CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206843Orig1s001, s003

MICROBIOLOGY/VIROLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
CLINICAL VIROLOGY REVIEW
NDA: 206843 **SDN**: 068-069 (ALLY-1,-2 sNDAs) **REVIEW COMPLETED:** 01/14/2016
Clinical Virology Reviewer: Patrick R. Harrington, Ph.D.

NDA#: 206843 **SDNs:** 68, 69 (S1, S2, S3; ALLY-1 and ALLY-2 trials)
Reviewer's Name: Patrick R. Harrington, Ph.D.

Sponsor's Name and Address: Bristol-Myers Squibb Company
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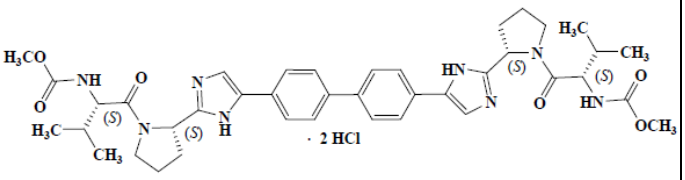
NDA #	**206843**
Proprietary Name	DAKLINZA™
Drug Name	daclatasvir (DCV, BMS-790052)
Drug Class	NS5A inhibitor
Associated IND #s	79599, (b) (4)
Chemical Name	Methyl((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl) amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate dihydrochloride
Structure	 **daclatasvir**
Molecular Formula	$C_{40}H_{50}N_8O_6 \cdot 2HCl$
Molecular Weight	(b) (4) 738.88 (free base)

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Amendments: none
Related/Supporting Documents:

- Clinical Virology Reviews of Original NDAs 206843 (b) (4) and NDA 206843 resubmission (SDN 36)
- Additional NDA 206843 resubmission SDNs (thru 01/11/2016): 84 (user fee, supplement clarifications), 85 (labeling), 94 (labeling), 97 (Safety update and AI444216 addendum), 108 (response to requests for information), 122 (response to clinical requests for information)

Dosage Form/Route of Administration: 30 and 60 mg tablets/oral
Dispensed: Rx X OTC__

Proposed Indication/Usage: DAKLINZA is indicated for use with sofosbuvir, with or without ribavirin, for the treatment of patients with chronic hepatitis C virus (HCV) infection.

Abbreviations: ASV, asunaprevir; DAA, direct acting antiviral agent; DCV, daclatasvir; EC, effective concentration; FC, fold-change; GT, genotype; HCV, hepatitis C virus; IFN(α), interferon (alfa); LDV, ledipasvir; LiPA, line-probe assay; LLOQ, lower limit of quantification; NDA, new drug application; NGS, next generation sequencing; Peg-IFNα, pegylated interferon alpha; PM, polymorphism; P/R, pegylated interferon alpha plus ribavirin; RBV, ribavirin; RT-PCR, reverse transcription polymerase chain reaction; SOF, sofosbuvir; SVR, sustained virologic response; VF, virologic failure; WT, wild-type

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EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1 Recommendation and Conclusion on Approvability

Pending final agreement on the label, Efficacy Supplements S-1, S-2 and S-3 for NDA 206843 are approvable from a Clinical Virology perspective for daclatasvir in combination with sofosbuvir, with or without ribavirin, for the treatment of chronic HCV genotype 1 or genotype 3 infection, including patients coinfected with human immunodeficiency virus (HIV-1), patents with compensated or decompensated cirrhosis, and patients with HCV recurrence after liver transplant.

1.2 Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

There are no new post-marketing recommendations at this time.

2. SUMMARY OF OND VIROLOGY ASSESSMENTS

Overview
This Clinical Virology review covers three supplemental New Drug Applications (sNDAs) for the HCV NS5A inhibitor daclatasvir (DCV, DAKLINZA™; NDA 206843), which is currently approved for use with sofosbuvir (SOF, SOVALDI™), an FDA-approved uridine nucleotide analogue NS5B polymerase inhibitor, for the treatment of chronic HCV GT3 infection. These efficacy supplements are to expand the indication for DCV to include patients who have received a liver transplant (S-1), patients with HIV-1 coinfection (S-2), and patients with decompensated cirrhosis (S-3). To support these expanded indications, the sponsor submitted data from two clinical trials, AI444215 (ALLY-1) and AI444216 (ALLY-2). The data submitted in these supplements are predominantly from subjects with HCV GT1 infection; thus, these supplements also support expansion of the DCV indication to HCV GT1 patients. Prior to conducting this review the review team determined that the numbers of subjects infected with HCV GTs 2, 4, 5 and 6 in ALLY-1 and ALLY-2 were inadequate for labeling/indications, and therefore analyses focused primarily only on HCV GT1 and GT3 infected subjects. This Clinical Virology review includes independent analyses of HCV RNA and drug resistance data from the ALLY-1 and ALLY-2 trials. Please also see the review by Virology Reviewer Lalji Mishra, Ph.D., for additional review of DCV focusing on nonclinical virology and resistance data.

Clinical Efficacy
Clinical trial AI444215 (ALLY-1) was a Phase 3, open-label study that evaluated DCV in combination with SOF and ribavirin (DCV/SOF/RBV) administered for 12 weeks in HCV infected subjects with cirrhosis who may require future liver transplantation, and in subjects who have previously received a liver transplant. SVR12 rates were 100/113 (88%) overall, and 56/65 (86%), 20/21 (95%) and 15/17 (88%) for subjects with HCV GT1a, GT1b and GT3, respectively. All 13 subjects who did not achieve SVR12 experienced virologic failure: 12 with virologic relapse and 1 with on-treatment virologic failure. DCV/SOF/RBV treatment efficacy was lower for HCV GT1a infected subjects with Child-Pugh C cirrhosis (4/9, 44%) compared to those with Child-Pugh A/B cirrhosis (22/25, 88%) or those in the Post-Transplant period (30/31, 97%). Due to insufficient numbers of subjects, it was not possible to determine if Child-Pugh status impacted efficacy for subjects with HCV GT1b or GT3.

Clinical trial AI444216 (ALLY-2) was a Phase 3, open-label study of DCV in combination with SOF (DCV/SOF, without RBV) administered for 8 or 12 weeks in subjects with HCV and HIV-1 coinfection. Treatment-naïve subjects were randomized to receive DCV/SOF for either 12 or 8 weeks, and treatment-experienced subjects received DCV/SOF for 12 weeks. Nearly all subjects were on concomitant HIV-1 antiretroviral therapy (ART). Among subjects who received DCV/SOF for 12 weeks, SVR12 rates were 98/101 (97%) and 51/52 (98%) for treatment-naïve and treatment-experienced subjects, respectively. The SVR12 rate for the 8-week duration arm was clearly lower at 38/50 (76%), and appeared to be lower for all represented HCV genotypes and subtypes 1a/1b. Fourteen subjects experienced virologic relapse, 11 of whom were in the 8-week duration arm. The review team did not consider the 8-week duration of DCV/SOF for labeling due to the high relapse rate observed. Among HCV GT1a infected subjects treated with DCV/SOF for 12 weeks, SVR12 rates were 78/80 (98%) and 18/20 (90%) for noncirrhotic and cirrhotic subjects, respectively; two subjects with cirrhosis experienced virologic relapse. Among HCV GT1b infected subjects treated with DCV/SOF for 12 weeks, the SVR12 rate was 20/20 (100%) for noncirrhotic subjects, and 2 subjects with cirrhosis achieved SVR12. All 10 HCV GT3 infected subjects (9 without cirrhosis, 1 with cirrhosis) achieved SVR12. The use of DCV/SOF did not appear to have a significant impact on HIV-1 virologic control.

Analyses of Treatment-Emergent Drug Resistance

Independent analyses of the sponsor's population nucleotide sequence analysis data were conducted to identify patterns of treatment-emergent amino acid substitutions in NS5A and NS5B among subjects who experienced virologic failure in ALLY-1 and ALLY-2.

Among HCV GT1a virologic failure subjects with available data, DCV resistance-associated substitutions in NS5A emerged in 9/11 (82%) and 1/7 (14%) subjects who received DCV+SOF±RBV for the 12-week and 8-week durations, respectively. Treatment-emergent substitutions most frequently occurred at position Q30. Considering those with pre-existing NS5A polymorphisms, all 11 HCV GT1a virologic failure subjects who received DCV/SOF±RBV for 12 weeks had an NS5A resistance-associated substitution or polymorphism at the time of virologic failure. Five of 10 HCV GT1a virologic failure subjects with available data who received DCV/SOF±RBV for 12 weeks had treatment emergent substitutions at NS5B positions potentially associated with SOF resistance. One HCV GT1b virologic failure subject who received DCV/SOF/RBV for 12 weeks had a treatment-emergent deletion at NS5A position P32 (P32del) and no NS5B substitutions of interest. Of the 3 HCV GT3 virologic failure subjects across the ALLY-1 and ALLY-2 trials, 2 subjects had virus with treatment-emergent NS5A Y93H, consistent with results from the previously reviewed AI444218 (ALLY-3) trial. The GT3 subject without treatment-emergent Y93H received the 8-week DCV/SOF treatment duration. Incomplete NS5B sequence data were obtained from the GT3 virologic failure subjects in the ALLY-1 and ALLY-2 trials.

Analyses of Baseline Resistance-Associated Amino Acid Polymorphisms

Independent analyses of the sponsor's population nucleotide sequence analysis data were conducted to assess if baseline polymorphisms at NS5A or NS5B resistance-associated amino acid positions were associated with virologic failure in the ALLY-1 and ALLY-2 trials. Subjects who failed to achieve SVR for reasons unrelated to virologic failure were censored from these analyses.

HCV NS5A polymorphisms appeared to impact DCV/SOF±RBV treatment efficacy for HCV GT1a infected subjects in the ALLY-1 and ALLY-2 trials. Considering four key DCV resistance-associated positions in NS5A (M28, Q30, L31 or Y93), and excluding subjects who received the suboptimal 8-week treatment duration in ALLY-2, SVR12 rates were 13/17 (76%) and 142/149 (95%) for HCV GT1a infected subjects with or without a key DCV NS5A resistance-associated polymorphism. The

specific polymorphisms observed among virologic failure subjects were M28T, L31M, L31M+H58P, or Y93N. The overall prevalence of polymorphisms at positions M28, Q30, L31 or Y93 was 19/203 (9%).

The impact of NS5A amino acid polymorphisms was restricted to HCV GT1a infected subjects with cirrhosis. All 4 subjects with key DCV resistance-associated polymorphisms who experienced virologic failure had Child-Pugh A or B cirrhosis; no subjects with Child-Pugh C cirrhosis had virus with a DCV resistance-associated polymorphism. Considering only those with Child-Pugh A/B cirrhosis, and excluding subjects who received the 8-week treatment duration, SVR12 was achieved in 2/6 (33%) and 38/39 (97%) GT1a subjects with or without key DCV NS5A resistance-associated polymorphisms, respectively. Pooling GT1a subjects without cirrhosis or in the ALLY-1 Post-Transplant Cohort, SVR12 was achieved in 11/11 (100%) and 100/101 (99%) subjects with and without NS5A polymorphisms, respectively. Two of the 4 virologic failure subjects with NS5A resistance-associated polymorphisms had additional treatment-emergent, resistance-associated substitutions in NS5A at the time of virologic failure, and 3 of the 4 subjects had a treatment-emergent NS5B substitution possibly associated with SOF resistance.

NS5A polymorphisms did not impact DCV/SOF ± RBV efficacy for HCV GT1b infected subjects in the ALLY-1 and ALLY-2 trials, although the available data are limited, particularly for those with cirrhosis. No HCV GT3 subjects in ALLY-1 or ALLY-2 had virus with the NS5A Y93H polymorphism, which was the critical polymorphism associated with reduced DCV/SOF treatment efficacy in ALLY-3. NS5B polymorphisms at potential SOF resistance-associated positions were infrequent among subjects with HCV GT1a, GT1b or GT3 infection in the ALLY-1, ALLY-2 and ALLY-3 trials, and when they were detected they were not clearly associated with treatment failure.

Reviewer's Perspective on Baseline Resistance Testing for NS5A Polymorphisms

This reviewer recommends that HCV GT1a infected patients with cirrhosis who are considering treatment with DCV/SOF±RBV be screened for the presence of NS5A amino acid polymorphisms at positions M28, Q30, L31, or Y93. Of the 6 HCV GT1a infected subjects with cirrhosis in ALLY-1 and ALLY-2 with an NS5A polymorphism at one of these positions, only 2 (33%) achieved SVR12. It is challenging to draw major conclusions about treatment efficacy and provide treatment recommendations based on results from such a small number of subjects, but these results were not entirely unexpected, as data from multiple other trials have demonstrated a clear impact of NS5A polymorphisms on DCV-based treatment efficacy. Based on numerous discussions internally and with the sponsor, the review team proposed including a screening recommendation in a subsection of Section 2 (Dosage and Administration) termed "2.1. Testing Prior to Initiation of Therapy" (or similar), with the following draft language: *"Consider screening for the presence of NS5A polymorphisms at amino acid positions M28, Q30, L31, and Y93 in patients with cirrhosis who are infected with HCV genotype 1a prior to the initiation of treatment with DAKLINZA and sofosbuvir with or without ribavirin [see Microbiology (12.4]), Table X]."*

3. ADMINISTRATIVE

3.1 Reviewers' Signatures

_____
Patrick R. Harrington, Ph.D.
Clinical Virology Reviewer, Division of Antiviral Products

3.2 Concurrence

_____
Julian J. O'Rear, Ph.D.
Clinical Virology Team Leader, Division of Antiviral Products

OND CLINICAL VIROLOGY REVIEW

1. INTRODUCTION AND BACKGROUND

1.1 Introduction and scope of this review

This Clinical Virology review covers three supplemental New Drug Applications (sNDAs) for daclatasvir (DCV, DAKLINZA™; NDA 206843). DCV is a hepatitis C virus (HCV) NS5A inhibitor and is currently approved for use with sofosbuvir (SOF, SOVALDI™), an FDA-approved uridine nucleotide analogue NS5B polymerase inhibitor, for the treatment of chronic HCV genotype 3 infection.

These efficacy supplements are to expand the indication for DCV to include patients who have received a liver transplant (S-01), patients with HIV-1 coinfection (S-02), or patients with decompensated cirrhosis (S-03). To support these expanded indications, the sponsor submitted clinical study reports and datasets from two clinical trials, AI444215 (ALLY-1) and AI444216 (ALLY-2). The data submitted in these supplements are predominantly from subjects with HCV genotype 1 (GT1) infection; thus, these supplements also support expansion of the DCV indication to include patients with HCV GT1 infection, the predominant HCV genotype in the U.S. Multiple highly effective, interferon-free, direct-acting antiviral (DAA)-containing regimens are now available for HCV GT1 infected patients, including patients with compensated cirrhosis, patients with HCV/HIV-1 coinfection, and patients with HCV recurrence after liver transplantation, but no regimens are currently approved for the treatment of patients with decompensated cirrhosis (Child-Pugh B or C).

This Clinical Virology review includes independent analyses of HCV RNA and drug resistance data from the ALLY-1 and ALLY-2 trials. Please also see the review by Virology Reviewer Lalji Mishra, Ph.D., for additional review of DCV focusing on the nonclinical (i.e., cell culture) virology and resistance characteristics of DCV for HCV GT1.

1.2 Methodology

HCV genotype/subtype determination
In clinical trials AI444215 (ALLY-1) and AI444216 (ALLY-2), HCV genotype determination for inclusion was based on the Abbott RealTime HCV Genotype II assay, which is an FDA-approved, real-time RT-PCR-based HCV genotyping assay. For samples with results that were unavailable or inconclusive, the Siemens Versant HCV genotype 2.0 line-probe assay (LiPA) was used. These analyses were conducted by (b) (4). Also, retrospective phylogenetic analyses of NS5A sequences were conducted to determine subtypes for non-GT1 genotypes.

HCV viral load assessments
In ALLY-1 and ALLY-2, HCV RNA levels were determined using the FDA-approved Roche COBAS® TaqMan® HCV v2.0 test, which has a lower limit of quantification (LLOQ) of 25 IU/mL. These analyses were conducted by (b) (4).

Resistance-related assessments
In ALLY-1 and ALLY-2, drug resistance testing on plasma samples was performed by population nucleotide sequence analysis of the HCV NS5A coding region for baseline samples from all subjects, as well as samples collected near the time of virologic failure for subjects who did not achieve a sustained virologic response (SVR). These analyses were conducted by (b) (4). Additional population nucleotide sequence analyses were conducted "in-house"

by the sponsor if data could not be generated by the contract laboratory. Analyses of NS5B sequences for assessment of sofosbuvir resistance were also conducted for subjects who experienced virologic failure, but only limited baseline analyses were conducted for subjects who achieved SVR. Site-directed mutant phenotypic analyses were previously conducted for specific NS5A substitutions, or combinations of substitutions, to assess their impact on DCV anti-HCV activity using the HCV replicon system.

Genotypic and phenotypic HIV-1 drug resistance testing for ALLY-2 was conducted by (b) (4) .

2. NONCLINICAL VIROLOGY

Please see the Virology reviews of the Original NDA 206843 and supplements S-01, S-02 and S-03 by Lalji Mishra, Ph.D., for detailed reviews of DCV nonclinical virology data including mechanism of action, cell culture antiviral activity, and resistance selection in cell culture. Appendix A of this review includes a listing of DCV resistance-associated substitutions for which site-directed mutant phenotype results in HCV GT1a, GT1b, and GT3 replicons are available; these data were used to support the drug resistance analyses for ALLY-1 and ALLY-2.

3. CLINICAL VIROLOGY REVIEW OF EFFICACY AND DRUG RESISTANCE

3.1 AI444215 (ALLY-1) efficacy analysis

3.1.1 AI444215 (ALLY-1) study design

Clinical trial AI444215 (ALLY-1) was a Phase 3 open-label study that assessed the efficacy of DCV in combination with the FDA-approved nucleos(t)ide analogues SOF and RBV (DCV/SOF/RBV) administered for 12 weeks in HCV infected subjects with cirrhosis who may require future liver transplantation, and in subjects who have previously received a liver transplant. Subjects with cirrhosis who underwent a liver transplant during treatment could have had their treatment extended for an additional 12 weeks after transplant. Subjects who experienced relapse following DCV/SOF/RBV treatment could be retreated with DCV/SOF/RBV for another 24 weeks. Subjects enrolled at 5 sites in the United States.

Eligible subjects could be infected with any major HCV GT (1-6). Both cohorts were capped at approximately 20% non-GT1. In addition for the Cirrhotic Cohort, Child-Pugh class C subjects were capped at approximately 12 (20%). Coinfection with human immunodeficiency virus or hepatitis B virus was exclusionary. Subjects could have been HCV treatment-naïve or treatment-experienced, although previous exposure to NS5A inhibitors was prohibited. The primary efficacy endpoint was SVR12, defined as HCV RNA <LLOQ 12 weeks after the end of treatment.

A total of 113 subjects were treated in this study, 60 subjects in the Cirrhotic Cohort and 53 subjects in the Post-Liver Transplant cohort. Three subjects (2 GT1a, 1 GT3) in the Cirrhotic Cohort underwent a liver transplant during treatment and had their treatment extended by another 12 weeks following transplant. Overall, 67/113 (59%) were HCV treatment-experienced, with a similar breakdown across both cohorts. Nine subjects (8%; 6 GT1a, 2 GT1b, 1 GT3A) previously received the FDA-approved NS3/4A protease inhibitors boceprevir or telaprevir in combination with P/R. No subjects were SOF-based treatment-experienced.

Note that one post-liver transplant subject (AI444215-3-18) with a mixed GT1a/GT3a coinfection was considered as having HCV GT3 infection for analyses of efficacy according to HCV genotype/subtype. This subject, who achieved SVR12, had HCV GT1a by the Abbott RealTime HCV Genotype II assay with cross-reactivity with HCV GT3, had an indeterminate HCV genotype result by the Siemens Versant HCV genotype 2.0 assay, and had HCV GT3a based on an NS5B subtyping assay. Subsequent population sequencing and phylogenetic analyses indicated the subject was coinfected with both GT1a and GT3a, which likely explained the inconclusive results at Screening. This subject was censored for all resistance analyses. According to the sponsor, this subject had no noted baseline resistance-associated amino acid polymorphisms in the GT1a NS5A and NS5B sequences and GT3 NS5B sequence, while S62T was detected in the GT3 NS5A sequence.

3.1.2 AI444215 (ALLY-1) efficacy results

Overall SVR12 and virologic failure rates are summarized in Table 1 (FDA analysis). All 13 subjects who did not achieve SVR12 experienced virologic failure; 12 subjects experienced virologic relapse and 1 subject experienced on-treatment virologic failure. Among HCV GT1 infected subjects, SVR12 rates were lower and virologic failure rates were higher for subjects infected with HCV GT1a compared to those with HCV GT1b, consistent with previous studies of DCV-containing regimens.

Four subjects in the Cirrhotic Cohort received a liver transplant during the treatment period. One subject (AI444215-3-100) discontinued therapy at the time of transplant and achieved SVR12. The 3 other subjects received <1 to 10 weeks of treatment and subsequently completed a 12-week extension period after transplant; all 3 achieved SVR12.

Prior to conducting this review the review team determined that the numbers of subjects infected with HCV GTs 2, 4, 5 and 6 (across ALLY-1 and ALLY-2) were inadequate for labeling/indications, and therefore subsequent efficacy and resistance analyses focused only on HCV GT1 and GT3 infected subjects; however, even the GT3 data are limited.

Table 1. AI444215 (ALLY-1) SVR12 and virologic failure results. Subjects received DCV/SOF/RBV for 12 weeks, with treatment extended for cirrhotic subjects who underwent liver transplant during treatment. Two subjects with missing SVR12 results who were later found to have achieved SVR24 were considered SVR12 responders in this analysis. Note that no subjects with HCV GT5 were enrolled.

	Cirrhotic w/ treatment extension	Cirrhotic w/o treatment extension	Post-transplant	Total
All GTs-SVR12	**3/3 (100%)**	**47/57 (82%)**	**50/53 (94%)**	**100/113 (88%)**
GT 1a-SVR12	**2/2 (100%)**	**24/32 (75%)**	**30/31 (97%)**	**56/65 (86%)**
On-Tx Failure	0/2	1/32 (3%)	0/31 (0%)	1/65 (2%)
Relapse	0/2	7/32 (22%)	1/31 (3%)	8/65 (12%)
GT 1b-SVR12	**0**	**11/11 (100%)**	**9/10 (90%)**	**20/21 (95%)**
Relapse		0/11	1/10 (10%)	1/21 (5%)
GT 2-SVR12	**0**	**4/5 (80%)**	**0**	**4/5 (80%)**
Relapse		1/5 (20%)		1/5 (20%)
GT 3-SVR12	**1/1 (100%)**	**4/5 (80%)**	**10/11 (91%)**	**15/17 (88%)**
Relapse	0/1	1/5 (20%)	1/11 (9%)	2/17 (12%)
GT 4-SVR12	**0**	**4/4 (100%)**	**0**	**4/4 (100%)**
GT 6-SVR12	**0**	**0**	**1/1 (100%)**	**1/1 (100%)**

Although the number of subjects for analysis was small DCV/SOF/RBV treatment efficacy appeared to be substantially lower for HCV GT1a infected subjects with Child-Pugh C cirrhosis compared to those with Child-Pugh A/B cirrhosis (Table 2, FDA analysis). The numbers of subjects were insufficient to determine if Child-Pugh status impacts the efficacy of DCV/SOF/RBV in patients with HCV GT1b or GT3.

Table 2. AI444215 (ALLY-1) SVR12 and virologic failure for HCV GT1 and GT3 subjects in the Cirrhotic Cohort, according to Child-Pugh category.

	Child-Pugh A	Child-Pugh B	Child-Pugh C
GT1a-SVR12	**7/8 (87.5%)**	**15/17 (88%)**	**4/9 (44%)**
Virologic Failure/Relapse	1/8 (12.5%)	2/17 (12%)	5/9 (56%)
GT1b-SVR12	**3/3 (100%)**	**7/7 (100%)**	**1/1 (100%)**
Virologic Failure/Relapse	0	0	0
GT3-SVR12	**n/a**	**3/3 (100%)**	**2/3 (67%)**
Virologic Failure/Relapse	n/a	0	1/3 (33%)

Eight of the 9 prior DAA treatment-experienced subjects (boceprevir or telaprevir) achieved SVR12; the single non-SVR subject had HCV GT1a infection and Child-Pugh C cirrhosis.

Retrospective phylogenetic analyses of NS5A sequences indicated that all 17 HCV GT3 infected subjects in ALLY-1 (including Subject AI444215-3-18 with GT1a/GT3 coinfection) were infected with subtype 3a.

As summarized in Section 3.4.1 of this review, the presence of HCV NS5A resistance-associated amino acid polymorphisms was associated with reduced DCV/SOF ± RBV treatment efficacy for HCV GT1a infected subjects in the ALLY-1 and ALLY-2 trials, particularly among subjects with cirrhosis.

3.2 AI444216 (ALLY-2) efficacy analysis

3.2.1 AI444216 (ALLY-2) study design

Clinical trial AI444216 (ALLY-2) was a Phase 3 open-label study that assessed the efficacy of DCV in combination with SOF (DCV/SOF, without RBV) administered for 8 or 12 weeks in subjects with HCV and HIV-1 coinfection. The DCV dose was 60 mg QD unless otherwise dictated by concomitant antiretroviral therapy (ART). Treatment-naïve subjects were randomized 2:1 to receive DCV/SOF for either 12 or 8 weeks, with randomization stratified by cirrhosis status and HCV genotype (and subtype 1a/1b). Treatment-experienced subjects received DCV/SOF for 12 weeks. Subjects with compensated cirrhosis were eligible and were capped at approximately 50% of the subjects in each cohort. Eligible subjects could be infected with any major HCV GT (1-6), although approximately 80% of subjects were to be infected with HCV GT1. Treatment experience could have included prior interferon-based treatment, NS3/4A protease inhibitors or other classes of HCV DAAs (including SOF), but previous exposure to NS5A inhibitors was prohibited.

A total of 203 subjects were treated in this study across 37 sites in the United States. Nearly all subjects (199/203, 98%) were on concomitant ART. Thirteen of the 52 subjects (25%) in the treatment-experienced group previously received a DAA-based regimen, including 3 subjects (1 GT1a, 2 GT3) who received SOF + RBV and 10 subjects (all GT1a) who received boceprevir or telaprevir plus P/R. Note that one additional HCV GT1a interferon/ribavirin treatment-experienced

subject was mistakenly randomized into the treatment-naïve DCV/SOF 12-week Arm (AI444216-29-149, achieved SVR12).

3.2.2 AI444216 (ALLY-2) efficacy results

Overall SVR12 and virologic failure rates are summarized in Table 3 (FDA analysis). SVR12 rates were clearly numerically higher in the 12-week treatment groups compared to the 8-week treatment group. Fourteen subjects experienced virologic relapse (note: analysis includes 2 subjects who were possible late virologic relapsers, additional details from 60-day safety update described below). Four subjects failed to achieve SVR12 for non-virologic reasons, including incarceration (n=2), premature discontinuation/noncompliance (n=1), or death (n=1). No subjects experienced on-treatment virologic breakthrough.

Although most of the subgroups were small, the reduced efficacy of the 8-week regimen was apparent for all represented HCV genotypes and subtypes 1a/1b. Furthermore, high relapse rates were observed among both cirrhotic (2/5 [40%] relapse rate overall, 2/4 [50%] for GT1a) and non-cirrhotic subjects (9/45 [20%] relapse rate overall, 6/31 [20%] for GT1a). These results from the 8-week arm are disappointing and somewhat surprising given the 94% SVR12 rate observed among treatment-naïve, non-cirrhotic, HCV GT1 infected subjects treated with SOF plus the NS5A inhibitor ledipasvir (LDV) for 8 weeks in the ION-3 trial (HARVONI™ label). Although it is possible that the presence of HIV-1 coinfection contributed to a lower SVR rate in the 8-week arm of ALLY-2, these results raise concerns that DCV is potentially less effective than LDV when used in combination with SOF, at least for HCV GT1 infected patients.

Prior to conducting this review the review team determined that the numbers of subjects infected with HCV GTs 2, 4, 5 and 6 (across ALLY-1 and ALLY-2 trials) were inadequate for labeling/indications. Furthermore, the review team is not considering the 8-week duration of DCV/SOF for labeling due to the high relapse rate observed with this duration. Therefore, subsequent efficacy and resistance analyses focused primarily on HCV GT1 and GT3 infected subjects, and excluding those who received the 8-week DCV/SOF regimen.

Table 3. AI444216 (ALLY-2) SVR12 and virologic failure results.

	Tx-Naïve DCV/SOF 12-Weeks	Tx-Naïve DCV/SOF 8-Weeks	Tx-Experienced DCV/SOF 12-Weeks
SVR12-All Subjects	**98/101 (97%)**	**38/50 (76%)**	**51/52 (98%)**
Relapse	2*/101 (2%)	11*/50 (22%)	1/52 (2%)
Non-VF	2/101 (2%)	2/50 (4%)	0/52 (0%)
SVR12 by HCV GT			
1a	68/71 (96%)	28/35 (80%)	32/33 (97%)
1b	12/12 (100%)	3/6 (50%)	11/11 (100%)
2	11/11 (100%)	5/6 (83%)	2/2 (100%)
3	6/6 (100%)	2/3 (67%)	4/4 (100%)
4	1/1 (100%)	0	2/2 (100%)

*Includes 1 subject in arm with late relapse after achieving SVR12 (Subject 16-141, GT2, in Tx-naïve 12-week arm; Subject 27-151, GT1a, in Tx-naïve 8-week arm)

Table 4 (FDA analysis) summarizes SVR12 and relapse rates according to cirrhosis status, considering only the 12-week durations, and only HCV GTs 1a, 1b, and 3. Among these groups, only 2 subjects experienced virologic relapse, both of whom had HCV GT1a and cirrhosis. Minimal

numbers of subjects with HCV GT1b or GT3 had cirrhosis. All 13 subjects with prior DAA-based treatment experience (10 boceprevir or telaprevir plus P/R, 3 SOF plus RBV) achieved SVR12. In general, the GT3 data from ALLY-2 do not add significant new information from what was previously obtained from the ALLY-3 trial (described in the current DCV DAKLINZA™ label). All 13 GT3 subjects had subtype 3a based on retrospective phylogenetic analysis of NS5A sequences.

Table 4. AI444216 (ALLY-2) SVR12 and virologic failure results for HCV GT1a, GT1b, and GT3 infected subjects who received DCV/SOF for 12-weeks, according to cirrhosis status.

	DCV/SOF 12-Weeks Treatment-Naïve		DCV/SOF 12-Weeks Treatment-Experienced		DCV/SOF 12-Weeks Total	
	SVR12	Relapse	SVR12	Relapse	SVR12	Relapse
GT1a Subjects						
No Cirrhosis	58/60 (97%)	0/60 (0%)	20/20 (100%)	0/20 (0%)	78/80 (98%)	0/80 (0%)
Cirrhosis	8/9 (89%)	1/9 (11%)	10/11 (91%)	1/11 (9%)	18/20 (90%)	2/20 (10%)
Cirrhosis Unknown	2/2 (100%)	0/2 (0%)	2/2 (100%)	0/2 (0%)	4/4 (100%)	0/4 (0%)
GT1b Subjects						
No Cirrhosis	12/12 (100%)	0/12 (0%)	8/8 (100%)	0/8 (0%)	20/20 (100%)	0/20 (0%)
Cirrhosis	none	none	2/2 (100%)	0/2 (0%)	2/2 (100%)	0/2 (0%)
Cirrhosis Unknown	none	none	1/1 (100%)	0/1 (0%)	1/1 (100%)	0/1 (0%)
GT3 Subjects						
No Cirrhosis	6/6 (100%)	0/6 (0%)	3/3 (100%)	0/3 (0%)	9/9 (100%)	0/9 (0%)
Cirrhosis	none	none	1/1 (100%)	0/1 (0%)	1/1 (100%)	0/1 (0%)

A 60-day safety update submission (SDN 97) included a clinical study report addendum for ALLY-2, which described virologic response data through Follow-up Week 24 (i.e., SVR24 assessment). SVR24 rates were lower than the SVR12 rates in ALLY-2 by a difference of 10 subjects, but most of this difference was not due to true virologic failure (Table 5; derived from sponsor's summaries). Based on subjects with available data, overall concordance of SVR12/SVR24 results were 95/96 (99%) for the treatment-naïve, 12-week arm, 45/46 (98%) for the treatment-naïve, 8-week arm, and 48/49 (98%) for the treatment-experienced, 12-week arm.

Table 5. Summary of subjects who achieved SVR12 but not SVR24.

Arm	Number of SVR12 Subjects w/o SVR24	Reasons for Not Achieving SVR24
DCV/SOF 12-Weeks Treatment-Naïve	5	Late relapse (n=1): Subject 16-141 (GT2) Non-virologic failure (n=4): Subjects 5-86 (missing SVR24 data, subsequently found with HCV RNA not detected), 28-187 (death), 30-108 and 32-3 (lost to follow-up)
DCV/SOF 8-Weeks Treatment-Naïve	2	Late relapse (n=1): Subject 27-151 (GT1a) Non-virologic failure (n=1): Subject 16-173 (missing data, noncompliance)
DCV/SOF 12-Weeks Treatment-Experienced	3	Late relapse (n=1): Subject 35-81 (GT1a) Non-virologic failure (n=2): Subjects 13-2 and 16-127 (missing SVR24 data, subsequently found with HCV RNA not detected)

Three SVR12-achieving subjects failed to achieve SVR24 for virologic reasons. Note that for two of these subjects (16-141 and 27-151) SVR24 data were reported in the original sNDA submission and these subjects are noted above in Table 3 as late relapses. Two of the three subjects had evidence

of reinfection (Table 6; derived from sponsor's summaries). The late relapse for subject 27-151 has little impact on assessments of HCV virologic response since the subject received the 8-week treatment duration, which is not being considered for labeling.

Table 6. Subjects who achieved SVR12 and were virologic failures at the SVR24 assessment.

USUBJID	Probable Reinfection?	Evidence
AI444216-16-141 (GT2, Tx-naïve, 12-week)	Yes	Different HCV GT at failure (GT3) compared to screening (GT2b). No NS5A resistance-associated substitutions detected at time of failure.
AI444216-27-151 (GT1a, Tx-naïve, 8-week)	No	Same HCV subtype at failure and screening, and similar NS5A polymorphism patterns (not at known resistance-associated positions). No NS5A resistance-associated substitutions detected at time of failure.
AI444216-35-81 (GT1a, Tx-exp., 12-week)	Yes	Different HCV GT at failure (GT1b) compared to screening (GT1a). No NS5A sequence analysis data reported at failure.

As summarized in Section 3.4.1 of this review, the presence of HCV NS5A resistance-associated amino acid polymorphisms was associated with reduced DCV/SOF ± RBV treatment efficacy for HCV GT1a infected subjects in the ALLY-1 and ALLY-2 trials, particularly among subjects with cirrhosis.

3.2.3 AI444216 (ALLY-2) HIV-1 virologic control

HIV-1 RNA levels were also analyzed to assess HIV-1 virologic control among those on concomitant ART (n=199). Four subjects were not on concomitant ART, and interestingly, three of these four subjects had remarkably low or not detected HIV-1 RNA levels (Table 7, FDA analysis). It was initially unknown if these results indicated a mistake in ART reporting or if these subjects were naturally controlling their HIV-1 infection. Less than 1% of patients with HIV-1 infection are considered elite controllers, maintaining plasma HIV-1 RNA levels "below the limits of clinical detection (<50-75 copies/mL)" in the absence of ART (Cockerham and Hatano, 2015).

A query about these four subjects not on ART was communicated to the sponsor on 10/20/2015. The sponsor provided the following additional information in SDN 108:

> *"Each of these subjects had their HIV-1 diagnosis verified at screening by HIV-1 antibody (Bayer ADVIA Centaur HIV 1/O/2 Enhanced Immunoassay) and confirmatory HIV-1 Western blot (INNO-LIA HIV I/II, Innogenetics) testing. The AI444216 study team at BMS had direct communication with each of the sites to affirm the non-cART status of these 4 subjects. In each case it was confirmed with the site that the subjects were not receiving antiretroviral therapy prior to the initiation of study medications; 3 of 4 sites specified in their response that the subject was considered an HIV elite controller/long-term non-progressor (Subjects AI444216-13-15, AI444216-18-218, and AI444216-24-71). None of the 4 subjects had an antiretroviral agent reported among their respective concomitant medications used throughout the AI444216 study."*

Table 7. HIV-1 RNA levels in 4 subjects not on concomitant ART. TND, target not detected

USUBJID	HCV GT	HCV Treatment Visit	HIV-1 RNA (copies/mL)
AI444216-7-58	3a	PRE-TREATMENT	<40 TND
		PRE-TREATMENT	<40 TND
		Treatment Week 1	<40 TND
		Treatment Week 2	<40 TND
		Treatment Week 4	<40 TND
		Treatment Week 6	<40 TND
		Treatment Week 8	<40 TND
		Treatment Week 12	<40 TND
		Post-Treatment Week 4	<40 TND
		Post-Treatment Week 12	<40 TND
AI444216-13-15	1a	PRE-TREATMENT	312
		PRE-TREATMENT	98
		Treatment Week 1	92
		Treatment Week 2	<40 Detected
		Treatment Week 4	<40 Detected
		Treatment Week 6	<40 TND
		Treatment Week 8	<40 TND
		Post-Treatment Week 4	42
		Post-Treatment Week 12	<40 TND
AI444216-18-218	2a OR 2c	PRE-TREATMENT	<40 Detected
		PRE-TREATMENT	<40 Detected
		Treatment Week 1	<40 Detected
		Treatment Week 2	<40 TND
		Treatment Week 4	<40 TND
		Treatment Week 6	<40 TND
		Treatment Week 8	<40 TND
		Treatment Week 12	<40 TND
		Post-Treatment Week 4	<40 TND
		Post-Treatment Week 12	<40 Detected
AI444216-24-71	1b	PRE-TREATMENT	3813
		PRE-TREATMENT	1390
		Treatment Week 1	1694
		Treatment Week 2	4158
		Treatment Week 4	1883
		Treatment Week 6	1766
		Treatment Week 8	2335
		Post-Treatment Week 4	3133
		Post-Treatment Week 12	3083
		Post-Treatment Week 24	3996

Among those on concomitant ART, 182/199 (91%) had HIV-1 RNA <40 copies/mL at baseline or the latest pre-HCV-treatment HIV-1 RNA measurement. The other 17 subjects (9%) had HIV-1 RNA between 41 and 126 copies/mL.

The use of DCV/SOF treatment did not appear to have a significant impact on HIV-1 virologic control. At any point during or following anti-HCV treatment, 10 (5%) subjects had at least 1 HIV-1 RNA measurement >200 copies/mL. Of these 10 subjects, 6 had HIV-1 RNA <200 copies/mL (4 subjects <40 copies/mL) at the last available measurement without adjustments to their ART. Four subjects

(2%) had HIV-1 RNA >200 copies/mL at their last measurement, of whom only 1 subject (19-138) had HIV-1 RNA >400 copies/mL. Overall, 179/199 (90%) of subjects on ART had HIV-1 RNA <40 copies/mL at their last measurement. Three subjects switched their ART regimen during the treatment period due to complications of tenofovir disoproxil fumarate; all three subjects had HIV-1 RNA <40 copies/mL throughout the study.

Two subjects (19-138 [noted above] and 12-14) had HIV-1 RNA virologic failure, defined as HIV-1 RNA >400 copies/mL either confirmed during the study or at the last available timepoint; antiretroviral drug resistance analyses were conducted for these two subjects. Subject 19-138 was on a regimen of tenofovir disoproxil fumarate/emtricitabine/raltegravir, was lost to follow-up after Treatment Week 6 (incarcerated), and was considered noncompliant to study medication. At the Week 6 timepoint this subject had plasma HIV-1 RNA of 629 copies/mL. Subject 12-14 was on a regimen of abacavir/ lamivudine/raltegravir/darunavir/ritonavir, had HIV-1 RNA of 4,442 copies/mL at the end of treatment, and 1,755 copies/mL at Follow-up Week 4, but <40 copies/mL Target Not Detected at Post-Treatment Week 12. Based on genotypic and phenotypic drug resistance assessments conducted by (b) (4) , the viruses for both subjects were reported as susceptible to their current ART drugs, except that testing for raltegravir was either not conducted or not reported.

3.3 AI444215/AI444216 (ALLY-1/ALLY-2) pooled treatment-emergent resistance analysis (HCV GT1 and GT3)

Independent analyses of the sponsor's population nucleotide sequence analysis data were conducted to identify patterns of treatment-emergent substitutions among subjects who experienced virologic failure in ALLY-1 and ALLY-2. These analyses included both NS5A for DCV, and NS5B for SOF. For NS5A analyses, the following positions that have been previously described as possibly being associated with resistance to DCV or other NS5A inhibitors were considered in these analyses: 24, 28, 29, 30, 31, 32, 54, 56, 58, 62, 92, and 93. The NS5A consensus sequences at multiple resistance-associated positions differ according to HCV genotype and subtype, as do DCV resistance pathways, therefore each major subtype was evaluated independently. For NS5B analyses, the following positions were considered as possibly being associated with virologic failure or resistance to SOF: D61, A/S112, N142, L159, E237, S282, C/F289, C316, L320, V321, and S/T473.

3.3.1 HCV GT1a treatment-emergent substitutions in NS5A

Analyses of NS5A sequences were conducted for 19/21 HCV GT1a infected subjects who did not achieve SVR in ALLY-1 and ALLY-2: 17 virologic relapsers, 1 on-treatment failure, and 1 non-compliant subject (3-148) who discontinued after 1 week of treatment. Two non-SVR subjects without treatment-emergent resistance data included one subject (27-151) who experienced late virologic relapse after achieving SVR12, and one subject (19-138) who discontinued the trial early due to incarceration.

The following analyses focused on positions M28, Q30, L31, H54, H58 and Y93. No polymorphisms or treatment-emergent substitutions were observed at NS5A positions K24, P29, P32, R56, or A92. An E62D polymorphism was observed in three subjects; one subject had a D/E62D enrichment at the time of virologic failure, but none of the 19 subjects had newly emergent substitutions at this position.

Table 8 (FDA analysis) summarizes the treatment-emergent substitutions observed in the 19 HCV GT1a non-SVR subjects with available data. The following treatment-emergent NS5A substitutions were observed: M28T, Q30E/H/K/R, L31M/V, H54R, H58D and Y93C/N. Treatment-emergent substitutions most frequently occurred at position Q30. Interestingly, few subjects who experienced

virologic relapse in the 8-week arm of ALLY-2 had treatment-emergent NS5A resistance-associated substitutions. Since this duration will not be recommended in labeling, subjects in this arm also should be excluded from the treatment-emergent resistance summary in the label.

Table 8. Treatment-emergent NS5A substitutions in HCV GT1a infected subjects who experienced treatment failure in ALLY-1 and ALLY-2.

	All Non-SVR[1] Subjects w/ Data	Excluding Non-VF and ALLY-2 8-Week Arm	ALLY-2 8-Week Arm Only
M28T	2/19 (11%)	2/11 (18%)	0/7 (0%)
Q30E/H/K/R	10/19 (53%)	8/11 (73%)	1/7 (14%)
L31M/V	2/19 (11%)	2/11 (18%)	0/7 (0%)
H54R	1/19 (5%)	1/11 (9%)	0/7 (0%)
H58D[2]	1/19 (5%)	1/11 (9%)	0/7 (0%)
Y93C/N	2/19 (11%)	2/11 (18%)	0/7 (0%)
Any[3]	11/19 (58%)	9/11 (82%)	1/7 (14%)
≥2 Substitutions[3]	5/19 (26%)	5/11 (45%)	0/7 (0%)
Any[3] at Failure (Emergent or Polymorphism)	13/19 (68%)	11/11 (100%)	1/7 (14%)

[1]Includes data from one non-compliant subject (AI444216-3-148) who discontinued after 1 week of treatment (non-virologic failure).
[2]One additional subject had a treatment-emergent H58P substitution, although another subject had the converse change at failure.
[3]From list of substitutions shown: M28T, Q30E/H/K/R, L31M/V, H54R, H58D or Y93C/N

A treatment-emergent H58P substitution was observed in one subject, but a second subject had the converse P58H treatment-emergent change indicating the H58P substitution was not preferentially selected by DCV based on this analysis. These data are consistent with phenotypic analysis data, which indicate the H58P substitution confers little or no phenotypic resistance either as a single substitution or in combination with other substitutions (see Appendix A). In contrast, an H58D substitution confers a 367-fold reduction in DCV anti-HCV activity in the GT1a replicon, and major reductions in DCV activity in combination with other substitutions.

An additional exploratory analysis was conducted to determine if there were any trends of treatment-emergent substitutions at potentially novel resistance-associated positions across the entire NS5A coding region (amino acids 1-448), considering only those that emerged in at least two subjects. The only change observed in at least two subjects was an R44K substitution, which is in this reviewer's opinion was not clearly associated with treatment failure. This position has not been described previously (to this reviewer's knowledge) as being associated with resistance to NS5A inhibitors. One subject had an R44K treatment-emergent substitution, a second subject had a K/R44R enrichment, and a third subject had a R/K44 mixture at baseline, which was enriched to the reference R44 sequence at Day 2 of treatment, and was subsequently observed as the R/K44 mixture at the time of virologic relapse. An analysis of baseline NS5A sequence data from 203 subjects across the ALLY-1 and ALLY-2 trials found that R44K was a common polymorphism, detected in 63/203 (31%) subjects. Among these subjects, 57/63 (90%) achieved SVR12 compared to 125/140 (89%) subjects without the R44K polymorphism. Considering the totality of these data, R44K appears to be a common natural polymorphism and not a *bona fide* DCV resistance-associated substitution.

3.3.2 HCV GT1a treatment-emergent substitutions in NS5B

Analyses of NS5B treatment-emergent substitutions were conducted for 18 HCV GT1a infected subjects with available data from ALLY-1 and ALLY-2: 8 subjects were from ALLY-1 and 10 subjects were from ALLY-2 (7 of whom received 8 weeks of treatment).

Four of the 18 subjects (22%) had a treatment-emergent substitution at an NS5B position previously associated with SOF resistance or failure: A112T (n=1), L159F (n=2), or E237G (n=1) (Table 9, FDA analysis). No treatment-emergent NS5B substitutions were detected at other NS5B positions of interest: D61, N142, S282, C289, C316, L320, V321 or S473. Much like the NS5A treatment-emergent resistance analyses, virologic relapse in the 8-week arm of ALLY-2 was not associated with the detection of treatment-emergent substitutions at any of these positions previously described as being associated with SOF failure. These data indicate that 8 weeks of treatment did not result in complete clearance of DCV+SOF-sensitive viral populations in these subjects, and provide further evidence that HCV populations carrying the A112T, L159F, or E237G substitutions were indeed selected by DCV/SOF treatment.

An additional exploratory analysis was conducted to determine if there were any trends of treatment-emergent substitutions at potentially novel resistance-associated positions across the entire NS5B coding region (amino acids 1-591). Two subjects had an emergent positively charged substitution at neutral NS5B position Q355, one Q355H and the other Q355R (Table 9). Position Q355 appeared to be relatively conserved in the limited group of pre-treatment isolates analyzed, with a Q355R polymorphism observed only in 1/62 (2%) subjects. Because the Q355H/R substitutions were observed at a conserved position in two independent virologic failure subjects, Q355H/R was considered as possibly associated with treatment failure. According to Dr. Eric Donaldson, Q355H also was previously observed as a treatment-emergent substitution in two HCV GT1b virologic failure subjects in a SOF+RBV treatment study of liver transplant patients.

Table 9. Treatment-emergent NS5B substitutions in HCV GT1a infected subjects who experienced treatment failure in ALLY-1 and ALLY-2.

	All Non-SVR Subjects w/ Data	Excluding Non-VF and ALLY-2 8-Week Arm	ALLY-2 8-Week Arm Only
A112T[1]	1/18 (6%)	1/10 (10%)	0/7 (0%)
L159F	2/18 (11%)	2/10 (20%)	0/7 (0%)
E237G	1/18 (6%)	1/10 (10%)	0/7 (0%)
Q355H/R	2/18 (11%)	1/10 (10%)	1/7 (14%)
N590del[1]	1/18 (6%)	1/10 (10%)	0/7 (0%)
Any from list above	6/18 (33%)	5/10 (50%)	1/7 (14%)

[1]A112T was detected with N590del in the same subject.

Substitutions at several other relatively conserved positions were observed in individual subjects, including H34Q, S42T, K106R, Q248K, A302S, L362H, A435T, and E455Q. Because no more than 1 subject had a substitution at each of these positions, the substitutions were not considered as being associated with virologic failure but are noted for possible future reference. A deletion at position N590 (N590del) was also observed in the subject who had treatment-emergent A112T detected in the same sample. The N590del is particularly interesting because it is near the 3' end of the sequence analyzed. Although sequence quality is a problem at times in this region, technical error likely does not explain the detection of N590del given that it requires a clean 3-nucleotide deletion, and no changes relative to reference were reported at flanking positions 589 and 591.

Of the 6 subjects with one of the noted NS5B treatment-emergent substitutions, 4 (67%) subjects also had at least 1 treatment-emergent NS5A DCV resistance-associated substitution, and 5 (80%) subjects had at least 1 NS5A DCV resistance-associated polymorphism/substitution detected at the

time of virologic failure regardless of treatment-emergence. Not surprisingly, the one subject without an NS5A resistance-associated substitution at the time of failure received the 8-week treatment.

3.3.3 HCV GT1b treatment-emergent substitutions in NS5A and NS5B

Only 2 subjects infected with HCV GT1b experienced virologic failure (both relapse) in ALLY-1 and ALLY-2, one Post-transplant subject in ALLY-1 (AI444215-4-42) who received DCV/SOF/RBV for 12 weeks, and one subject in ALLY-2 (AI444216-18-145) who received DCV/SOF for 8 weeks. Treatment-emergent resistance-analyses for these two subjects considered all known/possible DCV and SOF resistance-associated positions described above. Subject AI444215-4-42 had a treatment-emergent deletion at NS5A position P32 (P32del), which confers a >1 million-fold reduction in DCV activity in the HCV GT1b replicon (Appendix A). Subject AI444216-18-145, who was treated for only 8 weeks, had no treatment-emergent DCV resistance-associated substitutions, consistent with the findings in HCV GT1a subjects. As noted below in Section 3.4.2, both subjects had an NS5A Q54H polymorphism and Subject AI444216-18-145 also had a Q62E polymorphism, but this reviewer is not convinced these polymorphisms have a substantial impact on DCV/SOF ± RBV efficacy for HCV GT1b infected subjects. Neither subject had a treatment-emergent substitution at an NS5B position previously associated with SOF resistance or failure.

3.3.4 HCV GT3 treatment-emergent substitutions in NS5A and NS5B

Only 3 HCV GT3 infected subjects across the ALLY-1 and ALLY-2 trials experienced virologic failure (all 3 relapsers). Again, treatment-emergent resistance-analyses for these subjects considered all known/possible DCV and SOF resistance-associated positions described above.

Consistent with results from AI444218 (ALLY-3), virologic failure was associated with the emergence of the NS5A Y93H substitution (Table 10, FDA analysis). Two of the 3 HCV GT3 virologic failure subjects in ALLY-1 and ALLY-2 had virus with treatment-emergent NS5A Y93H. The subject without treatment-emergent Y93H received the suboptimal 8-week DCV/SOF treatment duration in ALLY-2, again consistent with findings in subjects with HCV GT1a and GT1b. No other NS5A substitutions emerged at known DCV resistance-associated positions. Pooling HCV GT3 data from all 3 ALLY trials, and excluding the subject who received 8 weeks of DCV/SOF, 11/19 (58%) subjects had treatment-emergent NS5A Y93H, and 17/19 (89%) subjects had Y93H detected at the time of virologic failure, including 6 subjects who had Y93H detected as a baseline polymorphism.

Table 10. Treatment-emergent NS5A substitutions in HCV GT3 infected subjects who experienced treatment failure in ALLY-1 and ALLY-2, and pooled with data from ALLY-3.

NS5A Position/ Substitution	AI444215/AI444216 (ALLY-1/2)		AI444218 (ALLY-3)		AI444218/216/218 ALLY-1/2/3 (*excl. 8-week*)	
	Number (%) w/Tx-Emergence (n=3)	Number (%) at Failure (n=3)	Number (%) w/Tx-Emergence (n=17)	Number (%) at Failure (n=17)	Number (%) w/Tx-Emergence (n=19)	Number (%) at Failure (n=19)
A30K/S[a]	0 (0%)	1 (33%)	0 (0%)	2 (12%)	0 (0%)	2 (11%)
L31I	0 (0%)	0 (0%)	1 (6%)	1 (6%)	1 (5%)	1 (5%)
S62A/L/P/R/T[b]	0 (0%)	2 (67%)	2 (12%)	10 (59%)	2 (11%)	11 (58%)
Y93H	2 (67%)[c]	2 (67%)	9 (53%)	15 (88%)	11 (58%)	17 (89%)

[a]Two other subjects had A30 polymorphisms (T or V) that were no longer detected at treatment failure.
[b]Position S62 was highly polymorphic, and the detection of polymorphisms at this position was not consistently associated with treatment failure. Only S62L emerged, in 2 subjects.
[c]The one subject who did not have treatment-emergent Y93H received the 8-week DCV/SOF regimen.

Treatment-emergent NS5B resistance analysis data were only obtained from a single HCV GT3 subject who experienced virologic failure (AI444215-3-97, Cirrhotic Cohort), with sequence data reported only for NS5B amino acids 134-558. No amino acid substitutions were detected within this region at any positions that have previously been associated with SOF failure.

Data from 16 subjects who experienced virologic failure in the ALLY-3 trial were also re-analyzed considering the eleven SOF resistance-associated NS5B positions noted above, as well as position Q355. Consistent with the original Clinical Virology review of the ALLY-3 trial, one subject (AI444218-19-13) had the S282T substitution at the time of virologic failure. The subject did not have baseline sequence data available to assess treatment-emergence of S282T, but it was assumed that this substitution emerged as a result of treatment, as it is rarely, if ever, detected as a natural baseline polymorphism. Interestingly, this subject also had a Q355H substitution (or polymorphism) detected with S282T at the time of failure, further confirming this position as being associated with SOF-based treatment failure. None of the other 15 subjects had an NS5B substitution or polymorphism of interest detected at the time of virologic failure.

3.4 AI444215/AI444216 (ALLY-1/ALLY-2) pooled baseline resistance analysis (HCV GT1 and GT3)

Independent analyses of the sponsor's population nucleotide sequence analysis data were conducted to assess if baseline polymorphisms at NS5A resistance-associated amino acid positions were associated with virologic failure in ALLY-1 and ALLY-2. As in the treatment-emergent resistance analyses, the following positions that have been previously described as possibly being associated with resistance to DCV or other NS5A inhibitors were considered: 24, 28, 29, 30, 31, 32, 54, 56, 58, 62, 92, and 93.

Similarly, baseline NS5B resistance data were analyzed to determine if there was an association between NS5B polymorphisms at potential SOF resistance-associated positions and treatment outcome; however, only a subset of subjects in ALLY-1 and ALLY-2 who achieved SVR had baseline samples analyzed for the presence of NS5B polymorphisms. As in the treatment-emergent resistance analyses, the following NS5B amino acid positions were considered: D61, A/S112, N142, L159, E237, S282, C/F289, C316, L320, V321, and S/T473. In addition, the Q355 position was considered, as 3 virologic failure subjects had substitutions at this position.

Certain baseline resistance analyses excluded subjects who received the 8-week treatment duration in ALLY-2 because the review team is not considering this duration for labeling due to the high relapse rate observed. Also, due to the limited data from GT3 subjects in ALLY-1 and ALLY-2, certain analyses of GT3 subjects focused only on the previously reviewed ALLY-3 trial.

3.4.1 HCV GT1a NS5A baseline resistance-associated amino acid polymorphisms

Baseline NS5A population nucleotide sequence data were reported for 203/204 (>99%) HCV GT1a infected subjects across the ALLY-1 and ALLY-2 trials. No polymorphisms were observed at NS5A positions P29, P32 and R56, and therefore these positions were not considered in the following analyses. Two subjects who failed to achieve SVR for reasons unrelated to virologic failure were censored from these analyses. In addition, since only limited follow-up HCV RNA data beyond Post-Treatment Week 12 (i.e., SVR12 assessment) were reported at the time of sNDA submission, Subject AI444216-27-151 (GT1a, non-cirrhotic, Tx-naïve 8-week arm) who experienced post-SVR12 relapse was censored from these analyses. Thus, 200 HCV GT1a infected subjects were included in the

baseline resistance analysis. Note that Subject AI444216-35-81 (GT1a, non-cirrhotic, Tx-exp. 12-week arm), who was reported in the 60-day safety update submission as an SVR24 failure with evidence of reinfection (see Table 6), was included as an SVR12 responder in these analyses; this subject had no NS5A polymorphisms at any positions of interest.

HCV NS5A polymorphisms possibly had an impact on DCV/SOF ± RBV treatment efficacy for HCV GT1a infected subjects, although it is difficult to draw major conclusions due to a limited number of subjects available for these analyses, particularly for certain key subgroups (e.g., cirrhotic subjects). Pooling all data across the ALLY-1 and ALLY-2 trials, SVR12 rates were 5-13% lower among subjects with NS5A resistance-associated polymorphisms compared to those without these polymorphisms depending on the NS5A polymorphism list considered (Table 11; independent analysis). No subjects with polymorphisms at positions K24, Q30, H54 or A92 experienced virologic failure. Three subjects with an E62D polymorphism, which is not known to represent a key DCV resistance-associated position, experienced virologic failure, although all 3 subjects also received the suboptimal 8-week treatment duration in ALLY-2. Excluding subjects who received the 8-week treatment duration in ALLY-2, 4 subjects with an NS5A resistance-associated polymorphism experienced virologic failure, and all 4 had a polymorphism at a critical DCV resistance-associated position (considering M28, Q30, L31 or Y93); the specific polymorphisms observed were M28T, L31M, L31M (+H58P), or Y93N.

Considering only the four key DCV resistance-associated positions in NS5A (M28, Q30, L31 or Y93), and excluding subjects who received the 8-week treatment duration in ALLY-2, SVR12 rates were 13/17 (76%) and 142/149 (95%) for those with or without the DCV NS5A resistance-associated polymorphisms (Table 11, FDA analysis). The overall prevalence of polymorphisms at any of these positions for the 203 subjects with available data was 19/203 (9%); a detailed listing of all 19 subjects is provided in Appendix B. Of note, no subjects with NS5A Q30 polymorphisms experienced virologic failure, which is somewhat surprising given that treatment-emergent substitutions were most frequently observed at this position for subjects who experienced virologic failure (see Table 8 above). Only a single subject with a Q30 polymorphism had cirrhosis across both trials, which may explain the lack of an association with treatment outcome. The prevalence of polymorphisms considering only positions M28, L31 or Y93 was 15/203 (7%). All subjects were enrolled at study sites in the U.S.

Table 11. SVR rates (non-VF censored) in HCV GT1a infected subjects with or without NS5A polymorphisms. Note that the individual polymorphism data shown below may include some subjects with additional polymorphisms at other positions.

NS5A Polymorphism(s)	SVR12 with Polymorphism(s)	SVR12 without Polymorphism(s)
K24N/Q/R	6/6 (100%)	176/194 (91%)
M28T/V	5/6 (83%)	177/194 (91%)
Q30H/L/R	7/7 (100%)	175/193 (91%)
L31M	1/3 (33%)	181/197 (92%)
H54C/Y	7/7 (100%)	175/193 (91%)
H58C/L/P/R/Y	16/17 (94%)	166/183 (91%)
E62D	8/11 (73%)[1]	174/189 (92%)
A92P	1/1 (100%)	181/199 (91%)
Y93C/H/L/N/S	5/6 (83%)	177/194 (91%)
Any NS5A Polymorphism (list above)	48/55 (87%)	134/145 (92%)
Any: M28, Q30, L31, H58, E62, A92, Y93[2]	36/43 (84%)	146/157 (93%)
Any: M28, Q30, L31, Y93[3]	15/19 (79%)	167/181 (92%)

AI444215 (ALLY-1) only	**SVR12 with Polymorphism(s)**	**SVR12 without Polymorphism(s)**
Any NS5A Polymorphism (list above)	13/16 (81%)	43/49 (88%)
Any: M28, Q30, L31, H58, E62, A92, Y93[2]	11/14 (79%)	45/51 (88%)
Any: M28, Q30, L31, Y93[3]	4/7 (57%)	52/58 (90%)
AI444216 (ALLY-2) only	**SVR12 with Polymorphism(s)**	**SVR12 without Polymorphism(s)**
Any NS5A Polymorphism (list above)	35/39 (90%)	91/96 (95%)
Any: M28, Q30, L31, H58, E62, A92, Y93[2]	25/29 (86%)	101/106 (95%)
Any: M28, Q30, L31, Y93[3]	11/12 (92%)	115/123 (93%)
AI444216 (ALLY-2) (Excl. 8-wk Dur.)	**SVR12 with Polymorphism(s)**	**SVR12 without Polymorphism(s)**
Any NS5A Polymorphism (list above)	26/27 (96%)	73/74 (99%)
Any: M28, Q30, L31, H58, E62, A92, Y93[2]	18/19 (95%)	81/82 (99%)
Any: M28, Q30, L31, Y93[3]	9/10 (90%)	90/91 (99%)
ALLY-1 + ALLY-2 (Excluding 8-wk Duration)	**SVR12 with Polymorphism(s)**	**SVR12 without Polymorphism(s)**
Any NS5A Polymorphism (list above)	39/43 (91%)	116/123 (94%)
Any: M28, Q30, L31, H58, E62, A92, Y93[2]	29/33 (88%)	126/133 (95%)
Any: M28, Q30, L31, Y93[3]	13/17 (76%)	142/149 (95%)

[1]All 3 subjects with the E62D polymorphism who experienced virologic failure received 8 weeks of treatment.
[2]Any polymorphism at these positions, from sponsor's list of NS5A positions of interest.
[3]Any polymorphism at these positions, considering the most critical DCV resistance-associated positions.

The impact of NS5A amino acid polymorphisms at positions M28, Q30, L31, or Y93 was most apparent in subjects with cirrhosis, although again the number of subjects for analysis was small (Table 12, FDA analysis). All 4 subjects with key DCV resistance-associated polymorphisms who experienced virologic failure had Child-Pugh A or B cirrhosis; no subjects with Child-Pugh C cirrhosis had an HCV population with a DCV resistance-associated polymorphism. Considering only those with Child-Pugh A or B cirrhosis in ALLY-1 and ALLY-2, and excluding the suboptimal 8-week treatment arm in ALLY-2, SVR12 was achieved in 2/6 (33%) and 38/39 (97%) subjects with or without key DCV NS5A resistance-associated polymorphisms, respectively. In other words, of the 5 virologic failure subjects with Child-Pugh A/B cirrhosis who received DCV/SOF ± RBV for 12 weeks, 4 of the 5 failures had virus with a key DCV resistance-associated polymorphism. Pooling subjects without cirrhosis or in the ALLY-1 Post-Transplant Cohort, SVR12 was achieved in 11/11 (100%) and 100/101 (99%) subjects with and without NS5A polymorphisms, respectively.

Table 12. SVR rates (non-VF censored) in HCV GT1a infected subjects with or without NS5A polymorphisms, according to cirrhosis/post-transplant status. Data were pooled across the ALLY-1 and ALLY-2 trials, excluding the 8-week treatment arm in ALLY-2. All compensated cirrhotic subjects in ALLY-2 were considered to have Child-Pugh A cirrhosis in this analysis. Four subjects in ALLY-2 without reported cirrhosis status were considered non-cirrhotic (all 4 achieved SVR). Polymorphisms considered were those at positions M28, Q30, L31, or Y93.

	SVR12 with Polymorphism(s)	SVR12 without Polymorphism(s)
Subjects with Cirrhosis (Child-Pugh A/B/C)	2/6 (33%)	42/48 (88%)
Subjects with Child-Pugh A/B Cirrhosis[1]	2/6 (33%)	38/39 (97%)
Subjects without Cirrhosis	9/9 (100%)	72/72 (100%)
Subjects Post-Transplant	2/2 (100%)	28/29 (97%)

[1]None of the 9 Child-Pugh C subjects with cirrhosis in ALLY-1 had DCV resistance-associated polymorphisms.

A subset of the Post-Transplant Cohort had F4 fibrosis. Table 13 summarizes and pools the resistance polymorphism data across the Pre- and Post-Transplant Cohorts according to cirrhosis/F4-fibrosis status.

Table 13. SVR rates (non-VF censored) in HCV GT1a infected subjects with or without NS5A polymorphisms, and pooling Pre- and Post-Transplant according to cirrhosis/F4-fibrosis status. Data were pooled across the ALLY-1 and ALLY-2 trials, again excluding the 8-week treatment arm in ALLY-2. All compensated cirrhotic subjects in ALLY-2 were considered to have Child-Pugh A cirrhosis in this analysis. Four subjects in ALLY-2 without reported cirrhosis status were considered non-cirrhotic (all 4 achieved SVR). NS5A polymorphisms considered were those at positions M28, Q30, L31, or Y93.

Group	SVR12 with Polymorphism(s)	SVR12 without Polymorphism(s)
All HCV GT1a infected subjects DCV+SOF±RBV (8-week duration excl.)	**13/17 (76%)**	**142/149 (95%)**
Pre-transplant		
All subjects pre-transplant	11/15 (73%)	114/120 (95%)
Subjects with Cirrhosis (Child-Pugh A/B/C)	2/6 (33%)	42/48 (88%)
Subjects with Child-Pugh A/B Cirrhosis[1]	**2/6 (33%)**	**38/39 (97%)**
Subjects without Cirrhosis	9/9 (100%)	72/72 (100%)
Post-Transplant		
All subjects Post-Transplant	2/2 (100%)	28/29 (97%)
Subjects with F4 Fibrosis	**1/1 (100%)**	**11/12 (92%)**
Subjects with F0-F3	1/1 (100%)	17/17 (100%)
Pre- PLUS Post-Transplant		
Non-cirrhotic (Pre-transplant) or F0-F3 (Post-transplant)	10/10 (100%)	89/89 (100%)
Child-Pugh A/B (Pre-transplant) or F4 Fibrosis (Post-transplant)	**3/7 (43%)**	**49/51 (96%)**

[1]None of the 9 Child-Pugh C subjects with cirrhosis in ALLY-1 had DCV resistance-associated polymorphisms.

Two of the four virologic failure subjects with baseline NS5A resistance-associated polymorphisms had additional treatment-emergent, resistance-associated substitutions in NS5A at the time of virologic failure (Table 14, FDA analysis). Both subjects had an L31M polymorphism and treatment-emergent substitutions at position Q30 (Q30K or Q30H), and one subject also had an H54R treatment-emergent substitution. Two other subjects (4-102 and 25-163) who had M28T or Y93N polymorphisms had no evidence of emergence of additional DCV resistance-associated substitutions. Both subjects also had high baseline HCV RNA levels (~7 $\log_{10}$ IU/mL; median for all GT1a subjects was 6.5 $\log_{10}$ IU/mL). An L31M substitution alone confers a 250-fold reduction in DCV activity in the HCV GT1a replicon, and the combination of L31M with Q30H or Q30K results in a substantially larger reduction in DCV activity, 7,500-fold and 173,000-fold, respectively (Appendix A). The M28T and Y93N substitutions alone confer 500-fold and 35,000-fold reductions in DCV activity, respectively (Appendix A).

Three of the four virologic failure subjects with baseline NS5A resistance-associated polymorphisms also had a treatment-emergent NS5B substitution of interest (Table 14, FDA analysis). The precise clinical impact of these NS5B substitutions is unclear, but this observation raises concerns that these subjects may have a viral population that is not optimally sensitive to SOF.

Table 14. Treatment-emergent NS5A and NS5B resistance analysis for 4 HCV GT1a infected, virologic failure subjects (relapsers) with resistance-associated polymorphisms. IND., indeterminate, i.e. prior P/R response unknown; INTOL, intolerant

USUBJID	Tx Exp./ CP Status	Baseline HCV RNA ($\log_{10}$ IU/mL)	Regimen	Visit	NS5A						NS5B[1]
					M28	Q30	L31	H54	H58	Y93	
AI444215-1-37	P/R NULL/ CP-B	6.4	DCV/SOF/RBV	PRE TREAT			M				
				F/U WK 12		K	M	R/H			E237G
AI444215-3-94	P/R IND./ CP-B	6.1	DCV/SOF/RBV	PRE TREAT			M		H/P		
				F/U WK 8		H	M				Q355H
AI444215-4-102	P/R INTOL/ CP-A	7.1	DCV/SOF/RBV	PRE TREAT	T						
				F/U WK 4	T						
AI444216-25-163	NAÏVE/ CP-A/comp.	7.0	DCV/SOF	PRE TREAT						Y/N	
				F/U WK 4						N	L159F

[1]Considering those shown above in Table 9 (A112T, L159F, E237G, Q355H/R, N590del).

3.4.2 HCV GT1b NS5A baseline resistance-associated amino acid polymorphisms

The two HCV GT1b virologic failure subjects across the ALLY-1 and ALLY-2 trials (AI444215-4-42 and AI444216-18-145) had viral populations with an NS5A Q54H polymorphism. Subject AI444216-18-145 also had a Q62E polymorphism. The Q54H polymorphism was detected in 24/49 (49%) HCV GT1b infected subjects, of whom only 2 (the two described here) experienced virologic failure. The Q62E polymorphism was detected in 3 subjects, and the only virologic failure subject (AI444216-18-145) received only 8 weeks of DCV/SOF treatment. These two substitutions engineered into HCV GT1b replicon, either alone or in combination, do not reduce DCV anti-HCV activity in cell culture.

Eleven other HCV GT1b infected subjects had polymorphisms at more critical DCV resistance-associated positions, including either R30K/M/Q (n=6), L31M (n=2) or Y93H (n=3); no HCV GT1b infected subjects had a polymorphism at position L28. Ten of the 11 subjects with polymorphisms at NS5A positions 30, 31 or 93 achieved SVR12 and 1 subject died after achieving SVR4.

Excluding Child-Pugh C subjects in ALLY-1 and subjects who received the 8-week treatment duration in ALLY-2, 9 HCV GT1b infected subjects treated with DCV/SOF ± RBV for 12 weeks had an NS5A polymorphism of interest: R30K/M/Q (n=4), L31M (n=2) or Y93H (n=3), and all 9 subjects achieved SVR12. Of these 9 subjects, 5 subjects were from the ALLY-2 trial and did not have cirrhosis (or was not reported), and 4 subjects were in the Post-Transplant Cohort in ALLY-1, of whom 2 had F4 fibrosis. The single GT1b subject with Child-Pugh C cirrhosis (achieved SVR12) did not have a polymorphism at NS5A position L28, R30, L31 or Y93. These data indicate that NS5A polymorphisms did not impact DCV/SOF ± RBV efficacy for HCV GT1b infected subjects in the ALLY-1 and ALLY-2 trials, although the available data are limited, particularly for those with cirrhosis or F4 fibrosis.

3.4.3 HCV GT3 NS5A baseline resistance-associated amino acid polymorphisms

Due to the small number of HCV GT3 subjects enrolled, baseline data from ALLY-1 and ALLY-2 provided little additional information beyond what was previously reviewed for ALLY-3. Baseline data are available from 29 subjects across ALLY-1 and ALLY-2. Of these subjects, the following polymorphisms at DCV resistance-associated positions were observed:

- M28V: 1 subject treated with DCV/SOF for 8 weeks in ALLY-2, achieved SVR
- A30E/T/S/V: 3 subjects, 2 from ALLY-1 (both achieved SVR) and 1 subject treated with DCV/SOF for 8 weeks in ALLY-2 (relapse)
- S54A: 1 subject from ALLY-1, achieved SVR
- S62L/P/T: 9 subjects, 6 from ALLY-1 (5/6 achieved SVR), and 3 from ALLY-2 (2/3 SVR, 1 relapser treated with DCV/SOF for 8 weeks)

Importantly, no HCV GT3 subjects in ALLY-1 or ALLY-2 had virus with the NS5A Y93H polymorphism, which was the critical polymorphism associated with reduced DCV/SOF treatment efficacy in ALLY-3. Therefore, Baseline data from ALLY-1 and ALLY-2 provide no additional information to characterize the impact of the Y93H polymorphism on DCV/SOF efficacy, or to identify regimens (e.g., addition of RBV) that may overcome its impact. For reference, the Y93H data from ALLY-3 are shown in Table 15 (from Clinical Virology review of DCV NDA resubmission, SDN 36). The prevalence of the Y93H polymorphism in ALLY-3 was 13/148 (9%), and 13/177 (7%) across all three trials.

Table 15. SVR12 rate according to detection of Y93H polymorphism and cirrhosis status in clinical trial AI444218 (ALLY-3). No HCV GT3 subjects in ALLY-1/-2 had the NS5A Y93H polymorphism.

	n	# Failure	#SVR	SVR rate
All subjects:				
Y93H	13	6	7	54%
No Y93H	135	11	124	92%
Cirrhotic subjects:				
Y93H	4	3	1	25%
No Y93H	28	9	19	68%
Noncirrhotic subjects:				
Y93H	8	3	5	63%
No Y93H	97	1	96	99%
Pooling noncirrhotic/not reported (as "noncirrhotic" in label):				
Y93H	9	3	6	67%
No Y93H	107	2	105	98%

3.4.4 HCV NS5B baseline resistance-associated amino acid polymorphisms

As noted above, incomplete NS5B baseline nucleotide sequence data were obtained from subjects in the pooled ALLY-1 and ALLY-2 trials. Nevertheless, analyses were conducted to determine if there was an association between NS5B polymorphisms at 12 potential SOF resistance-associated amino acid positions (considering any change at D61, A/S112, N142, L159, E237, S282, C/F289, C316, L320, V321, Q355 or S/T473) and treatment outcome.

Among HCV GT1a infected subjects in the ALLY-1 and ALLY-2 trials, baseline NS5B sequence data were available for 62 subjects. Of these subjects, only 2 (3%) had virus with a polymorphism at an NS5B position of interest, including E237K (n=1) or Q355R (n=1). Both subjects had Child-Pugh B cirrhosis, received DCV/SOF + RBV for 12 weeks, and achieved SVR12. Excluding subjects with Child-Pugh C cirrhosis in ALLY-1 or subjects who received the 8-week treatment duration in ALLY-2, baseline NS5B data were reported for only 33 HCV GT1a infected subjects, including the two with the polymorphisms of interest noted above.

Among HCV GT1b infected subjects in the ALLY-1 and ALLY-2 trials, baseline NS5B sequence data were available for only 6 subjects, and none of these subjects had an NS5B amino acid polymorphism of interest. One of these subjects was from the ALLY-1 trial and had Child-Pugh C cirrhosis.

Among HCV GT3 infected subjects in the ALLY-1 and ALLY-2 trials, baseline NS5B sequence data were available for only 7 subjects, and none of these subjects had an NS5B amino acid polymorphism of interest. One of these subjects was from the ALLY-1 trial and had Child-Pugh C cirrhosis, and another subject received the 8-week treatment duration in ALLY-2.

Baseline NS5B sequence data from the ALLY-3 trial were available for 150 subjects with HCV GT3 infection. In the original Clinical Virology review of the ALLY-3 trial, it was concluded that no subjects had polymorphisms at amino acid positions L159, S282, C316, L320 or V321, including 7 subjects who previously were treated with a SOF-containing regimen. These data were re-analyzed considering the expanded list of 12 NS5B amino acid positions of interest. Note that 20 subjects (all achieved SVR12) had missing data at positions D61 and S112. Also, none of the 7 subjects who previously were treated with a SOF-containing regimen had a polymorphism or substitution at any of these positions (2 subjects missing data at positions D61 and S112). A total of 11 subjects had a polymorphism of interest including N142S/T (n=5), Q355H/R (n=3), or T473A/M (n=3). All but one of these subjects achieved SVR12; the one virologic failure subject (AI444218-1-85) had cirrhosis and the N142S polymorphism. Interestingly, the N142S polymorphism was no longer detected at the time of virologic failure, and no other treatment-emergent changes were observed at any of the NS5B positions of interest. Given that subject AI444218-1-85 had cirrhosis, which has a major impact on DCV/SOF efficacy for HCV GT3, and the fact that the polymorphism was no longer detected at the time of virologic failure, it is not possible to conclude that the N142S polymorphism affected treatment outcome.

Taken together, NS5B polymorphisms at potential SOF resistance-associated positions were infrequent among subjects with HCV GT1a, GT1b or GT3 infection in the ALLY-1, ALLY-2 and ALLY-3 trials, and when they were detected they were not clearly associated with treatment failure.

3.5 Reviewer's Perspective on Baseline Resistance Testing for NS5A Amino Acid Polymorphisms Associated with DCV Resistance

3.5.1 NS5A Polymorphism Screening for HCV GT1a Infected Patients with Cirrhosis

This reviewer recommends that HCV GT1a infected patients with cirrhosis who are considering treatment with DCV+SOF±RBV be screened for the presence of NS5A amino acid polymorphisms at positions M28, Q30, L31, or Y93. As described in Section 3.4.1, among HCV GT1a infected subjects with or without cirrhosis treated with DCV+SOF±RBV for 12 weeks in the ALLY-1 and ALLY-2 trials, SVR12 rates were 13/17 (76%) and 142/149 (95%) for those with or without NS5A amino acid polymorphisms at one of these four key positions associated with resistance to DCV and other NS5A inhibitors. Further subgroup analyses demonstrated that all four GT1a subjects with key DCV resistance-associated polymorphisms who experienced virologic failure had Child-Pugh A or B cirrhosis, and no subjects with Child-Pugh C cirrhosis had virus with one of these DCV resistance-associated polymorphisms. Considering those with Child-Pugh A or B cirrhosis in ALLY-1 and ALLY-2, SVR12 was achieved in 2/6 (33%) and 38/39 (97%) subjects with or without key DCV NS5A resistance-associated polymorphisms, respectively. In other words, of the 5 virologic failure subjects with Child-Pugh A/B cirrhosis who received DCV+SOF± RBV for 12 weeks, 4 of the 5 failures had virus with a key DCV resistance-associated polymorphism. Pooling subjects without cirrhosis or in the ALLY-1 Post-Transplant Cohort, SVR12 was achieved in 11/11 (100%) subjects with NS5A polymorphisms. Therefore, although the number of subjects is small, there was no signal of NS5A polymorphisms reducing DCV+SOF± RBV treatment efficacy in non-cirrhotic or post-transplant subjects.

These results raise concerns that DCV+SOF±RBV for 12 weeks has poor efficacy for HCV GT1a infected patients with cirrhosis and one or more NS5A amino acid polymorphisms at positions M28, Q30, L31, or Y93. It is challenging to draw major conclusions about treatment efficacy and provide treatment recommendations based on results from such a small number of subjects studied across two clinical trials (n=6). Nevertheless, these results were not entirely unexpected, as data from multiple other trials have demonstrated a clear impact of NS5A polymorphisms on DCV-based treatment efficacy in the context of other DCV-containing regimens or HCV genotypes/subtypes.

Numerous discussions were held with the review team to consider these results and the possibility of adding language to the DCV label that recommends pre-treatment NS5A resistance screening for HCV GT1a infected patients with cirrhosis. One approach that was considered was to describe the data in the Microbiology (12.4) section of the label, but due to the limited data provide no screening recommendation in Section 1 (Indications and Usage) or Section 2 (Dosage and Administration). However, this approach is not optimal because the primary argument against a screening recommendation is not the lack of a signal that NS5A polymorphisms reduce treatment efficacy, but rather the data showing this signal are limited, which is largely due to the relatively small size of the sponsor's clinical trial database for cirrhotic HCV GT1 infected patients treated with DCV+SOF± RBV. Furthermore, to illustrate how concerning these limited data are, if the number of cirrhotic HCV GT1a subjects with NS5A resistance-associated polymorphisms were doubled to include another 6 subjects, and all 6 subjects achieved SVR, the overall SVR rate for this population would increase only to 8/12 (67%), which is still concerning in the current era of HCV treatment in which GT1 SVR rates with approved or emerging treatment regimens are approaching near 100%, even in patients with cirrhosis.

The review team concluded that based on these limited data and the previous evidence that DCV-based treatment efficacy is often impacted by NS5A resistance-associated polymorphisms, there is sufficient rationale to include language prominently in the DCV label that recommends pre-treatment NS5A resistance screening for HCV GT1a infected patients with cirrhosis. Additional factors that contributed to this position include the following:

- HCV GT1a is the most common subtype in the U.S.
- Reasonable alternative treatment options that seem to be impacted less by NS5A polymorphisms are available (e.g., HARVONI™) or emerging (e.g., Curry et al., 2015; note that these data have not been independently reviewed).
- There were possible resistance consequences of virologic failure in those with NS5A polymorphisms that may impact subsequent re-treatment: Two of the four virologic failure subjects had additional treatment-emergent NS5A resistance-associated substitutions, and three subjects had treatment-emergent NS5B substitutions potentially associated with SOF resistance.
- There are possible clinical consequences of treatment failure in this population with more advanced liver disease.
- At least two assays are commercially available to identify NS5A polymorphisms in HCV GT1a virus isolates.

Also of note, another NDA currently under review for elbasvir/grazoprevir (EBR/GZR, NS3 protease inhibitor plus NS5A inhibitor, NDA 208261) showed that GT1a subjects with NS5A polymorphisms had reduced treatment efficacy, regardless of cirrhosis status, and the label for NDA 208261 will recommend screening for NS5A polymorphisms for the broader GT1a population. Based on currently available data, the 12-week DCV+SOF±RBV regimen would not be a reasonable alternative treatment option for cirrhotic HCV GT1a patients who do not use EBR/GZR due to the presence of NS5A polymorphisms.

The review team determined that the screening recommendation should be included in a subsection of Section 2 (Dosage and Administration) termed “2.1. Testing Prior to Initiation of Therapy” (or similar), with the following draft language:

> *“Consider screening for the presence of NS5A polymorphisms at amino acid positions M28, Q30, L31, and Y93 in patients with cirrhosis who are infected with HCV genotype 1a prior to the initiation of treatment with DAKLINZA and sofosbuvir with or without ribavirin [see Microbiology (12.4]), Table X].”*

Providing the screening consideration in Section 2.1 in this manner was preferred over a Limitation of Use statement in Section 1 (Indications and Usage). The review team was concerned about a Limitation of Use statement as this would strongly restrict the possible use of any DCV-containing regimen in HCV GT1a infected patients with cirrhosis and an NS5A polymorphism. Furthermore, to support such a strong recommendation ideally an FDA-approved test would be available, yet no NS5A sequence analysis tests are currently FDA-approved. The proposed language in Section 2.1 reflects the general limitations of the data and takes into account the lack of an FDA-approved NS5A polymorphism test. In addition, while the language provides guidance to promote the optimal use of DCV, it still potentially allows for the use of DCV in cirrhotic HCV GT1a infected patients with an NS5A polymorphism in circumstances when it remains a reasonable treatment choice in the opinion of the care provider. Note that the screening language for elbasvir/grazoprevir will similarly be placed in 2.1, and this consistent approach across both programs should help minimize confusion in practice.

During the review, we communicated to the sponsor our plans to add the screening language to the DCV label. The sponsor generally agreed with our concerns and the inclusion of the language in Section 2. However, the sponsor raised some concerns about the specific screening algorithm and proposed the screening focuses on specific individual NS5A amino acid polymorphisms that were either detected in HCV GT1a virologic failure subjects or confer a major phenotypic reduction in DCV anti-HCV activity in cell culture. The sponsor also considered data from trials in which DCV was administered with other DAAs. Consequently, the sponsor recommended screening only for the specific NS5A polymorphisms M28T, Q30H, L31M or Y93H/N.

While this reviewer agrees that certain specific polymorphisms are likely to have less of an impact than others on treatment efficacy, there should be clear clinical efficacy data to justify screening for the presence of a specific polymorphism but not other polymorphisms at the same position. Due to the sponsor's limited dataset, it is not possible to differentiate the impact of specific polymorphisms within a position. For example, the NS5A M28V polymorphism is relatively more common than other NS5A polymorphisms and by itself does not reduce DCV anti-HCV activity in cell culture, but only a single subject with cirrhosis had this polymorphism (achieved SVR12). Similarly, no HCV GT1a infected subjects in ALLY-1 or ALLY-2 with NS5A Q30 polymorphisms experienced virologic failure, but only a single subject had cirrhosis. We informed the sponsor that we are open to amending the screening algorithm in the label to identify specific polymorphisms of concern if supported by clinical efficacy data, and the sponsor has indicated a desire to collect and submit such data. In the meantime, as a conservative approach, and one that is less likely to be confusing in clinical practice, this reviewer strongly recommends including any polymorphism at position M28, Q30, L31, or Y93 in the screening language. This approach is further justified by (1) describing the available data in the Microbiology section of the label for transparency, and (2) including the screening consideration language in Section 2.1 of the label rather than as a Limitation of Use, which still allows DCV to be used at care providers' discretion. Of note, this approach and the specific NS5A amino acid positions are expected to be consistent with the screening language and data presentation in the elbasvir/grazoprevir label.

3.5.2 NS5A Polymorphism Screening for HCV GT3 Infected Patients

The NS5A Y93H polymorphism was a key factor associated with reduced efficacy of DCV+SOF in HCV GT3 infected subjects in ALLY-3, including in subjects with or without cirrhosis (see Table 15). No HCV GT3 subjects in ALLY-1 or ALLY-2 had virus with the NS5A Y93H polymorphism, so available data on the impact of the Y93H polymorphism are restricted to subjects in ALLY-3 who received DCV+SOF without RBV. During the original review of the ALLY-3 trial, the review team considered adding a Limitation of Use to statement in Section 1 (Indications and Usage) to restrict the use of DCV in HCV GT3 infected patients with the NS5A Y93H polymorphism. However, the review team ultimately decided to describe the data in the Microbiology (12.4) section of the label and not include a Limitation of Use statement. At the time, an assay to identify the Y93H polymorphism in HCV GT3 infected patients was not commercially available and it was unclear when one might become available, and drug resistance-related risks for subjects with the Y93H polymorphism appeared to be small in that additional major DCV resistance-associated substitutions did not emerge in virologic failures with the Y93H polymorphism. In addition, available alternative treatment options, such as SOF+RBV for 24 weeks or SOF+P/R for 12 weeks, were not considered ideal for all GT3 patients with the NS5A Y93H polymorphism.

During the review of these NDA supplements, the review team reconsidered whether to include a screening recommendation for the NS5A Y93H polymorphism for HCV GT3 infected patients, specifically in Section 2.1 as a pre-treatment testing "consideration" (similar to language for GT1a

patients with cirrhosis). We have been aware of at least two assays to detect the Y93H polymorphism in HCV GT3 infected patients that should be available in the near future, and indeed the sponsor recently informed the review team that one such assay has become available. However, the available alternative treatment options for such patients (e.g., SOF+RBV±Peg-IFNα) have not changed. Furthermore, given the suboptimal efficacy of DCV+SOF±RBV for 12 weeks in HCV GT3 infected subjects with cirrhosis, current HCV treatment guidelines recommend a 24-week treatment duration in this population; the impact of the Y93H polymorphism with this longer treatment duration is unknown (b) (4). Another emerging IFN-free, NS5A inhibitor-containing regimen may be impacted less by the NS5A Y93H polymorphism in GT3 based on a published study (Foster et al., 2015), but these data have not been independently and fully reviewed, and the impact of the Y93H polymorphism specifically in GT3 patients with cirrhosis is unclear.

This reviewer recommends that HCV GT3 infected patients who are considering treatment with DCV+SOF±RBV be screened for the presence of the NS5A Y93H polymorphism to optimize treatment decision-making if or when an optimal alternative treatment regimen becomes available. Given that an ideal, interferon-free alternative treatment regimen for HCV GT3 patients with NS5A Y93H is not approved, it is not critical that a prominent screening recommendation is included in the DCV label at this time. This issue will be revisited in the future as more data are obtained to guide the optimal treatment of HCV GT3 infected patients with the NS5A Y93H polymorphism.

Of note, unlike for GT1a, the totality of data across the ALLY-1, ALLY-2 and ALLY-3 trials would strongly support including only one specific amino acid polymorphism (Y93H) in an NS5A screening algorithm for GT3, as NS5A Y93H is the principal DCV resistance pathway in GT3. Furthermore, changes at this position other than Y93H are expected to be exceptionally rare. Based on an analysis of the entire GT3 ALLY-1/-2/-3 NS5A dataset, which includes data from 204 GT3 clinical isolates from 178 subjects (178 pre-treatment, 26 post-baseline), a polymorphism or substitution at NS5A amino acid position Y93 was detected in 31 isolates, and in all 31 cases only the Y93H variant was observed, with no other changes reported (apart from Y/H mixtures).

3.6 Persistence of Daclatasvir Resistance-Associated Amino Acid Substitutions

No long-term follow-up data are available from subjects who experienced virologic failure in the ALLY-1 or ALLY-2 trials regarding the long term persistence of DCV resistance-associated substitutions. A long-term follow-up study (AI444046) of subjects who received DCV-containing regimens in clinical trials is ongoing, but no data have been submitted from this study since the original DCV NDA 206843 submission (confirmed by the sponsor in SDN 108).

4. CONCLUSIONS

Pending final agreement on the label, Efficacy Supplements S-1, S-2 and S-3 for NDA 206843 are approvable from a Clinical Virology perspective for daclatasvir in combination with sofosbuvir, with or without ribavirin, for the treatment of chronic HCV genotype 1 or genotype 3 infection, including patients coinfected with human immunodeficiency virus (HIV-1), patients with compensated or decompensated cirrhosis, and patients with HCV recurrence after liver transplant.

5. PACKAGE INSERT

The final approved DCV package insert was not available at the time of finalization of this review.

5.1 Initial Package Insert Recommendations

Below is a "clean" version of key virology-related sections of the label that were edited by the Sponsor and Division and communicated to the sponsor on 12/23/2015. Due to the extensive edits the MS Word track changes format was not included in this review; see the track changes label communicated to the sponsor on 12/23/2015.

2 DOSAGE AND ADMINISTRATION
2.1 Testing Prior to Initiation of Therapy

NS5A Resistance Testing in HCV Genotype 1a Infected Patients with Cirrhosis
Consider screening for the presence of NS5A polymorphisms at amino acid positions M28, Q30, L31, and Y93 in patients with cirrhosis who are infected with HCV genotype 1a prior to the initiation of treatment with DAKLINZA and sofosbuvir with or without ribavirin *[see Microbiology (12.4)], Table XX*.

(b) (4)

12.4 Microbiology

Mechanism of Action
Daclatasvir is an inhibitor of NS5A, a nonstructural protein encoded by HCV. Daclatasvir binds to the N-terminus of NS5A and inhibits both viral RNA replication and virion assembly. Characterization of daclatasvir-resistant viruses, biochemical studies, and computer modeling data indicate that daclatasvir interacts with the N-terminus within Domain 1 of the protein, which may cause structural distortions that interfere with NS5A functions.

Antiviral Activity
Daclatasvir had median EC_{50} values of 0.008 nM (range 0.002-0.03 nM; n=35), 0.002 nM (range 0.0007-0.006 nM; n=30), and 0.2 nM (range 0.006-3.2 nM; n=17) against hybrid replicons containing genotypes 1a, 1b, and 3a subject-derived NS5A sequences, respectively, without detectable daclatasvir resistance-associated polymorphisms at NS5A amino acid positions 28, 30, 31, or 93. Daclatasvir activity was reduced against genotypes 1a, 1b, and 3a subject-derived replicons with resistance-associated polymorphisms at positions 28, 30, 31, or 93, with median EC_{50} values of 76 nM (range 4.6-2409 nM; n=5), 0.05 nM (range 0.002-10 nM; n=12), and 13.5 nM (range 1.3-50 nM; n=4). Similarly, the EC_{50} values of daclatasvir against 3 genotype 3b and 1 genotype 3i subject-derived NS5A sequences with polymorphisms (relative to a genotype 3a reference) at positions 30, 31, or 62 were ≥3620 nM.

Daclatasvir was not antagonistic with interferon alfa, HCV NS3/4A protease inhibitors, HCV NS5B nucleoside analog inhibitors, and HCV NS5B non-nucleoside inhibitors in cell culture combination antiviral activity studies using the cell-based HCV replicon system.

Resistance

In Cell Culture

HCV genotype 1a, 1b, and 3a replicon variants with reduced susceptibility to daclatasvir were selected in cell culture, and the genotype and phenotype of daclatasvir-resistant NS5A amino acid variants were characterized. Phenotypic analysis of stable genotype 1a (b) (4) replicons (b) (4) single NS5A M28T, Q30E, Q30H, Q30R, L31V, Y93C, Y93H and Y93N substitutions (b) (4) exhibited (b) (4) -fold reduced susceptibility to daclatasvir, respectively. For genotype 1b, L31V and Y93H single substitutions and L31M/Y93H and L31V/Y93H combinations exhibited (b) (4) -fold reduced susceptibility to daclatasvir, respectively. A P32-deletion (P32X) in genotype 1b reduced DCV susceptibility by >1,000,000-fold. For genotype 3a, single A30K, (b) (4) L31F, (b) (4) and Y93H substitutions exhibited (b) (4) -fold reduced susceptibility to daclatasvir, respectively.

In Clinical Studies

Among subjects with HCV genotype 1 or genotype 3 infection and treated in the ALLY-1, -2, and -3 trials with DAKLINZA and sofosbuvir with or without ribavirin for 12 weeks, 31 subjects (11 with genotype 1a, 1 with genotype 1b, and 19 with genotype 3) qualified for resistance analysis due to virologic failure. Post-baseline NS5A and NS5B population-based nucleotide sequence analysis results were available for 31 (b) (4) and 28 (b) (4) subjects, respectively.

Virus from all 31 subjects at the time of virologic failure harbored one or more of the following NS5A resistance-associated substitutions (including pre-existing amino acid polymorphisms or treatment-emergent substitutions): M28T, Q30H/K/R, L31M/V, H54R, H58D/P, or Y93C/N for genotype 1a subjects, P32-deletion (P32X) for the genotype 1b subject, and A30K/S, L31I, S62A/L/P/R/T, or Y93H for genotype 3 subjects. Among HCV genotype 1a virologic failure subjects, the most common NS5A amino acid substitutions occurred at position Q30 (Q30H/K/R; 73% [8/11], all treatment-emergent). Among HCV genotype 3 virologic failure subjects, the most common NS5A amino acid polymorphism or treatment-emergent substitution was Y93H (89% [17/19], treatment-emergent in 11 of 17 subjects).

For NS5B, 6 of 28 subjects at the time of virologic failure had virus with NS5B substitutions possibly associated with sofosbuvir resistance or exposure: A112T, L159F, E237G, Q355H (genotype 1a), or S282T+Q355H (genotype 3).

Persistence of Resistance-Associated Substitutions

Limited data for DAKLINZA and sofosbuvir regimens on the persistence of daclatasvir resistance-associated substitutions are available. In a separate long-term follow-up study of predominately HCV genotype 1-infected subjects treated with daclatasvir-containing regimens in phase 2/3 clinical trials, viral populations with treatment-emergent NS5A resistance-associated substitutions persisted at detectable levels for more than 1 year in most subjects.

Effect of Baseline HCV Amino Acid Polymorphisms on Treatment Response

Genotype 1a NS5A polymorphisms:

In HCV genotype 1a infected subjects with cirrhosis, the presence of an NS5A amino acid polymorphism at position M28, Q30, L31 or Y93 (defined as any change from reference identified by population-based nucleotide sequencing) was associated with reduced efficacy of DAKLINZA and sofosbuvir with or without ribavirin for 12 weeks in the ALLY-1 and ALLY-2 trials (see Table X). (b) (4) all (b) (4) subjects with baseline NS5A polymorphisms at these positions achieved SVR12. Based on an analysis of 1,026 HCV GT1a NS5A amino acid sequences from pooled clinical trials, the prevalence of polymorphisms at these positions was 11% overall, and xx% in the U.S. Due to limited sample sizes, insufficient data are available to determine the impact of specific NS5A polymorphisms on SVR12 rates. (b) (4) M28T/V (n=3), Q30H/L/R (n=5), L31M (n=1) and Y93C/H/S (n=4).

Table X: Impact of NS5A amino acid polymorphisms on SVR12 rates in subjects with HCV genotype 1a or genotype 3 infection in Phase 3 trials of DAKLINZA + sofosbuvir ± ribavirin

NS5A Polymorphisms	SVR12 Rates after 12 weeks of treatment with DAKLINZA + sofosbuvir ± ribavirin[a]	
	With NS5A polymorphism(s) % (n/N)	Without NS5A polymorphism(s) % (n/N)
HCV Genotype 1a Infected Subjects: M28*, Q30*, L31*, or Y93*	76% (13/17)	(b) (4)
Without cirrhosis	100% (11/11)	99% (100/101)
With cirrhosis	33% (2/6)	(b) (4)
HCV Genotype 3 Infected Subjects: Y93H	54% (7/13)	92% (b) (4)
Without cirrhosis	67% (6/9)	98% (b) (4)
With cirrhosis	25% (1/4)	(b) (4)

[a]HCV genotype 1a infected subjects received DAKLINZA + sofosbuvir ± ribavirin for 12 weeks in the ALLY-1 and ALLY-2 trials. HCV genotype 3 infected subjects received DAKLINZA + sofosbuvir for 12 weeks in the ALLY-3 trial; no data on the impact of Y93H are available for HCV genotype 3 infected subjects treated with DAKLINZA + sofosbuvir + ribavirin.
*Any change from genotype 1a reference.

(b) (4)

(b) (4)

Cross Resistance

Based on resistance patterns observed in cell culture replicon studies and HCV-infected subjects, cross-resistance between daclatasvir and other NS5A inhibitors is expected. Cross-resistance between daclatasvir and other classes of direct-acting antivirals is not expected. The impact of prior daclatasvir treatment experience on the efficacy of other NS5A inhibitors has not been studied. Conversely, the efficacy of DAKLINZA in combination with sofosbuvir has not been studied in subjects who have previously failed treatment with regimens that include an NS5A inhibitor.

5.2 Package Insert Revisions

(b) (4)

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

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APPENDIX A: Site-Directed Mutant Replicon Phenotype Analyses for Daclatasvir

(from previous Clinical Virology reviews of the Original NDA 206843 and resubmission)

HCV Genotype 1a

GT	NS5A Substitution	EC_{50} (nM)	FC EC_{50}	EC_{90} (nM)	FC EC_{90}	Rep. Capacity (%)	Comment
1a	WT (H77c)	0.006	1.0	0.020	1.0	100	
1a	M28A	20.0	3,333.3	70.0	3,500.0	27	
1a	M28I	0.006	1.0	0.020	1.0	200	
1a	M28T	3.0	500.0	8.0	400.0	31	
1a	M28V	0.006	1.0	0.040	2.0	16	
1a	Q30D	1,481.0	246,833.3	ND	ND	171	All Values >
1a	Q30E	111.0	18,500.0	232.0	11,600.0	130	
1a	Q30G	38.0	6,333.3	48.0	2,400.0	54	
1a	Q30H	6.5	1,083.3	11.0	550.0	75	
1a	Q30K	108.0	18,000.0	193.0	9,650.0	19	
1a	Q30N	6.6	1,100.0	9.7	485.0	11	
1a	Q30R	5.4	900.0	31.0	1,550.0	41	
1a	Q30T	0.1	15.0	0.2	10.0	122	
1a	L31I	1.0	166.7	1.5	75.0	34	
1a	L31M	1.5	250.0	4.0	200.0	55	
1a	L31V	15.0	2,500.0	42.0	2,100.0	117	
1a	H54C	0.003	0.5	0.010	0.5	76	
1a	H54N	0.000	0.1	0.008	0.4	46	
1a	H54Y	0.007	1.2	0.010	0.5	129	EC50 <
1a	H58C	0.003	0.5	0.009	0.5	49	
1a	H58D	2.2	366.7	4.9	245.0	92	
1a	H58N	0.008	1.3	0.030	1.5	136	
1a	H58P	0.005	0.8	0.030	1.5	266	
1a	H58Q	0.003	0.5	0.009	0.5	168	
1a	H58R	0.002	0.3	0.009	0.5	76	
1a	H58S	0.004	0.7	0.020	1.0	21	
1a	E62D	0.009	1.5	0.030	1.5	89	
1a	E62G	0.004	0.7	0.020	1.0	72	
1a	E62Q	0.005	0.8	0.020	1.0	96	
1a	E62V	0.010	1.7	0.1	2.5	76	
1a	Y93C	8.2	1,366.7	23.0	1,150.0	12	
1a	Y93F	0.4	66.7	0.6	30.0	489	
1a	Y93H	34.0	5,666.7	72.0	3,600.0	44	
1a	Y93N	209.0	34,833.3	446.0	22,300.0	13	
1a	Y93S	42.0	7,000.0	103.0	5,150.0	58	
1a	H58Y	0.003	0.5	0.009	0.5	96	
1a	M28A,Q30K	2,090.0	348,333.3	4,012.0	200,600.0	29	
1a	M28A,Q30R	1,262.0	210,333.3	2,000.0	100,000.0	45	EC90 >
1a	M28T,L31M	336.0	56,000.0	408.0	20,400.0	5	
1a	M28T,Q30H	461.0	76,833.3	817.0	40,850.0	32	
1a	M28T,Q30K	1,481.0	246,833.3	ND	ND	16	All Values >
1a	M28T,Q30R	264.0	44,000.0	409.0	20,450.0	76	
1a	M28T,Y93H	357.0	59,500.0	817.0	40,850.0	NA	
1a	M28V,L31M	3.5	583.3	4.9	245.0	87	
1a	M28V,Q30H	2.3	383.3	4.3	215.0	14	
1a	M28V,Q30K	20.0	3,333.3	55.0	2,750.0	41	
1a	M28V,Q30R	1.4	233.3	6.7	335.0	147	
1a	Q30E,E62V	263.0	43,833.3	599.0	29,950.0	138	
1a	Q30E,L31M	492.0	82,000.0	1,502.0	75,100.0	2	
1a	Q30E,Y93N	1,778.0	296,333.3	3,319.0	165,950.0	67	
1a	Q30H,L31M	45.0	7,500.0	75.0	3,750.0	96	
1a	Q30H,L31V	453.0	75,500.0	720.0	36,000.0	145	
1a	Q30H,Y93H	589.0	98,166.7	662.0	33,100.0	64	
1a	Q30H,Y93N	539.0	89,833.3	645.0	32,250.0	58	
1a	Q30K,L31M	1,036.0	172,666.7	1,557.0	77,850.0	80	

GT	NS5A Substitution	EC_{50} (nM)	FC EC_{50}	EC_{90} (nM)	FC EC_{90}	Rep. Capacity (%)	Comment
1a	**WT (H77c)**	**0.006**	**1.0**	**0.020**	**1.0**	**100**	
1a	Q30L,Y93H	3.5	583.3	10.0	500.0	NA	
1a	Q30R,H58D	1,867.0	311,166.7	10,000.0	500,000.0	60	EC90 >
1a	Q30R,L31M	868.0	144,666.7	2,000.0	100,000.0	54	EC90 >
1a	Q30R,L31V	2,000.0	333,333.3	2,000.0	100,000.0	91	All Values >
1a	Q30R,Y93C	85.0	14,166.7	150.0	7,500.0	13	
1a	Q30R,Y93H	316.0	52,666.7	846.0	42,300.0	6	
1a	L31M,H58D	295.0	49,166.7	871.0	43,550.0	41	
1a	L31M,Y93C	464.0	77,333.3	604.0	30,200.0	192	
1a	L31V,H58P	54.0	9,000.0	168.0	8,400.0	100	
1a	L31V,H58R	0.7	116.7	1.1	55.0	112	
1a	L31V,Y93C	2,000.0	333,333.3	2,000.0	100,000.0	NA	All Values >
1a	L31V,Y93H	741.0	123,500.0	741.0	37,050.0	20	All Values >
1a	H54Y,Y93H	35.0	5,833.3	74.0	3,700.0	170	
1a	E62D,Y93C	6.6	1,100.0	9.1	455.0	97	
1a	M28V,H58P,E62(?)	0.005	0.8	0.020	1.0	168	
1a	M28T,Q30K,L31M	5,000.0	833,333.3	5,000.0	250,000.0	0.5	All Values >
1a	M28T,Q30R,H54Y	104.0	17,333.3	125.0	6,250.0	2	
1a	Q30E,L31M,H58P	638.0	106,333.3	1,244.0	62,200.0	9	
1a	Q30H,E62V,Y93H	421.0	70,166.7	513.0	25,650.0	14	
1a	Q30R,L31M,H54C	359.0	59,833.3	444.0	22,200.0	32	
1a	Q30R,L31M,Y93C	1,277.0	212,833.3	1,811.0	90,550.0	53	
1a	Q30R,L31M,Y93N	5,000.0	833,333.3	5,000.0	250,000.0	35	All Values >
1a	Q30R,L31V,H58P	1,959.0	326,500.0	4,302.0	215,100.0	57	
1a	Q30R,L31V,Y93C	2,000.0	333,333.3	2,000.0	100,000.0	NA	All Values >
1a	L31M,H58P,Y93C	513.0	85,500.0	608.0	30,400.0	13	
1a	M28V,H58P,E62D,Y93C	0.4	66.7	0.9	45.0	225	

FC, fold-change; WT, wild-type

HCV Genotype 1b

GT	NS5A Substitution	EC_{50} (nM)	FC EC_{50}	EC_{90} (nM)	FC EC_{90}	Rep. Capacity (%)	Comment
1b	**WT (Con1)**	**0.003**	**1.0**	**0.005**	**1.0**	**100**	
1b	L28I	0.009	3.0	0.030	6.0	126	
1b	L28M	0.004	1.3	0.010	2.0	122	
1b	L28V	0.007	2.3	0.030	6.0	78	
1b	P29X	5,000.0	1,666,666.7	5,000.0	1,000,000.0	NA	All Values >
1b	R30G	0.3	100.0	1.1	220.0	65	
1b	R30H	0.020	6.7	0.1	20.0	39	
1b	R30K	0.003	1.0	0.010	2.0	261	
1b	R30L	0.001	0.3	0.006	1.2	29	
1b	R30Q	0.002	0.7	0.007	1.4	24	
1b	L31F	0.009	3.0	0.1	16.0	147	
1b	L31I	0.003	1.0	0.009	1.8	54	
1b	L31M	0.008	2.7	0.030	6.0	100	
1b	L31V	0.1	33.3	0.5	100.0	55	
1b	P32X	5,000.0	1,666,666.7	5,000.0	1,000,000.0	30	All Values >
1b	Q54H	0.003	1.0	0.010	2.0	85	
1b	Q54L	0.001	0.3	0.004	0.8	80	
1b	Q54N	0.003	1.0	0.010	2.0	83	
1b	Q54Y	0.004	1.3	0.010	2.0	90	
1b	P58A	0.002	0.7	0.009	1.8	118	
1b	P58L	0.001	0.3	0.003	0.6	37	
1b	P58S	0.002	0.7	0.008	1.6	121	
1b	P58T	0.003	1.0	0.010	2.0	203	
1b	Q62A	0.002	0.7	0.007	1.4	99	
1b	Q62E	0.003	1.0	0.006	1.2	99	
1b	Q62H	0.003	1.0	0.010	2.0	68	
1b	Q62N	0.002	0.7	0.007	1.4	69	
1b	Q62R	0.003	1.0	0.010	2.0	39	
1b	Q62S	0.003	1.0	0.010	2.0	107	

GT	NS5A Substitution	EC_{50} (nM)	FC EC_{50}	EC_{90} (nM)	FC EC_{90}	Rep. Capacity (%)	Comment
1b	**WT (Con1)**	**0.003**	**1.0**	**0.005**	**1.0**	**100**	
1b	A92E	0.004	1.3	0.020	4.0	17	
1b	A92T	0.003	1.0	0.007	1.4	60	
1b	A92V	0.001	0.3	0.006	1.2	98	
1b	Y93C	0.006	2.0	0.040	8.0	62	
1b	Y93F	0.002	0.7	0.010	2.0	436	
1b	Y93H	0.1	30.0	0.5	100.0	5	
1b	Y93N	0.1	33.3	1.0	200.0	19	
1b	Y93S	0.020	6.7	0.1	14.0	160	
1b	L28I,R30Q	0.020	6.7	0.1	10.0	33	
1b	L28M,R30L	0.003	1.0	0.020	4.0	49	
1b	L28M,R30Q	0.003	1.0	0.030	6.0	2	
1b	L28M,Y93H	3.0	1,000.0	11.0	2,200.0	70	
1b	L28V,R30Q	0.001	0.3	0.003	0.6	2	
1b	R30H,Y93H	8.0	2,666.7	46.0	9,200.0	24	
1b	R30L,L31M	0.009	3.0	0.020	4.0	75	
1b	R30Q,A92K	231.0	77,000.0	631.0	126,200.0	49	
1b	R30Q,L31M	0.1	16.7	0.1	20.0	71	
1b	R30Q,Q54H	0.001	0.3	0.004	0.8	231	
1b	R30Q,Y93H	0.6	200.0	1.4	280.0	146	
1b	R30Q,Y93S	0.1	23.3	0.2	40.0	224	
1b	L31F,P32X	5,000.0	1,666,666.7	5,000.0	1,000,000.0	12	All Values >
1b	L31F,Y93H	15.0	5,000.0	ND	ND	29	
1b	L31I,A92V	0.003	1.0	0.010	2.0	65	
1b	L31I,Y93H	5.0	1,666.7	20.0	4,000.0	6	
1b	L31M,A92K	3,844.0	1,281,333.3	5,000.0	1,000,000.0	26	EC90 >
1b	L31M,P58L	0.6	200.0	2.6	520.0	37	
1b	L31M,P58S	0.1	30.0	0.4	80.0	36	
1b	L31M,Q54H	0.004	1.3	0.020	4.0	111	
1b	L31M,Y93H	48.0	16,000.0	137.0	27,400.0	53	
1b	L31M,Y93N	86.0	28,666.7	407.0	81,400.0	16	
1b	L31V,Y93H	101.0	33,666.7	349.0	69,800.0	10	
1b	Q54H,Q62E	0.001	0.3	0.006	1.2	137	
1b	Q54H,Y93H	0.020	6.7	0.3	60.0	23	
1b	Q54H,Y93S	0.008	2.7	0.1	12.0	279	
1b	Q54Y,Y93H	0.2	66.7	0.5	100.0	25	
1b	P58L,Y93H	0.7	233.3	3.1	620.0	24	
1b	P58S,A92T	0.001	0.3	0.005	1.0	43	
1b	Q62E,Y93H	0.1	33.3	0.4	80.0	36	
1b	A92T,Y93H	0.1	33.3	0.6	120.0	2	
1b	L28I,R30P,P32F	234.0	78,000.0	727.0	145,400.0	12	
1b	L28I,R30Q,P32L	104.0	34,666.7	429.0	85,800.0	3	
1b	L28M,R30L,Q54H	0.001	0.3	0.003	0.6	18	
1b	L28M,R30Q,A92K	3,932.0	1,310,666.7	5,000.0	1,000,000.0	49	EC90 >
1b	L28M,R30Q,A92T	0.005	1.7	0.030	6.0	16	
1b	L28M,R30Q,Y93H	5,000.0	1,666,666.7	5,000.0	1,000,000.0	5	All Values >
1b	L28M,R30Q,Y93S	2.0	666.7	8.0	1,600.0	9	
1b	L28T,R30Q,Y93H	125.0	41,666.7	841.0	168,200.0	2	
1b	L28V,R30Q,Y93H	8.3	2,766.7	37.0	7,400.0	42	
1b	P29S,R30Q,Y93S	649.0	216,333.3	1,665.0	333,000.0	NA	
1b	R30H,P58S,Y93H	18.0	6,000.0	78.0	15,600.0	22	
1b	R30Q,L31F,Y93H	155.0	51,666.7	1,421.0	284,200.0	NA	
1b	R30Q,L31M,Y93H	61.0	20,333.3	270.0	54,000.0	88	
1b	R30Q,Q54H,A92K	26.0	8,666.7	213.0	42,600.0	36	
1b	L31F,Q54H,Y93H	19.0	6,333.3	163.0	32,600.0	161	
1b	L31I,A92V,Y93H	11.0	3,666.7	56.0	11,200.0	15	
1b	L31I,P58S,Y93H	164.0	54,666.7	234.0	46,800.0	16	
1b	L31M,A92V,Y93H	58.0	19,333.3	160.0	32,000.0	22	
1b	L31M,P58A,Y93H	195.0	65,000.0	556.0	111,200.0	7	
1b	L31M,P58G,Y93H	4,061.0	1,353,666.7	5,000.0	1,000,000.0	17	EC90 >
1b	L31M,P58L,Y93H	39.0	13,000.0	127.0	25,400.0	12	
1b	L31M,P58S,Y93H	212.0	70,666.7	437.0	87,400.0	10	
1b	L31M,Q54H,A92E	0.3	100.0	1.4	280.0	33	
1b	L31M,Q54H,Y93H	12.7	4,233.3	58.0	11,600.0	88	

GT	NS5A Substitution	EC_{50} (nM)	FC EC_{50}	EC_{90} (nM)	FC EC_{90}	Rep. Capacity (%)	Comment
1b	WT (Con1)	0.003	1.0	0.005	1.0	100	
1b	L31M,Q54Y,Y93H	19.4	6,466.7	91.0	18,200.0	41	
1b	L31V,P58A,Y93H	612.0	204,000.0	1,000.0	200,000.0	12	EC90 >
1b	L31V,P58S,Y93H	421.0	140,333.3	2,225.0	445,000.0	17	
1b	L31V,Q54H,Y93H	26.0	8,666.7	122.0	24,400.0	31	
1b	L31V,Q54Y,Y93H	76.0	25,333.3	331.0	66,200.0	4	
1b	L31V,Q62E,Y93H	202.0	67,333.3	623.0	124,600.0	87	
1b	Q54H,P58A,Q62E	0.002	0.7	0.007	1.4	176	
1b	Q54H,P58S,A92K	49.0	16,333.3	104.0	20,800.0	15	
1b	Q54H,P58S,Y93H	0.6	200.0	6.5	1,300.0	42	
1b	L28M,L31V,P58S,Y93N	5,000.0	1,666,666.7	5,000.0	1,000,000.0	28	All Values >
1b	L28M,R30H,L31V,Y93H	5,000.0	1,666,666.7	5,000.0	1,000,000.0	21	All Values >
1b	L28M,R30H,Q54H,Y93H	115.0	38,333.3	656.0	131,200.0	20	
1b	L28M,R30Q,L31I,Y93H	583.0	194,333.3	1,709.0	341,800.0	21	
1b	L28M,R30Q,L31V,Y93H	1,672.0	557,333.3	3,637.0	727,400.0	NA	
1b	L28M,R30Q,Q54H,A92T	0.002	0.7	0.007	1.4	46	
1b	R30Q,L31M,P58S,Y93H	132.0	44,000.0	867.0	173,400.0	2.5	
1b	R30Q,L31M,Q54H,Y93H	14.0	4,666.7	123.0	24,600.0	154	
1b	R30Q,L31V,P58S,Y93H	229.0	76,333.3	909.0	181,800.0	9.7	
1b	L31I,Q54H,P58S,Y93H	42.0	14,000.0	278.0	55,600.0	95	
1b	L31M,Q54H,A92E,Y93H	340.0	113,333.3	1,499.0	299,800.0	32	
1b	L31M,Q54H,A92V,Y93H	13.0	4,333.3	68.0	13,600.0	12	
1b	L31M,Q54H,P58S,Y93H	53.0	17,666.7	510.0	102,000.0	35	
1b	L31M,Q54H,Q62E,Y93H	28.0	9,333.3	134.0	26,800.0	46	
1b	L31M,Q54Y,P58S,Y93H	150.0	50,000.0	757.0	151,400.0	21	
1b	L31V,Q54H,P58S,Y93H	334.0	111,333.3	1,239.0	247,800.0	11	
1b	L31V,Q54H,Q62D,Y93H	94.0	31,333.3	318.0	63,600.0	203	
1b	L31V,Q54H,Q62E,Y93H	95.0	31,666.7	308.0	61,600.0	34	

FC, fold-change; WT, wild-type

HCV Genotype 3

GT	NS5A Substitution	EC_{50} (nM)	FC EC_{50}	EC_{90} (nM)	FC EC_{90}	Rep. Capacity (%)
3a	WT (AI444031-30-154)	0.3	1	0.5	1	100
3a	M28V	0.006	<0.1	0.019	<0.1	125
3a	A30E	335	1117	501	1002	5
3a	A30K	35	117	53	106	98
3a	A30S	0.6	2	1.3	3	34
3a	A30T	0.2	1	0.44	1	40
3a	A30V	0.023	0.1	0.074	0.1	155
3a	L31F	80	320	ND	ND	153
3a	L31I	72	240	101	202	84
3a	L31M	209	697	330	660	138
3a	S54T	0.4	1	0.9	2	60
3a	S54W	0.3	1	0.5	1	130
3a	S54Y	ND	ND	ND	ND	ND
3a	P58A	0.6	2	1	2	33
3a	P58S	0.2	1	0.5	1	16
3a	S62A	0.4	1	0.8	2	88
3a	S62D	0.6	2	1.1	2	139
3a	S62I	0.6	2	0.9	2	198
3a	S62L	0.3	1	0.7	1	125
3a	S62N	1.2	4	2	4	75
3a	S62P	ND	ND	ND	ND	ND
3a	S62Q	0.9	3	1.7	3	82
3a	S62T	0.7	2	1.3	3	70
3a	S62V	ND	ND	ND	ND	ND
3a	E92A	0.005	0	0.02	0	95
3a	E92D	4.6	15	7.2	14	NA
3a	Y93H	1120	3733	1369	2738	35
3a	A30E,S62T	375	1250	606	1212	6

3a	A30K,L31M	3640	12133	4306	8612	31
3a	A30K,P58A	68	227	114	228	17
3a	A30K,S62A	39	130	60	120	20
3a	A30K,S62I	105	350	162	324	22
3a	A30K,S62L	111	370	161	322	27
3a	A30K,S62P	158	527	219	438	10
3a	A30K,S62T	143	477	189	378	14
3a	A30K,S62V	125	417	225	450	47
3a	A30K, E92D	347	1157	1002	2004	ND
3a	A30S,S62T	1.8	6	3.4	7	42
3a	A30T,S62P	1.1	4	2.2	4	23
3a	A30T,S62T	0.4	1	0.6	1	115
3a	A30V,Y93H	4.6	15	9.3	19	52
3a	S54A,Y93H	1308	4360	2115	4230	14
3a	P58R,S62V	ND	ND	ND	ND	ND
3a	P58S, Y93H	1784	5947	2833	5666	9
3a	S62A, Y93H	1447	4823	1662	3324	43
3a	S62I,Y93H	1412	4707	3172	6344	35
3a	S62L, Y93H	3083	10277	4342	8684	18
3a	S62R,Y93H	304	1013	494	988	14
3a	S62T,Y93H	1355	4517	1688	3376	23
3a	E92A,Y93H	135	450	263	526	108
3a	M28V,S62P,Y93H	545	1817	746	1492	7
3a	A30S,S62A,Y93H	359	1197	569	1138	19
3a	A30V,S62P,Y93H	27	90	54	108	20
FC, fold-change; ND, not determined						

APPENDIX B: HCV genotype 1a infected subjects in ALLY-1 and ALLY-2 with key DCV resistance-associated polymorphisms in NS5A (positions M28, Q30, L31 or Y93)

USUBJID	TREATMENT	HCVHIST	CIRR CAT.	CP-CAT	BL HCV RNA (log10)	Tx Outcome	K24	**M28**	**Q30**	**L31**	H54	H58	E62	A92	**Y93**
AI444215-1-37	D/S/R 12W	P/R EXP	Cirrhotic	B	6.4	Relapse				M					
AI444215-2-26	D/S/R 12W	NAÏVE	Post-transplant		6.7	SVR		V							
AI444215-2-70	D/S/R 12W	NAÏVE	Post-transplant		6 3	SVR		T	R						
AI444215-3-43	D/S/R 12W	P/R EXP	Cirrhotic	B	6.1	SVR		V							
AI444215-3-94	D/S/R 12W	P/R EXP	Cirrhotic	B	6.1	Relapse				M		H/P			
AI444215-4-102	D/S/R 12W	P/R EXP	Cirrhotic	A	7.1	Relapse		T							
AI444215-4-31	D/S/R 12W	NAÏVE	Cirrhotic	B	6 3	SVR			R						
AI444216-1-95	D/S 8W	NAÏVE	Non-cirrhotic		6 2	SVR		V/M							
AI444216-10-114	D/S 12W	NAÏVE	Non-cirrhotic		7.6	SVR			Q/H						
AI444216-22-171	D/S 12W	NAÏVE	Non-cirrhotic		6.7	SVR			Q/R						
AI444216-25-163	D/S 12W	NAÏVE	Cirrhotic	Comp.	7 0	Relapse									Y/N
AI444216-26-36	D/S 12W	NAÏVE	Non-cirrhotic		7 0	SVR		V	L						
AI444216-29-153	D/S 12W	NAÏVE	Non-cirrhotic		7.1	SVR									C/Y
AI444216-31-43	D/S 12W	NAÏVE	Non-cirrhotic		6.6	SVR									Y/S
AI444216-34-53	D/S 12W	SOF EXP	Non-cirrhotic		6 2	SVR			H						
AI444216-5-5	D/S 12W	NAÏVE	Non-cirrhotic		5 8	SVR				M/L					
AI444216-6-203	D/S 8W	NAÏVE	Non-cirrhotic		7.1	SVR			L/Q			P/H			H/Y/L
AI444216-9-159	D/S 12W	NAÏVE	Non-cirrhotic		6.7	SVR									Y/C
AI444216-9-168	D/S 12W	NAÏVE	Non-cirrhotic		7 3	SVR					H/Y			A/P	Y/H

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/s/

PATRICK R HARRINGTON
01/14/2016

JULIAN J O REAR
01/15/2016

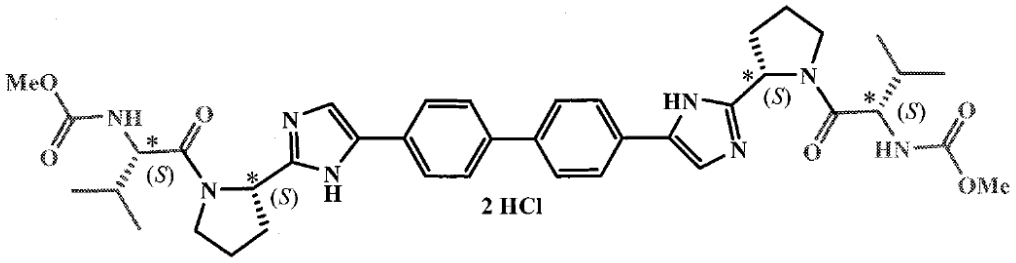
VIROLOGY REVIEW
DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
NDA 206843 SDN 68; Review Completed: 11/30/15

Reviewer: LALJI MISHRA, Ph.D.
Date Submitted: 08/05/15
Date Received: 08/05/15
Date Assigned: 08/05/15

Sponsor: Bristol-Myers Squibb Company
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660
Charles D. Wolleben, Ph.D.
203-677-3817
203-677-3818 (FAX)

Product Names:
Proprietary: Daklinza
Non-proprietary: BMS-790052, daclatasvir
Chemical Names: [(1,1'-biphenyl]-4,4'-diylbis[1*H*-imidazole-4,2-diyl(2*S*)-2,1-pyrrolidinediyl[(1*S*)-1-(1-methylethyl)-2-oxo-2,1-ethanediyl]]]bis-carbamic acid, dimethyl ester, dihydrochloride

Structure:



BMS-790052

Molecular formula: $C_{40}H_{50}N_8O_6 \bullet 2HCl$
Molecular weight (free base): 738.88
Drug category: Antiviral
Indication: Treatment of hepatitis C virus genotype (GT)-1a, GT-1b and GT-3 infected subjects with compensated or decompensated cirrhosis, and those with HCV recurrence after liver transplantation and those coinfected with human immunodeficiency virus (HIV-1)

Dosage Form/Route of administration: Oral solution

Additional submissions reviewed:

Submission #	Date of Correspondence	Date of Receipt	Date Assigned
N206843 SDN 069	08/05/15	08/05/15	08/05/15

N205843 SDN 084	09/01/15	09/01/15	09/04/15
N206843 SDN 085	09/03/15	09/03/15	09/04/15
N206843 SDN 094	09/22/15	09/22/15	09/24/15

BACKGROUND

BMS has submitted supplements S-001. S-002 and S-003 to NDA 206843 and seeks marketing approval of daclastasvir (DCV) in combination with sofosbuvir (SFV) with or without ribavirin (RBV) for the treatment of chronic hepatitis C virus genotype (GT)-1a, GT-1b and GT-3 infected subjects with compensated or decompensated cirrhosis, and those with HCV recurrence after liver transplantation and those co-infected with human immunodeficiency virus (HIV-1). Daclatasvir in combination with sofosbuvir was approved for the treatment of chronic hepatitis C virus, genotype 3 infection on July 24, 2015.

In support of the proposed indication, BMS has submitted results of clinical studies AI444215 (ALLY-1; patients with compensated or decompensated cirrhosis, and those with HCV recurrence after liver transplantation and AI444216 (ALLY-2; HIV/HCV coinfection) to NDA 206843 S-001, S-002 and S-003, respectively. Additionally, BMS has submitted addendum 01 to the final clinical study report for Study AI444218.

AI444215 (ALLY-1) was an open-label, study of 12 weeks of DCV/SOF/RBV therapy in subjects with cirrhosis (Child-Pugh class A, B, or C) or who had HCV recurrence post-liver transplant. Treatment-naive or treatment-experienced subjects with HCV GT-1, -2, -3, -4, or -6 were treated.

AI444216 (ALLY-2, HCV/HIV-1 coinfection) was an open-label, Phase 3 study of 8 or 12 weeks of DCV/SOF therapy without RBV (and with or without concomitant cART) in HCV treatment-naive or treatment-experienced subjects with HCV/HIV-1 co-infection.

AI444218 (ALLY-3) was an open-label, 2-cohort, Phase 3 study evaluating 12 weeks of therapy with DCV and SOF without RBV in treatment-naive and treatment-experienced subjects infected with hepatitis C virus GT-3.

For efficacy and safety analyses of the above mentioned clinical studies, please see review of Statistical Reviewer Wen Zeng, Ph.D. and Medical Officer Wendy Carter, D.O. For review of clinical virology including resistance analyses, please see review of Virology Reviewer Pat Harrington, Ph.D.

The sponsor has referred to the original NDA submission for non-clinical studies. Non-clinical virology and Phase II clinical virology reports submitted in support of the NDA 206843 were previously reviewed (Virology review of NDA 206843 SDN 001 dated 07/08/14). BMS submitted additional data on the antiviral activity of DCV against HCV genotypes 1a, 1b, 2, 3a, 3b, 4, 5 and 6 in the resubmitted NDA 206843. These HCV isolates were derived from the

clinical specimens. These data were reviewed previously (see Virology Review of NDA 206843 SDN 36 dated 06/02/15). The proposed label is reviewed here. Deletions are marked in red font strikethrough. Insertions are shown in blue font.

Proposed Label (08/05/15) version.

(b) (4)

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

(b) (4)

RECOMMENDATION

With respect to virology, the sponsor is requested to incorporate proposed changes in the final version of the label.

_____

Lalji Mishra, Ph.D.
Microbiologist, HFD-530

Concurrence

Julian O'Rear, Ph.D._____Signature _____Date
HFD-530/Micro TL

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/s/

LALJI MISHRA
12/21/2015

JULIAN J O REAR
12/21/2015