	[42]	[35]	[33]	.	.	.	.
	Benign schwannoma	0	0	0	1	0.222	.	.	0.475
		[39]	[42]	[35]	[33]	.	.	.	.
	Fibroma	0	1	1	1	0.250	0.517	0.482	0.475
		[39]	[42]	[35]	[33]	.	.	.	.
	Keratoacanthoma	2	0	1	4	0.031	1.000	0.866	0.292
		[40]	[42]	[36]	[33]	.	.	.	.
	Papilloma: squamous cell	0	0	1	0	0.456	.	0.482	.
		[39]	[42]	[35]	[33]	.	.	.	.
SKIN_M		(65)	(65)	(65)	(65)	.	.	.	.
	SQ_CELL_PAPILLOMA+KERATOACANTH	2	0	2	4	0.036	1.000	0.664	0.292
		[40]	[42]	[36]	[33]	.	.	.	.
STOMACH		(65)	(65)	(65)	(65)	.	.	.	.
	Papilloma: squamous cell	0	0	0	1	0.222	.	.	0.482
		[39]	[42]	[35]	[33]	.	.	.	.
SUBCUTANEOUS_TI		(65)	(65)	(65)	(65)	.	.	.	.
	FIBROSARCOMA+FIBROMA	3	2	4	2	0.524	0.834	0.473	0.788
		[40]	[42]	[36]	[33]	.	.	.	.
TESTIS		(65)	(65)	(65)	(65)	.	.	.	.
	Adenoma: interstitial cell	1	2	0	3	0.115	0.526	1.000	0.280
		[39]	[42]	[35]	[34]	.	.	.	.
THYROID		(65)	(65)	(65)	(65)	.	.	.	.
	Adenoma: C-cell	4	4	5	2	0.742	0.682	0.468	0.875
		[39]	[42]	[36]	[33]	.	.	.	.
	Adenoma: follicular cell	2	1	2	2	0.314	0.891	0.654	0.654
		[40]	[43]	[35]	[33]	.	.	.	.

Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Vehicle control, low, medium and high dose goups)

Organ Name	Tumor Name	0 mg Cont N=65	5 mg Low N=65	15 mg Med N=65	50 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
	Carcinoma: C-cell	0	2	2	0	0.692	0.270	0.235	.
		[39]	[42]	[35]	[33]	.	.	.	.
	Carcinoma: follicular cell	1	3	2	1	0.613	0.335	0.472	0.728
		[39]	[42]	[35]	[33]	.	.	.	.
THYROID_GLAND		(65)	(65)	(65)	(65)	.	.	.	.
	C_CELL_ADENOMA+CARCINOMA	4	6	7	2	0.820	0.429	0.232	0.875
		[39]	[42]	[36]	[33]	.	.	.	.
	F_CELL_ADENOMA+CARCINOMA	3	4	4	3	0.447	0.538	0.445	0.614
		[40]	[43]	[35]	[33]	.	.	.	.
URINARY BLADDER		(65)	(65)	(65)	(65)	.	.	.	.
	Papilloma: transitional cell	0	1	0	0	0.738	0.517	.	.
		[39]	[42]	[35]	[33]	.	.	.	.
ZYMBAL'S GLAND		(65)	(65)	(65)	(65)	.	.	.	.
	Carcinoma: squamous cell	0	1	3	0	0.650	0.517	0.116	.
		[39]	[42]	[37]	[33]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Rats (Vehicle control, low, medium and high dose groups)

Organ Name	Tumor Name	0 mg Cont N=65	5 mg Low N=65	15 mg Med N=65	50 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ADRENAL		(65)	(65)	(65)	(65)	.	.	.	.
	Adenoma: cortical	0	2	0	2	0.181	0.280	.	0.253
		[42]	[48]	[46]	[43]	.	.	.	.
	Benign pheochromocytoma	1	0	1	1	0.381	1.000	0.769	0.758
		[42]	[48]	[46]	[43]	.	.	.	.
	Carcinoma: cortical	1	0	0	0	1.000	1.000	1.000	1.000
		[42]	[48]	[46]	[43]	.	.	.	.
	Malignant pheochromocytoma	0	1	1	0	0.627	0.532	0.517	.
		[42]	[48]	[46]	[43]	.	.	.	.
ADRENAL_GLAND		(65)	(65)	(65)	(65)	.	.	.	.
	CORTICAL_ADENOMA+CARCINOMA	1	2	0	2	0.318	0.548	1.000	0.509
		[42]	[48]	[46]	[43]	.	.	.	.
	M+B_PHEOCHROMOCYTOMA	1	1	2	1	0.488	0.784	0.525	0.758
		[42]	[48]	[46]	[43]	.	.	.	.
ALL_SITES		(65)	(65)	(65)	(65)	.	.	.	.
	HEMANGIOMA+HEMANGIOSARCOMA	1	0	1	0	0.751	1.000	0.774	1.000
		[42]	[48]	[47]	[43]	.	.	.	.
	HISTIOCYTIC_SARCOMA	0	2	0	1	0.432	0.280	.	0.506
		[42]	[48]	[46]	[43]	.	.	.	.
BRAIN		(65)	(65)	(65)	(65)	.	.	.	.
	Benign meningioma	0	1	0	0	0.765	0.532	.	.
		[42]	[48]	[46]	[43]	.	.	.	.
	Malignant astrocytoma	1	0	0	0	1.000	1.000	1.000	1.000
		[42]	[48]	[46]	[43]	.	.	.	.
CERVIX		(65)	(64)	(65)	(65)	.	.	.	.
	Benign granular cell tumor	0	0	0	2	0.057	.	.	0.247
		[42]	[48]	[46]	[43]	.	.	.	.
	Benign schwannoma	1	0	0	0	1.000	1.000	1.000	1.000
		[42]	[48]	[46]	[43]	.	.	.	.
	Polyp: endometrial stromal	1	0	0	1	0.424	1.000	1.000	0.753
		[42]	[48]	[46]	[43]	.	.	.	.
	Sarcoma: endometrial stromal	0	0	0	1	0.240	.	.	0.506
		[42]	[48]	[46]	[43]	.	.	.	.
COLON		(65)	(65)	(65)	(65)	.	.	.	.
	Hemangiosarcoma	0	0	1	0	0.500	.	0.522	.
		[42]	[48]	[47]	[43]	.	.	.	.
	Leiomyosarcoma	0	0	1	0	0.500	.	0.522	.
		[42]	[48]	[47]	[43]	.	.	.	.
DIGESTIVE_SYSTE		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA	2	2	1	1	0.741	0.738	0.891	0.879

Table 3B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Rats (Vehicle control, low, medium and high dose groups)

Organ Name	Tumor Name	0 mg Cont N=65	5 mg Low N=65	15 mg Med N=65	50 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		[42]	[48]	[46]	[43]	.	.	.	.
	SQ_CELL_CARCINOMA	0	1	1	1	0.291	0.537	0.522	0.500
		[42]	[49]	[47]	[43]	.	.	.	.
HEMOLYM. TISSUE		(65)	(65)	(64)	(65)	.	.	.	.
	Histiocytic sarcoma	0	1	0	1	0.310	0.532	.	0.500
		[42]	[48]	[46]	[43]	.	.	.	.
	Malignant lymphoma	1	0	0	1	0.424	1.000	1.000	0.758
		[42]	[48]	[46]	[43]	.	.	.	.
KIDNEY		(65)	(65)	(65)	(65)	.	.	.	.
	Carcinoma: squamous cell	0	0	1	0	0.500	.	0.522	.
		[42]	[48]	[47]	[43]	.	.	.	.
	Hemangiosarcoma	0	0	1	0	0.500	.	0.522	.
		[42]	[48]	[47]	[43]	.	.	.	.
	Liposarcoma	0	0	1	0	0.497	.	0.517	.
		[42]	[48]	[46]	[43]	.	.	.	.
L.NODE MESENTER		(65)	(65)	(65)	(65)	.	.	.	.
L.NODE MESENTER	Hemangioma	1	0	0	0	1.000	1.000	1.000	1.000
		[42]	[48]	[46]	[43]	.	.	.	.
LIVER		(65)	(65)	(65)	(65)	.	.	.	.
	Adenoma: hepatocellular	1	0	0	1	0.424	1.000	1.000	0.753
		[42]	[48]	[46]	[43]	.	.	.	.
LUNG		(65)	(65)	(65)	(65)	.	.	.	.
	Carcinoma: alveolar/bronchiola	0	0	0	1	0.240	.	.	0.506
		[42]	[48]	[46]	[43]	.	.	.	.
MAMMARY GLAND		(65)	(65)	(65)	(65)	.	.	.	.
	Adenocarcinoma	9	11	11	8	0.621	0.502	0.422	0.669
		[45]	[51]	[47]	[43]	.	.	.	.
	Adenoma	8	7	9	3	0.938	0.794	0.558	0.970
		[44]	[50]	[48]	[43]	.	.	.	.
	Fibroadenoma	20	23	27	26	0.144	0.514	0.205	0.205
		[45]	[50]	[50]	[47]	.	.	.	.
MAMMARY_GLAND		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA+FIBROADENOMA	25	26	30	26	0.417	0.692	0.359	0.543
		[46]	[51]	[51]	[47]	.	.	.	.
OVARY		(65)	(65)	(65)	(65)	.	.	.	.
	Adenoma: tubulostromal	0	1	0	0	0.765	0.532	.	.
		[42]	[48]	[46]	[43]	.	.	.	.

Table 3B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Rats (Vehicle control, low, medium and high dose groups)

Organ Name	Tumor Name	0 mg Cont N=65	5 mg Low N=65	15 mg Med N=65	50 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
	Benign granulosa-theca cell tu	1	0	0	0	1.000	1.000	1.000	1.000
		[42]	[48]	[46]	[43]	.	.	.	.
	Cystadenoma	0	1	0	1	0.310	0.532	.	0.506
		[42]	[48]	[46]	[43]	.	.	.	.
PANCREAS		(65)	(65)	(65)	(64)	.	.	.	.
	Adenoma: islet cell	1	2	1	0	0.880	0.548	0.769	1.000
		[42]	[48]	[46]	[43]	.	.	.	.
	Carcinoma: acinar cell	0	1	0	0	0.765	0.532	.	.
		[42]	[48]	[46]	[43]	.	.	.	.
	Carcinoma: islet cell	1	1	2	1	0.488	0.784	0.525	0.753
		[42]	[48]	[46]	[43]	.	.	.	.
PITUITARY		(64)	(65)	(65)	(65)	.	.	.	.
	Adenoma: pars distalis	55	55	58	56	0.481	0.697	0.265	0.599
		[60]	[61]	[61]	[61]	.	.	.	.
	Carcinoma: pars distalis	4	1	1	1	0.859	0.980	0.977	0.974
		[42]	[48]	[46]	[43]	.	.	.	.
PITUITARY_GLAND		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA+CARCINOMA	59	56	59	57	0.764	0.950	0.660	0.914
		[60]	[61]	[61]	[61]	.	.	.	.
SKIN		(65)	(65)	(65)	(65)	.	.	.	.
	Fibroma	0	0	1	0	0.497	.	0.517	.
		[42]	[48]	[46]	[43]	.	.	.	.
	Fibrosarcoma	0	0	0	1	0.240	.	.	0.500
		[42]	[48]	[46]	[43]	.	.	.	.
SKIN_M		(65)	(65)	(65)	(65)	.	.	.	.
	SQ_CELL_PAPILLOMA+CARCINOMA	0	0	1	1	0.182	.	0.522	0.500
		[42]	[48]	[47]	[43]	.	.	.	.
	SQ_CELL_PAPILLOMA+CARCINOMA+KE	0	0	2	2	0.066	.	0.270	0.247
		[42]	[48]	[47]	[43]	.	.	.	.
STOMACH		(65)	(65)	(65)	(65)	.	.	.	.
	Benign neuroendocrine cell tum	0	1	0	0	0.765	0.532	.	.
		[42]	[48]	[46]	[43]	.	.	.	.
SUBCUTANEOUS_TI		(65)	(65)	(65)	(65)	.	.	.	.
	FIBROSARCOMA+FIBROMA	2	2	1	6	0.024	0.738	0.891	0.148
		[42]	[48]	[46]	[44]	.	.	.	.

Table 3B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Rats (Vehicle control, low, medium and high dose groups)

Organ Name	Tumor Name	0 mg Cont N=65	5 mg Low N=65	15 mg Med N=65	50 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
THYROID		(65)	(65)	(65)	(65)	.	.	.	.
	Adenoma: C-cell	7	6	6	7	0.395	0.812	0.779	0.632
		[42]	[49]	[47]	[43]	.	.	.	.
	Adenoma: follicular cell	1	1	0	1	0.524	0.784	1.000	0.753
		[42]	[48]	[46]	[43]	.	.	.	.
	Carcinoma: C-cell	1	0	1	0	0.749	1.000	0.769	1.000
		[42]	[48]	[46]	[43]	.	.	.	.
	Carcinoma: follicular cell	0	1	1	1	0.292	0.532	0.517	0.506
		[42]	[48]	[46]	[43]	.	.	.	.
THYROID_GLAND		(65)	(65)	(65)	(65)	.	.	.	.
	C_CELL_ADENOMA+CARCINOMA	8	6	7	7	0.467	0.869	0.758	0.714
		[43]	[49]	[47]	[43]	.	.	.	.
	F_CELL_ADENOMA+CARCINOMA	1	2	1	2	0.338	0.548	0.769	0.509
		[42]	[48]	[46]	[43]	.	.	.	.
TONGUE		(65)	(65)	(65)	(65)	.	.	.	.
	Carcinoma: squamous cell	0	0	0	1	0.240	.	.	0.500
		[42]	[48]	[46]	[43]	.	.	.	.
UTERUS		(65)	(64)	(65)	(65)	.	.	.	.
	Adenoma: endometrial	0	0	1	0	0.497	.	0.517	.
		[42]	[48]	[46]	[43]	.	.	.	.
	Polyp: endometrial stromal	0	2	0	2	0.181	0.280	.	0.247
		[42]	[48]	[46]	[43]	.	.	.	.
	Sarcoma: endometrial stromal	0	1	0	0	0.765	0.532	.	.
		[42]	[48]	[46]	[43]	.	.	.	.
UTERUS_CERVIX		(65)	(65)	(65)	(65)	.	.	.	.
	SARCOMA+POLYP	1	3	0	4	0.092	0.358	1.000	0.187
		[42]	[48]	[46]	[43]	.	.	.	.
VAGINA		(65)	(64)	(65)	(65)	.	.	.	.
	Fibroma	0	1	0	0	0.765	0.532	.	.
		[42]	[48]	[46]	[43]	.	.	.	.
ZYMBAL'S GLAND		(65)	(65)	(65)	(65)	.	.	.	.
	Carcinoma: squamous cell	0	1	0	0	0.767	0.537	.	.
		[42]	[49]	[46]	[43]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 4A: Intercurrent Mortality Rate
Male Mice

	WATER_CONTROL		VEHICLE_CONTROL		LOW		MEDIUM		HIGH	
	NO.OF		NO.OF		NO.OF		NO.OF		NO.OF	
Week	DEATH	PERCENT	DEATH	PERCENT	DEATH	PERCENT	DEATH	PERCENT	DEATH	PERCENT
0-10	1	4.0%	.	.	1	4.0%	.	.	.	.
11-15	.	.	.	.	1	8.0%	.	.	.	.
16-20	1	8.0%	1	4.0%	.	.	.	.	1	4.0%
21-26	1	12.0%	.	.	1	12.0%	1	4.0%	1	8.0%
Term. Sac.	22	100.0%	24	100.0%	22	100.0%	24	100.0%	23	100.0%

Table 4B: Intercurrent Mortality Rate
Female Mice

	WATER_CONTROL		VEHICLE_CONTROL		LOW		MEDIUM		HIGH	
	NO.OF		NO.OF		NO.OF		NO.OF		NO.OF	
Week	DEATH	PERCENT	DEATH	PERCENT	DEATH	PERCENT	DEATH	PERCENT	DEATH	PERCENT
0-10	.	.	.	.	.	.	.	.	.	.
11-15	.	.	.	.	.	.	.	.	.	.
16-20	.	.	.	.	.	.	.	.	.	.
21-25	.	.	1	4.0%	.	.	.	.	1	4.0%
Term. Sac.	25	100.0%	24	100.0%	25	100.0%	25	100.0%	23	100.0%

Table 5A: Intercurrent Mortality Comparison
Male Mice

Test	P-Value (across five groups)	P-Value (water control vs vehicle control)	P-Value (water control vs low)	P-Value (water control vs medium)	P-Value (water control vs high)
Dose Response	0.9503	0.7727	0.9976	0.7636	0.8805
Homogeneity	0.6932	0.3073	0.9930	0.2874	0.6330

Test	P-Value (across four groups)	P-Value (vehicle control vs low)	P-Value (vehicle control vs medium)	P-Value (vehicle control vs high)
Dose Response	0.9750	0.7682	0.9977	0.8852
Homogeneity	0.6211	0.2974	0.9885	0.5557

Table 5B: Intercurrent Mortality Comparison
Female Mice

Test	P-Value (across five groups)	P-Value (water control vs vehicle control)	P-Value (water control vs low)	P-Value (water control vs medium)	P-Value (water control vs high)
Dose Response	0.9926	0.9977	1.0000	0.8875	0.9977
Homogeneity	0.7304	0.9885	0.3713	0.3713	0.9885

Test	P-Value (across four groups)	P-Value (vehicle control vs low)	P-Value (vehicle control vs medium)	P-Value (vehicle control vs high)
Dose Response	0.9943	0.9977	0.8875	1.0000
Homogeneity	0.5682	0.3173	0.3173	1.0000

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Mice (Vehicle control, low, medium and high dose groups)

Organ Name	Tumor Name	0 mg Cont N=25	30 mg Low N=25	100 mg Med N=25	300 mg High N=25	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ALL_SITES		(25)	(25)	(25)	(25)	.	.	.	.
	HEMANGIOMA	0	1	0	1	0.352	0.500	.	0.510
		[5]	[8]	[8]	[7]	.	.	.	.
HARDERIAN GLAND		(25)	(25)	(25)	(25)	.	.	.	.
	Adenoma	0	3	2	1	0.634	0.109	0.255	0.510
		[5]	[7]	[8]	[7]	.	.	.	.
LIVER		(25)	(25)	(25)	(25)	.	.	.	.
	Adenoma: hepatocellular	0	0	2	0	0.502	.	0.255	.
		[5]	[7]	[8]	[6]	.	.	.	.
LUNG		(25)	(25)	(25)	(25)	.	.	.	.
	ADENOMA+CARCINOMA	5	4	5	4	0.624	0.769	0.665	0.769
		[5]	[8]	[8]	[6]	.	.	.	.
	Adenoma: bronchioloalveolar ce	5	3	3	3	0.785	0.864	0.890	0.878
		[5]	[7]	[8]	[6]	.	.	.	.
	Carcinoma: bronchioloalveolar	0	1	2	1	0.300	0.500	0.255	0.500
		[5]	[8]	[8]	[6]	.	.	.	.
SKIN		(25)	(25)	(25)	(25)	.	.	.	.
	Hemangiosarcoma	0	0	0	1	0.259	.	.	0.510
		[5]	[7]	[8]	[7]	.	.	.	.
SYSTEMIC NEOPLA		(25)	(25)	(25)	(25)	.	.	.	.
	Lymphoma (ML)	0	0	0	1	0.231	.	.	0.500
		[5]	[7]	[8]	[6]	.	.	.	.
THYMUS		(25)	(25)	(25)	(25)	.	.	.	.
	Hemangiosarcoma	0	1	0	0	0.815	0.500	.	.
		[5]	[8]	[8]	[6]	.	.	.	.
	Thymoma: predominantly epithel	1	0	0	0	1.000	1.000	1.000	1.000
		[5]	[7]	[8]	[6]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Mice (Vehicle control, low, medium and high dose groups)

Organ Name	Tumor Name	0 mg Cont N=25	30 mg Low N=25	100 mg Med N=25	300 mg High N=25	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ALL_SITES		(25)	(25)	(25)	(25)	.	.	.	.
	HEMANGIOMA	1	1	2	1	0.423	0.755	0.500	0.755
		[6]	[7]	[7]	[5]	.	.	.	.
BONE MARROW, FE		(25)	(25)	(25)	(25)	.	.	.	.
	Hemangiosarcoma	0	0	0	1	0.200	.	.	0.500
		[6]	[7]	[7]	[5]	.	.	.	.
HARDERIAN GLAND		(25)	(25)	(25)	(25)	.	.	.	.
	Adenoma	0	2	0	0	0.810	0.245	.	.
		[6]	[7]	[7]	[5]	.	.	.	.
ILEUM		(25)	(25)	(25)	(25)	.	.	.	.
	Hemangiosarcoma	0	0	1	0	0.480	.	0.500	.
		[6]	[7]	[7]	[5]	.	.	.	.
LUNG		(25)	(25)	(25)	(25)	.	.	.	.
	ADENOMA+CARCINOMA	2	2	1	2	0.397	0.695	0.883	0.695
		[6]	[7]	[7]	[5]	.	.	.	.
	Adenoma: bronchioloalveolar ce	2	2	1	2	0.397	0.695	0.883	0.695
		[6]	[7]	[7]	[5]	.	.	.	.
SPLEEN		(25)	(25)	(25)	(25)	.	.	.	.
	Hemangiosarcoma	0	1	0	0	0.760	0.500	.	.
		[6]	[7]	[7]	[5]	.	.	.	.
STOMACH		(25)	(25)	(25)	(25)	.	.	.	.
	Papilloma: squamous cell	0	0	1	0	0.480	.	0.500	.
		[6]	[7]	[7]	[5]	.	.	.	.
SYSTEMIC NEOPLA		(25)	(25)	(25)	(25)	.	.	.	.
	Lymphoma (ML)	3	3	2	1	0.870	0.666	0.826	0.945
		[6]	[7]	[7]	[5]	.	.	.	.
UTERUS		(25)	(25)	(25)	(25)	.	.	.	.
	Hemangiosarcoma	1	0	1	0	0.740	1.000	0.755	1.000
		[6]	[7]	[7]	[5]	.	.	.	.

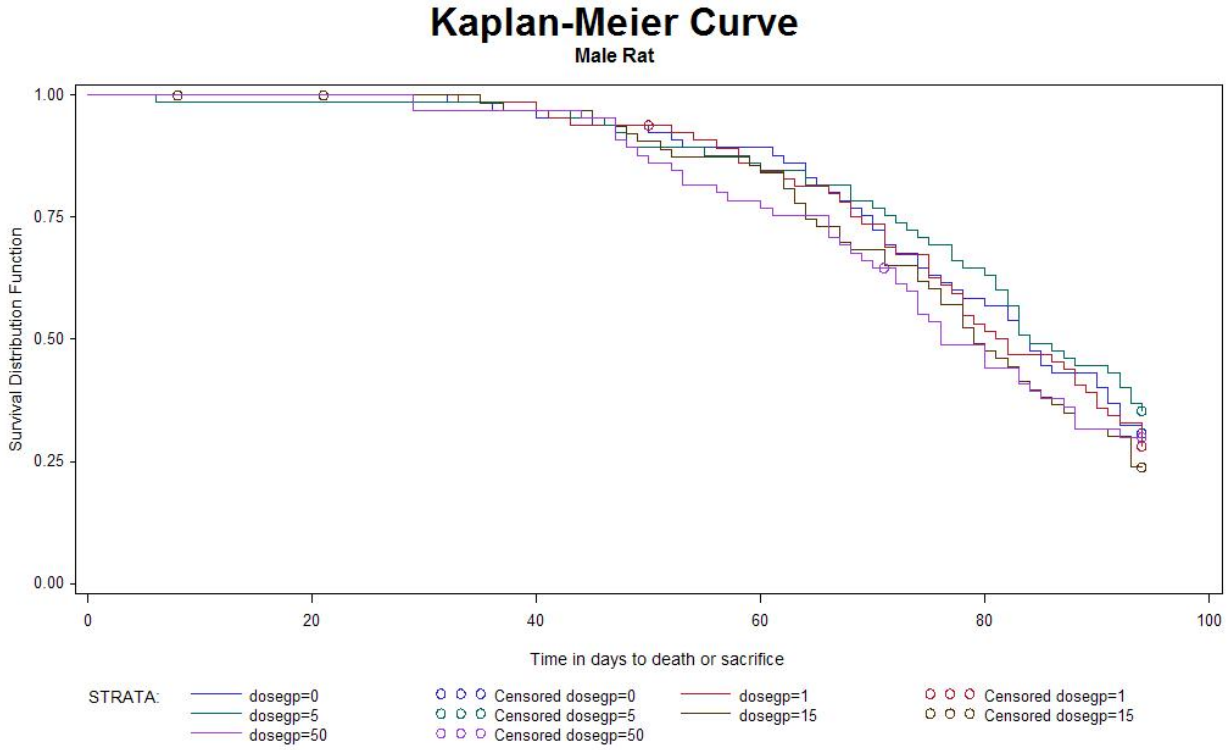
Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

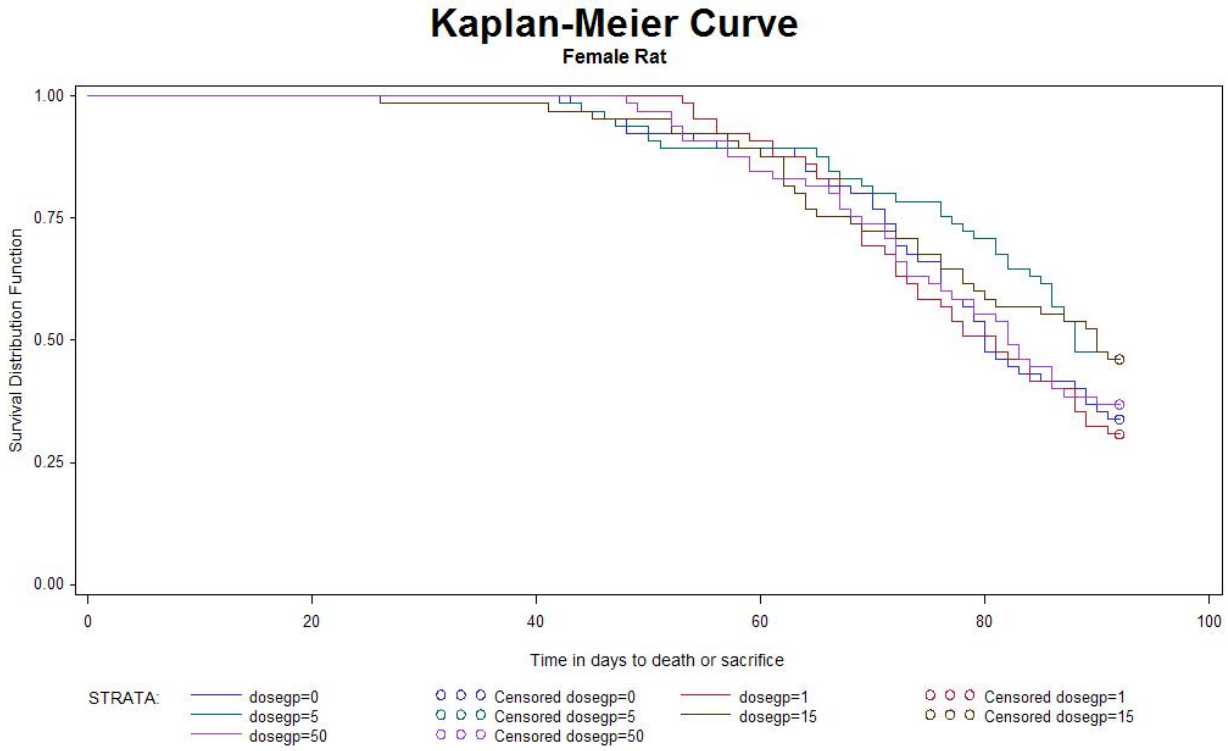
Male Rats (water and vehicle controls, low, medium and high dose groups)



X-Axis: Weeks, Y-Axis: Survival rates

Figure 1B: Kaplan-Meier Survival Functions for Female Rats

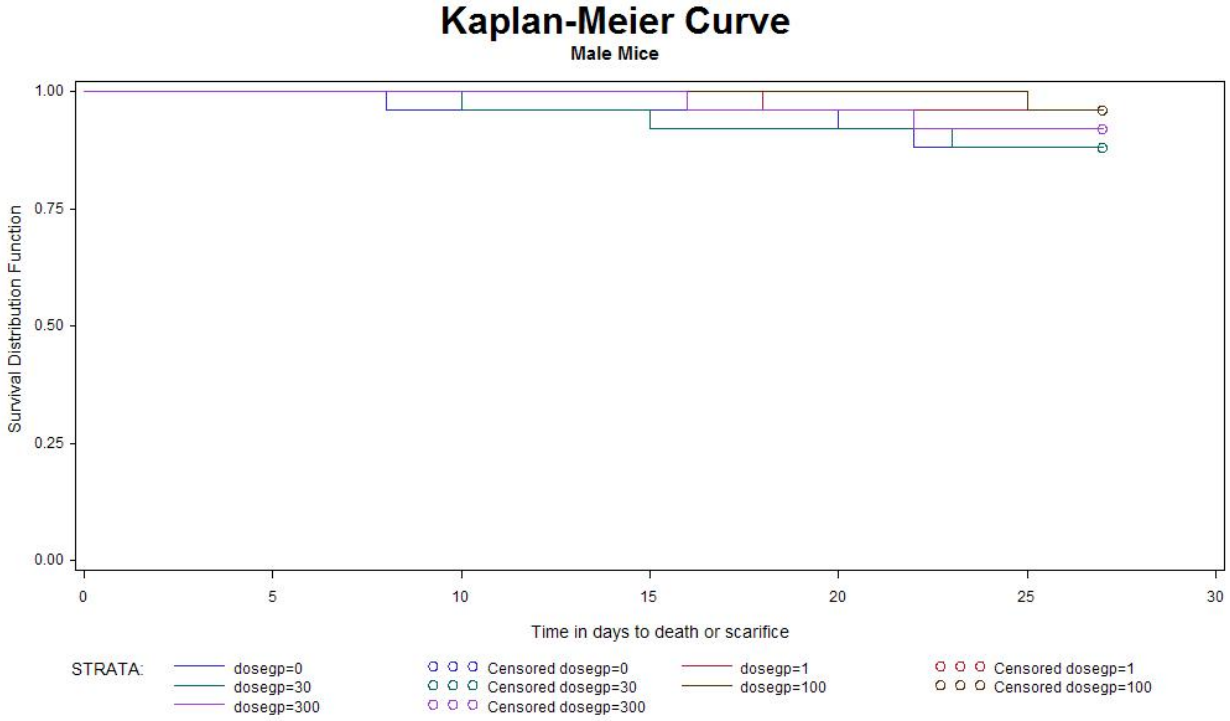
Female Rats (water and vehicle controls, low, medium and high dose groups)



X-Axis: Weeks, Y-Axis: Survival rates

Figure 2A: Kaplan-Meier Survival Functions for Male Mice

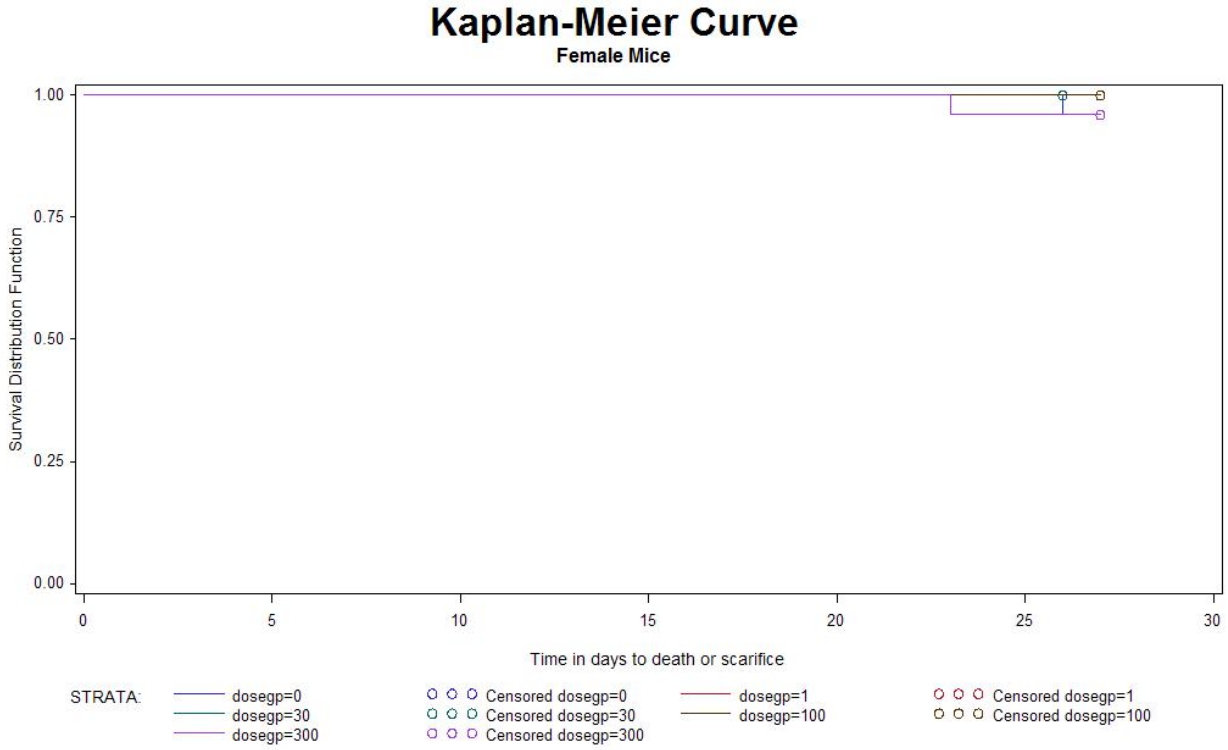
Male Mice (water and vehicle controls, low, medium and high dose groups)



X-Axis: Weeks, Y-Axis: Survival rates

Figure 2B: Kaplan-Meier Survival Functions for Female Mice

Female Mice (water and vehicle controls, low, medium and high dose groups)



X-Axis: Weeks, Y-Axis: Survival rates

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