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APPLICATION NUMBER:

206843Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA Resubmission
Application Number(s) 206-843
Priority or Standard N/A

Submit Date(s) February 13, 2015
Received Date(s) February 13, 2015
PDUFA Goal Date August 13, 2015
Division / Office DAVP/OAP

Reviewer Name(s) Wendy Carter, D.O.
Review Completion Date June 29, 2015

Established Name Daclatasvir (DCV)
(Proposed) Trade Name Daklinza
Therapeutic Class DCV: NS5A replication inhibitor

Applicant Bristol-Myers Squibb Company
Formulation(s) DCV 30 mg and 60 mg tablets
Dosing Regimen DCV 60 mg once daily by oral route

Indication(s) DCV in combination with sofosbuvir for treatment of chronic hepatitis C genotype 3 in adults

Intended Population(s) Adult patients (18 years and older) with genotype 3 chronic hepatitis C virus infection

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

After clinical review of this resubmission NDA, I recommend approval of daclatasvir (DCV) 60 mg once daily in combination with sofosbuvir (SOF; Solvaldi[®]) 400mg once daily for treatment of adult patients with genotype 3 chronic hepatitis C virus (HCV) infection. This recommendation is based on data contained in the NDA resubmission 206843.

The efficacy and safety of DCV/SOF for 12 weeks in HCV genotype 3 is demonstrated in the phase 3 trial AI444218 (ALLY-3). In addition, DCV efficacy has been demonstrated in combination with other anti-hepatitis C treatment in various HCV genotypes; however, in regimens for which the Applicant is not seeking indications. The safety database for the resubmission NDA was 868 subjects (363 subjects received DCV/SOF ± RBV and 505 subjects received DCV/pegINF/RBV). Additionally, 1265 subjects were exposed to DCV 60 mg once daily for 24 weeks in the phase 3 trials (DCV in combination with asunaprevir (ASV) [DUAL] regimen and DCV/ASV/pegylated interferon and ribavirin [QUAD] regimens) in the original NDA; for a total of 2,133 subjects from the pivotal and supportive clinical trials in the original and resubmission NDAs. The total safety database from the DCV clinical development program is greater than 7,900 DCV-exposed subjects. Additionally more than 4,800 patients have been exposed to DCV under expanded access programs and an estimated 25,466 post-marketing patients have been exposed to DCV, predominately in Japan. The overall risk benefit for DCV is favorable and no safety issues or deficiencies in the NDA application have been identified that would preclude the approval.

1.2 Risk Benefit Assessment

The overall risk benefit assessment is favorable for DCV. This assessment is based upon the demonstrated efficacy results of DCV/SOF and the observed safety profile of DCV alone and in combination with SOF as an interferon- and ribavirin-free, once daily treatment regimen for adults with chronic HCV genotype 3.

Efficacy

The efficacy of DCV/SOF in subjects with chronic HCV genotype 3 is demonstrated in the phase 3 trial ALLY-3. The primary efficacy endpoint is sustained virologic response, defined as HCV RNA less than the lower limit of quantification (LLOQ) 12 weeks after discontinuation of treatment (SVR12). Overall, SVR12 was achieved in 135/152 (89%

with 95% confidence interval (CI) of (83%, 93%)) of treated subjects. Given the single arm design of ALLY-3, the demonstration of efficacy was determined by comparing to historical SVR12 rates for the current standard of care (SOC) for HCV genotype 3. A non-inferiority (NI) margin was calculated by FDA statisticians using various historical treatment regimens to provide comparisons (see Section 6) and demonstrate the efficacy of the regimen. The overall SVR12 rate difference between DCV/SOF for 12 weeks and current approved standard of care treatment for HCV genotype 3 (SOF/RBV for 24 weeks) is 3% with 95% CI of (-4%,9%). The lower bound of the 95% CI is -4%, which is less than the determined lowest NI margin of 17%; therefore, even without clinical consideration for a shorter treatment duration or a RBV-free regimen, the results demonstrate that DCV/SOF for 12 weeks is non-inferior to SOF/RBV for 24 weeks duration. Further discussions of these analyses are in Section 6 Review of Efficacy.

A limitation of the efficacy data is identified for the subpopulation of subjects with baseline cirrhosis. SVR12 rates were approximately 30% lower among subjects with baseline cirrhosis compared to subjects without baseline cirrhosis; however, this comparison is based on a limited number of subjects with cirrhosis (n=32). The SVR12 rate for subjects with baseline cirrhosis was 63% (20/32) with 95% CI of (44%, 79%), and was 96% (115/120) with 95% CI of (91%, 99%) for subjects without baseline cirrhosis. A total of 11 subjects had indeterminate or missing cirrhosis status; these subjects were included in the non-cirrhotic cohort as a more conservative clinical approach rather than excluding them from the analyses. This difference in SVR12 rates between subjects with cirrhosis and those without cirrhosis suggests that the DCV/SOF 12 week duration regimen may not be the optimal regimen for subjects with baseline cirrhosis. However, despite the lower SVR rates for subjects with baseline cirrhosis, the SVR12 rates are generally comparable to the SVR rates attained with treatment with the SOC regimen SOF/RBV for 24 weeks; both the data from ALLY-3 and the data supporting the SOF/RBV regimen in subjects with cirrhosis are limited by small sample sizes.

Resistance-associated baseline polymorphisms impact the efficacy of some direct acting antiviral therapy. For DCV/SOF, there is a clear impact on SVR12 rates for those with the NS5A resistance-associated polymorphism Y93H at baseline, regardless of baseline cirrhosis status. Because the presence of the Y93H baseline polymorphism is a key factor associated with reduced efficacy of DCV/SOF in HCV genotype 3 subjects in ALLY-3, these data will be described in Sections 12.4 (Microbiology) in the product label. The review team considered a Limitations of Use statement in the product label regarding the reduction in SVR associated with the Y93H baseline polymorphism and a recommendation to consider pre-screening. However, because currently there is no commercially available screening test for the Y93H baseline polymorphism in genotype 3 HCV and because the prevalence of the Y93H baseline polymorphism is limited to a small subset of the overall HCV population [the prevalence of the genotype 3 in the US is approximately 10% and the prevalence of the baseline Y93H polymorphism in ALLY-

3 is 9%], it was unclear how clinicians would incorporate this information into clinical decision making. Ultimately, the decision was to provide the data in the Microbiology section of the label, which would allow for its clinical use should a commercial test become available.

Safety

The observed safety profile of DCV/SOF is favorable. Safety data were evaluated from 868 subjects from phase 2 and 3 clinical trials provided in support of this DCV NDA resubmission. Safety data were reviewed in the original NDA from 1265 subjects in the phase 3 DUAL and QUAD trials who were exposed to DCV 60 mg once daily for 24 weeks. In addition evaluation of safety data was made from over 7,900 DCV-exposed subjects (as of end of November 2014) in the overall DCV clinical development program and the more than 4,800 patients who were exposed to DCV under expanded access programs and the estimated 25,466 post-marketing patients, primarily from Japan.

In ALLY-3 (n=152), there were no deaths, no discontinuations due to AEs and only one unrelated on-treatment SAE of GI hemorrhage (due to varices) was reported. The most common adverse reactions (frequency of 10% or greater) were headache and fatigue. All adverse reactions were mild to moderate in severity. There were no clinically significant trends for laboratory abnormalities.

The Warnings and Precautions section of the package insert will include a recently identified drug-drug interaction (DDI) describing the risk of severe, life-threatening bradycardia associated with use of amiodarone co-administered with sofosbuvir in combination with another HCV direct acting antiviral, including DCV. This DDI was not identified in the clinical trials (where amiodarone use was prohibited) but was observed in the large expanded access program where DCV was used in combination with SOF with and without ribavirin and use of amiodarone was allowed. The patient population in the expanded access program represents those with more advanced liver disease and complex comorbid conditions requiring multiple concomitant medications compared to the clinical trials population.

The DCV/SOF treatment duration of 12 weeks has a similar safety profile overall and in subjects with baseline cirrhosis. No unique safety concerns are identified based on analyses of sex, race and age. The exposure of DCV in females is approximately 30% higher compared to males. However, no clinically relevant trends in clinical adverse events or laboratory findings have been identified across the development program.

In summary, DCV/SOF for 12 weeks provides an all-oral treatment option for patients with chronic HCV genotype 3 infection. Treatment with DCV/SOF has the clinical benefit of a ribavirin-free regimen, a shorter duration of 12 weeks compared to the standard-of-care SOF/RBV duration of 24 weeks and once daily dosing; and provides a

therapeutic option for patients who cannot take RBV, addressing an unmet need in this population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket Risk Evaluation and Mitigation Strategies (REMS) are recommended for daclatasvir.

1.4 Recommendations for Postmarket Requirements and Commitments

The optimal regimen and duration of treatment for genotype 3 HCV infected patients with baseline cirrhosis has not been determined based on review of the data supporting this NDA. The consequence of virologic failure for cirrhotic subjects has not been fully characterized and is considered a safety concern for use of DCV/SOF for 12 weeks duration in this subpopulation. Therefore, the following postmarket requirement has been determined:

Conduct a trial to determine if a longer duration of treatment or addition of ribavirin improves the efficacy (i.e., sustained virologic response rate) of daclatasvir plus sofosbuvir for hepatitis C virus genotype 3 infected subjects with cirrhosis.

With respect to the Pediatric Research Equity Act requirements, the Sponsor has requested a partial waiver of pediatric studies for pediatric subjects less than 3 years of age and a deferral for the DAA-only (interferon-free) trials for all pediatric subjects aged ≥ 3 years through <18 years of age. Please refer to Section 7.6.3 Pediatrics and Assessment of Effects on Growth for details.

2 Introduction and Regulatory Background

Globally it is estimated that approximately 170-200 million people are infected with HCV, including approximately 3-5 million people in the United States (US) (<http://www.epidemic.org/thefacts/theepidemic/worldPrevalence/>). In the United States, approximately 70% of chronic HCV infections are caused by genotype 1, 15-20% by genotype 2, 10-12% genotype 3, 1% genotype 4 and $<1\%$ genotype 5 or 6. HCV genotype 3a is the most prevalent GT3 subtype in the U.S., and has been associated with intravenous drug use (Clement, 2010; Zein 2000; Morice, 2006). The natural history of chronic HCV infection (CHC) involves progression to cirrhosis, hepatocellular carcinoma, liver failure, and death. In the US, CHC is currently the most common reason for liver transplantation and there are more yearly deaths related to HCV than human immunodeficiency virus (HIV) infection (Ly 2012). Genotype 3 HCV infection has been associated with a higher risk of steatosis leading to accelerated fibrosis and a higher risk of hepatocellular carcinoma (HCC) (Tapper 2013).

The ultimate goal of HCV treatment is to reduce the occurrence of end-stage liver disease and its related complications, and achieving sustained HCV viral eradication. Successful HCV treatment is associated with improvements in clinical outcomes such as decreased development of hepatocellular carcinoma, hepatic events, fibrosis, and all-cause mortality (van der Meer 2012; Backus 2011; Singal 2010; Veldt 2007). Historically, when the standard of care was a pegylated interferon and ribavirin based regimen, several host and viral baseline factors were identified as more likely to result in treatment failure. These factors included: high baseline viral load, significant fibrosis or cirrhosis (Metavir fibrosis score F3 or F4), older age and IL28B non-C/C genotype (Ge 2009; Ghany 2009; Jacobson 2011; Poordad 2012). These factors remain part of the evaluation of new DAA regimens to determine if there are significant differences among subpopulations of patients infected with chronic HCV.

The current resubmission of this NDA refocuses the approval request for daclatasvir for use in combination with sofosbuvir (DCV/SOF) for the treatment of chronic genotype 3 HCV infection in adults.

2.1 Product Information

Table 1 summarizes the pertinent product information for this resubmission NDA.

Table 1: Product Information

	NDA 206843
Generic Name	Daclatasvir
Trade Name	Daklinza
Chemical Class	New molecular entity
Pharmacological Class	NS5A replication inhibitor
Proposed indication	Treatment of hepatitis C
Dosage	60 mg once daily (dose adjustments to 30 or 90 mg once daily based on drug-drug interactions)
Dosage form	Oral tablet
Age Groups	Adults

2.2 Tables of Currently Available Treatments for Proposed Indications

The data submitted in support of the resubmission of NDA 206843 are specific to treatment of subjects with genotype 3 chronic hepatitis C. Therefore, Table 2 includes only US approved agents used in combination for treatment of HCV genotype 3.

Table 2: Currently US Approved Agents for Treatment of Chronic HCV Genotype 3 Infection

Drug Class	Generic Name	Trade Name
Pegylated interferons	Peginterferon alfa-2a	Pegasys [®]
	Peginterferon alfa-2b	PegIntron [®]
Interferons	Interferon alfa-2b	Intron-A [®]
Nucleoside Analogue	Ribavirin	Rebetol [®] , Copegus [®]
NS5B Inhibitor	Sofosbuvir	Sovaldi [™]

Ledipasvir (in combination with sofosbuvir (LDV/SOF), marketed as Harvoni[®]) is the only other approved NS5A inhibitor; however, currently Harvoni[®] is only indicated for treatment of genotype 1 chronic hepatitis C.

2.3 Availability of Proposed Active Ingredient in the United States

Daclatasvir is not currently available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

As stated previously, LDV/SOF is a fixed-dose combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor, and is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults. Product labeling includes a Warnings and Precaution for serious symptomatic bradycardia when coadministered with amiodarone. This safety issue has also been observed in subjects receiving DCV/SOF and is discussed in detail in Section 7.3.5.

Additionally, the safety profile of LDV/SOF includes the following adverse reactions: fatigue, headache, nausea, diarrhea and insomnia. Bilirubin elevations of greater than 1.5 x ULN and transient asymptomatic lipase elevations above 3x ULN in $\leq 3\%$ of clinical trials subjects have been reported.

The SOF label contains safety information pertaining to creatine kinase elevations, lipase elevations, depression and suicidal events.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On November 25, 2014 a Complete Response Letter was issued for DCV after the Applicant withdrew the NDA for asunaprevir (ASV) as a result of a business decision. A proposal for an ALLY-3 resubmission was submitted on November 19, 2014. Additional

clarification on resubmission plans was provided on December 8, 2014, December 15, 2014 and December 22, 2014. FDA agreement with the proposed ALLY-3 submission was obtained during a teleconference on December 17, 2014.

2.6 Other Relevant Background Information

The Applicant submitted phase 2 safety and efficacy data from trial AI444040 evaluating the combination of daclatasvir and sofosbuvir (DCV/SOF) with and without RBV for genotype 1, 2 and 3 subjects, who were treatment-naïve or prior telaprevir or boceprevir failures. However, the Applicant did not provide a right of reference to sofosbuvir and therefore, only the safety data supporting DCV were reviewed from AI444040 in this Application.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Audits by Division of Scientific Investigations (DSI) were conducted for this NDA at three clinical investigator sites with high enrollment in ALLY-3. The pending classifications for the sites are No Action Indicated. For the pending classifications, a summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspectional Report (EIR). Overall the data submitted from these sites are considered acceptable and may be used in support of the application.

3.2 Compliance with Good Clinical Practices

The Applicant certified that their clinical trials were conducted in accordance with ICH Good Clinical Practice guidelines. The trial protocols and amendments were reviewed and approved by Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs). Written informed consent was obtained from all subjects prior to any trial-related procedures. Inspections of 3 selected clinical sites by DSI found no regulatory violations (refer to Section 3.1).

3.3 Financial Disclosures

BMS has adequately disclosed financial interests/arrangements with clinical investigators in accordance with 21CFR Part 54. The Applicant provided certification (Form 3454) which indicates that the investigators and sub-investigators who participated in ALLY-3 had no financial arrangements with the Applicant. No subjects had disclosable financial information. Only one sub-investigator was listed with an outstanding financial disclosure; however, based on a note to file dated 10-Feb-14, this

person was listed on the initial 1572 but was no longer participating at the time the site was activated. Therefore, this sub-investigator was not included in my assessment of outstanding financial disclosures and no other investigators or sub-investigators met that criterion.

Based on the lack of any investigators with a financial interest and the objective nature of the trial design including a central laboratory HCV RNA PCR based efficacy endpoint, the likelihood that the trial results were substantively biased based on financial interest is minimal.

Also see the Financial Disclosure Template in Appendix 9.4.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Daclatasvir dihydrochloride (b)(4) tablets, 30 mg and 60 mg (as the free base), contain daclatasvir dihydrochloride drug substance. The drug substance is a white to yellow powder with the 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-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate dihydrochloride.

The clinical formulation of DCV used during phase 3 clinical trials was oral (b)(4) tablets containing daclatasvir dihydrochloride, anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, silicon dioxide and magnesium stearate. Opadry® Green is used as the film coat.

Please refer to the CMC Review for further details on manufacturing processes, process controls, formulation specifications, and the adequacy of data provided to assure drug stability, strength, purity and quality for DCV.

4.2 Clinical Microbiology

Mechanism of Action and Antiviral Activity in Cell Culture

DCV is an NS5A inhibitor. The mechanism of action of DCV has been characterized in HCV replicon resistance selection studies, (b)(4) biochemical assays evaluating phosphorylation of NS5A, and NS5A binding studies, although the precise mechanism of NS5A inhibition and the resulting inhibition of HCV replication is unclear. Based on drug resistance mapping, NS5A inhibitors like DCV appear to target

primarily the N-terminus of the protein. Inhibition of HCV replicons with picomolar EC₅₀ values indicates that DCV targeting of NS5A results in inhibition of HCV RNA replication.

Antiviral Activity in Cell Culture

Daclatasvir had a median EC₅₀ value of 0.2 nM (range 0.006-3.2 nM, n=17) against hybrid replicons containing genotype-3a subject-derived NS5A sequences without detectable daclatasvir resistance-associated polymorphisms at NS5A amino acid positions 28, 30, 31 or 93. Daclatasvir activity was reduced against genotype-3a subject-derived replicons with resistance-associated polymorphisms at positions 28, 30, 31 or 93, with a median EC₅₀ value of 13.5 nM (range 1.3-50 nM). Similarly, the EC₅₀ 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 or 31 were ≥3,620 nM.

The median EC₅₀ values of daclatasvir for genotypes-1a, -1b, -2, -4, and -5 subject-derived NS5A hybrid replicons were 0.008 nM (range 0.002 - 2,409 nM, n = 40), 0.002 nM (range 0.0007 - 10 nM, n = 42), 16 nM (range 0.005 - 60 nM, n = 16), 0.025 nM (range 0.001 - 158 nM, n = 14), and 0.004 nM (range 0.003 - 0.019 nM, n =3), respectively. The EC₅₀ value against a single HCV genotype-6 derived replicon was 0.054 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.

Effect of Individual Amino Acid Substitutions on DCV Anti-HCV Activity in the Replicon System

In general, DCV has a low resistance barrier, although the resistance barrier varies by HCV genotype and subtype. HCV genotype-3a replicon variants with reduced susceptibility to daclatasvir were selected in cell culture, and the genotype and phenotype of daclatasvir resistant variants characterized. Phenotypic analysis of stable replicon cell lines showed that variant replicons containing A30K, A30T, L31F, S62L and Y93H substitutions exhibited 56-, 1-, 603-, 1.75-, and 2737-fold reduced susceptibility to daclatasvir, respectively.

Please also see the Clinical Virology review by Dr. Lalji Mishra for a detailed review of DCV nonclinical virology. Clinical virology related antiviral activity and the development of resistance is included with the discussion of efficacy in Section 6.1.4.

4.3 Preclinical Pharmacology/Toxicology

Please see the original NDA for the preclinical pharmacology/toxicology. No additional nonclinical data were submitted with the resubmission of this NDA.

4.4 Clinical Pharmacology

Brief summaries of the key clinical pharmacology findings are provided in this section. Please see the clinical pharmacology review by Dr. Stanley Au for additional details.

4.4.1 Mechanism of Action

Daclatasvir is an NS5A replication inhibitor.

4.4.2 Pharmacodynamics

DCV is metabolized by CYP3A and is a CYP3A substrate. Because DCV is a CYP3A substrate, DCV has proposed dose adjustments with strong inhibitors and moderate inducers. DCV is contraindicated in combination with strong CYP3A inducers. For further discussion on the CYP450 and transporters as well as drug-drug interactions and dose adjustments see Section 7.5.5 Drug-Drug Interactions.

Based on the in vitro study results, DCV is a P-gp substrate but not an OATP1B1 or OATP1B3 substrate and does not appear to be a BCRP substrate, though BCRP inhibitors were not evaluated in the in vitro study. The in vitro studies also indicate that DCV potentially inhibits P-gp, BCRP, OATP1B1 and OATP1B3. Inhibitory effects on digoxin exposure, a P-gp substrate, and rosuvastatin (OATP and BCRP substrate), were observed in drug-drug interaction trials with DCV [REDACTED] (b) (4)

Please see the Clinical Pharmacology review for further details.

4.4.3 Pharmacokinetics

The pharmacokinetic properties of DCV were evaluated in healthy adult subjects and in subjects with chronic HCV. Administration of DCV in HCV-infected subjects resulted in approximately dose-proportional increases in C_{max}, AUC, and C_{min} up to 60 mg once daily. Steady state is anticipated after approximately 4 days of once-daily daclatasvir administration. Exposure of daclatasvir was similar between healthy and HCV-infected subjects. A food effect was not observed with administration.

Distribution

With multiple dosing, protein binding of daclatasvir in HCV-infected subjects was approximately 99% and independent of dose at the dose range studied (1-100 mg).

Metabolism

Daclatasvir is a substrate of CYP3A, with CYP3A4 being the primary CYP isoform responsible for metabolism. Following single-dose oral administration of 25 mg ¹⁴C-daclatasvir in healthy subjects, the majority of radioactivity in plasma was predominately attributed to parent drug (97% or greater).

Elimination

Following single-dose oral administration of 25 mg ¹⁴C-daclatasvir in healthy subjects, 88% of total radioactivity was recovered in feces (53% of the dose as unchanged daclatasvir) and 6.6% of the dose was excreted in the urine (primarily as unchanged daclatasvir). Following multiple-dose administration of daclatasvir in HCV-infected subjects, with doses ranging from 1 mg to 100 mg once daily, the terminal elimination half-life of daclatasvir ranged from approximately 12 to 15 hours. In subjects who received daclatasvir 60 mg tablet orally followed by 100 µg [¹³C, ¹⁵N]-daclatasvir intravenous dose, the total clearance was 4.2 L/h.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Data to support the resubmission of DCV are from the following trials.

Table 3: Summary of Clinical Trials Supporting Resubmission of NDA 206843

Regimen	Trial	Genotype(s)	Duration	Number of Subjects
DCV/SOF	AI444218; ALLY-3	3	12 weeks	152
DCV/SOF +/- RBV	AI444040	1, 2 and 3	12 or 24 weeks	211
DCV (60mgQD) + pegIFN/RBV	AI444014	1	48 weeks	12
	AI444010	1 and 4	12 or 24 weeks	158
	AI444011	1	24 weeks	199
	AI444021	1	24 weeks	19
	AI444022	1	24 weeks	17
DCV/PegIFN/RBV	AI444031	2 and 3	12 or 16 weeks	100
Total			12 weeks or longer	505
Total Overall Safety Database for DCV				868

The total number of subjects with clinical data from phase 2 and 3 supporting DCV from the original NDA and the resubmission is 2,052 (note the 505 subjects from the DCV/pegIFN/RBV are common to both the original NDA and the resubmission and overlap, 1265 subjects are from the phase 3 trials supporting the combination of DCV/ASV).

5.2 Review Strategy

This reviewer, Dr. Wendy Carter, is the primary clinical reviewer for this NDA resubmission. The clinical, statistical and clinical virology reviewers collaborated extensively during the review process. In addition, there were significant interactions with the FDA clinical pharmacology, pharmacology/toxicology, and chemistry manufacturing and controls reviewers. Their assessments are summarized in this document in the relevant sections and may also refer back to the original NDA reviews; however complete descriptions of their findings are also available in the respective discipline NDA resubmission reviews.

The clinical review of this resubmission is based primarily on the phase 3 trial AI444218 (ALLY-3). Supportive activity data for DCV are from the phase 2 trials of DCV in combination with pegIFN/RBV and from original NDA submission which provided data evaluating the combination of daclatasvir and asunaprevir (ASV- NDA 206844 withdrawn) with and without pegIFN/RBV (DUAL and QUAD regimens). Safety data from the phase 2 trial AI444040 were reviewed as part of the original NDA review. However, efficacy data were not reviewed or included in the clinical or statistical reviews from AI444040 due to a lack of a right of reference to sofosbuvir (at the time of the trial SOF was not-approved and the trial did not use the proposed U.S. commercial formulation of sofosbuvir). ALLY-3 evaluated the proposed U.S. commercial formulation of DCV and the U.S. commercially available formulation of SOF; therefore, no right of reference is necessary for full FDA review of ALLY-3. The efficacy and safety sections in this review focus on the findings from the phase 3 trial ALLY-3 which supports the proposed indication in subjects with genotype 3 HCV infection. Where appropriate, supportive safety data from the phase 2 trials (AI444040 and DCV/pegIFN/RBV trials) which were also reviewed during the original NDA are included. However, the totality of safety data of DCV 60 mg once daily for 12 weeks or longer, was evaluated and considered in the overall safety review of DCV including data from: the 868 subjects from the NDA resubmission, the 1265 subjects the DCV/ASV DUAL and QUAD phase 3 trials in the original NDA, the > 7,900 DCV-exposed subjects in the overall clinical-trials safety database, the >4,800 patients in the expanded access program and the estimated 25,466 post-marketing patients, primarily from Japan.

5.3 Discussion of Individual Studies/Clinical Trials

Title

AI444218 (ALLY-3)

“A Phase 3 Evaluation of Daclatasvir and Sofosbuvir in Treatment-Naïve and Treatment-Experienced Subjects with Genotype 3 Chronic Hepatitis C Infection”

Study Sites

30 sites in the United States and 1 site in Puerto Rico

Study Dates

The study was initiated on 24-Jan-2014 (first patient first visit/date of first signed informed consent); last patient last visit for the final CSR was on 22-Sep-2014 and database lock was on 13-Oct-2014.

Summary of Trial Design

ALLY-3 is an open-label, phase 3 trial in subjects with chronic HCV genotype 3 infection, conducted in the U.S. and Puerto Rico. Approximately 150 subjects were to receive 12 weeks of daclatasvir 60 mg once daily in combination with sofosbuvir (Solvaldi®) 400mg once daily for 12 weeks and were then followed for 24 weeks after treatment. Trial medication was taken with or without a meal. The trial included 2 parallel groups of study populations based on the following HCV treatment histories:

- **HCV Treatment-naïve:** no previous exposure to an interferon formulation, ribavirin or other HCV-specific direct acting antiviral (DAA)
- **HCV Treatment-experienced:** previous treatment with either 1) IFN α \pm RBV, 2) SOF/RBV (except subjects who discontinued SOF/RBV due to intolerance other than exacerbations of anemia), and 3) other anti-HCV agents (e.g., cyclophilin inhibitors and inhibitors of microRNA). Previous exposure to NS5A inhibitors was prohibited.

Study subjects were males and females greater than or equal to 18 years of age with chronic HCV genotype 3 infection, who had HCV RNA level \geq 10,000 IU/mL, and a body mass index of 18 to 35 kg/m². Chronic HCV was defined as positive HCV RNA and anti-HCV antibody at screening and either positive anti-HCV Ab, HCV RNA or HCV genotype 6 months prior or liver biopsy consistent with chronic HCV (cirrhosis or evidence of fibrosis and/or inflammation).

Subjects with compensated cirrhosis were permitted (up to 50% of subjects in each group). Subjects were considered ‘cirrhotic’ if the met the following criteria:

- Liver biopsy showing cirrhosis (i.e. Metavir $>$ F3, Ishak $>$ 4, or the equivalent) at any time prior to screening OR;
- Fibroscan showing cirrhosis or results $>$ 14.6 kPa within 1 year of Baseline OR;

- A FibroTest[®] score of ≥ 0.75 and an aspartate aminotransferase (AST): platelet ratio index (APRI) of > 2 performed during Screening.

Subjects were considered 'noncirrhotic' if they met the following criteria:

- Most recent liver biopsy (within ≤ 36 months of Screening) showing the absence of cirrhosis (Metavir F0-F3, Ishak 0-4, or equivalent) OR;
- Fibroscan with a result of ≤ 9.6 kPa within 1 year of Baseline/Day 1 OR;
- A FibroTest[®] score of ≤ 0.48 and APRI of ≤ 1 performed during Screening.

[Note: subjects that were evaluated by more than 1 testing method that provided conflicting results, determination of cirrhosis was made with the following hierarchy: Liver biopsy > Fibroscan > FibroTest[®]].

Subjects with decompensated liver disease, other chronic liver diseases, or subjects who were coinfecting with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) were excluded.

The primary efficacy endpoint was the proportion of treated subjects who achieved SVR12, defined as HCV RNA $< \text{LLOQ}$ (Target Detected [TD] or Target Not Detected [TND]) at Follow-up Week 12.

Virologic Failure was defined as:

- Virologic breakthrough: Confirmed $\geq 1 \log_{10}$ IU/mL HCV RNA on-treatment increase over nadir, or confirmed increase in HCV RNA $\geq \text{LLOQ}$ if HCV RNA previously declined to $< \text{LLOQ}$, TD or TND
- Relapse: HCV RNA $< \text{LLOQ}/\text{TND}$ at end-of-treatment followed by confirmed HCV RNA $\geq \text{LLOQ}$ during follow-up

HCV RNA was measured by the Roche COBAS[®] TaqMan[®] HCV Test v2.0 from the central laboratory. The lower and upper limits of quantification of the assay were 25 IU/mL and 3.91×10^8 IU/mL, respectively, whereas HCV RNA $< \text{LLOQ}$, TND was 10 IU/mL. Population nucleotide sequence analyses were to be conducted on Baseline samples for all subjects, and during or following treatment for subjects who experienced virologic failure and had HCV RNA $\geq 1,000$ IU/mL.

6 Review of Efficacy

Efficacy Summary

The efficacy analyses in support of this NDA resubmission are derived primarily from the ALLY-3 trial; which studied DCV dosed in combination with SOF for 12 weeks in subjects with chronic HCV genotype 3 infection. The focus of this clinical efficacy review is on data from ALLY-3. However, data were reviewed in the original NDA

supporting the efficacy of DCV with other drug combinations (e.g. DCV/ASV, DCV/ASV/pegIFN/RBV, DCV/pegIFN/RBV) for which the Applicant is no longer seeking indications, but are considered supportive to the overall demonstration of efficacy and the contribution of DCV to a combination anti-HCV regimen.

Overall, 152 subjects with chronic HCV genotype 3 enrolled into ALLY-3. The trial enrolled treatment-naïve and treatment-experienced subjects; subjects with compensated cirrhosis were also included. Baseline demographics and characteristics were similar between the treatment-naïve and treatment-experienced cohorts except for the expected slightly higher age of the prior treatment-experienced group. Most subjects (84%) had prior treatment experience with a pegIFN/RBV based regimen; however, 7 subjects (14%) had failed prior SOF/RBV therapy and 2 subjects (4%) had prior exposure to a cyclophilin inhibitor. A total of 32 subjects (21%) had compensated cirrhosis at baseline (19 treatment-naïve, 13 treatment-experienced); 109 subjects (72%) were non-cirrhotic, and 11 subjects (7%) did not have a cirrhosis status reported.

Overall, 89% (135/152) of subjects achieved SVR12 with 95% confidence interval (CI) of (83%, 93%). The SVR12 rate for treatment-naïve cohort was 90% (91/101) with 95% CI of (83%, 95%), and the SVR12 rate was 86% (44/51) with 95% CI of (74%, 94%) in the treatment-experienced cohort. The SVR12 rates are comparable, despite the limited number of treatment-experienced subjects compared to treatment-naïve subjects.

The current standard-of-care (SOC) treatment for patients with genotype 3 HCV infection is SOF/RBV for 24 weeks; for which the overall SVR12 rate was 84% (210/250). The statistical reviewer calculated the potential non-inferiority (NI) margins using historical SVR12 data from SOF monotherapy, pegINF/RBV for 24 weeks, SOF/RBV 12 weeks and SOF/RBV 24 weeks treatment regimens. NI margins for the treatment-naïve, treatment-experienced cohorts and the overall combined populations were calculated using the various historical treatment arms as putative placebos to provide the comparisons. Depending on the selection of the comparator arm (putative placebo, using historical SVR data from the various other regimens) and the treatment cohort, an appropriate NI margin calculation ranged from a low of 17% to a high of 34% (M1), without regard to clinical considerations for a shorter duration or RBV-free regimen. The overall SVR12 rate difference between DCV/SOF for 12 weeks and the SOC (SOF/RBV for 24 weeks) is 3% with 95% CI of (-4%,9%). The lower bound of the 95% CI of -4% is less than the determined lowest NI margin of 17%; therefore, even without clinical consideration for a shorter duration or RBV-free regimen, the results demonstrate that DCV/SOF for 12 weeks is non-inferior to SOF/RBV for 24 weeks duration. Efficacy has been demonstrated and DCV/SOF for 12 weeks provides another treatment option for patients with genotype 3 HCV infection.

SVR12 rates were approximately 30% lower among subjects with baseline cirrhosis compared to subjects without baseline cirrhosis. The SVR12 rate for subjects with baseline cirrhosis was 63% (20/32) with 95% CI of (44%, 79%), and was 96% (115/120)

with 95% CI of (91%, 99%) for subjects without baseline cirrhosis [note: the non-cirrhotic group includes the 11 subjects with indeterminate or missing cirrhosis status as a more clinically conservative analysis]. Despite the small number of subjects with baseline cirrhosis, there was a compelling reduction in SVR12 rate in subjects with baseline cirrhosis compared to subjects without baseline cirrhosis; which suggests that the DCV/SOF 12 week regimen may not be the optimal duration and/or regimen for genotype 3 HCV-infected subjects with baseline cirrhosis. Additional data are needed to determine if the addition of RBV and/or a longer duration will improve the SVR12 rates for HCV genotype 3 patients with cirrhosis.

Of the 17 subjects who did not achieve SVR12, 16 (94%) subjects experienced virologic relapse post-treatment and 1 (6%) subject had low, quantifiable HCV RNA (53 IU/mL) at the end of treatment; thus, all non-SVR12 results were attributed to virologic failure. Overall, 12 (71%) of the 17 subjects who had virologic failure also had baseline cirrhosis.

Resistance-associated polymorphisms have been demonstrated to impact the efficacy for some direct acting antiviral (DAA) therapy. The baseline NS5A resistance polymorphism Y93H impacted SVR12 rates in ALLY-3. The SVR12 rate for HCV genotype 3 subjects from ALLY-3 with baseline NS5A Y93H polymorphism was 54% (7/13) with 95% CI of (25%, 81%), compared to 92% (128/139) with 95% CI of (86%, 96%) for subjects without NS5A baseline Y93H polymorphism. There is a clear impact on SVR12 rates for those with Y93H NS5A baseline polymorphism, regardless of baseline cirrhosis status. However, the prevalence of the Y93H at baseline was 9% in this US HCV genotype 3 population; and therefore, its impact is limited to this small subset of the overall U.S. HCV population. Because the presence of the Y93H baseline polymorphism is a key factor associated with reduced efficacy of DCV/SOF in HCV genotype 3 subjects in ALLY-3, these data will be described in Section 12.4 (Microbiology) in the product label.

Virus from all 17 subjects at the time of virologic failure harbored one or more of the NS5A resistance-associated polymorphisms A30K/S, L31I, S62A/L/P/T or Y93H. The most common substitution at failure was Y93H (15/17 subjects) which was observed at baseline in 6 subjects and emerged in 9 subjects. For NS5B, 1 of 16 subjects had virus with the emergent NS5B resistance-associated substitution S282T at failure.

Currently, because SOF/RBV is the only other approved IFN-free treatment option available for genotype 3 patients, DCV/SOF provides an IFN and RBV-free treatment option with generally overall similar SVR rates (samples sizes are small for cirrhotic subjects with both regimens) and the advantage of a shorter treatment duration. Despite the reduction in SVR rates associated with baseline cirrhosis and the Y93H resistance-associated polymorphism, DCV/SOF provides an alternative shorter duration treatment option for patients, and addresses an unmet medical need by providing a treatment option for those who are unable to take RBV (i.e. patients with hereditary

bleeding disorders, those with other significant anemia, or other medical contraindications to RBV).

6.1 Indication

The Applicant requested the following indication for daclatasvir:

DAKLINZA (daclatasvir) is indicated for the treatment of chronic hepatitis C virus (HCV)

 (b) (4)

-  (b) (4)

6.1.1 Methods

The efficacy data from the phase 3 trial AI444218 (ALLY-3) was reviewed in support of the use of DCV in combination with SOF for 12 weeks duration for treatment of treatment-naïve and treatment-experienced genotype 3 HCV infection. Supportive efficacy data for DCV are available from the original NDA review of the phase 3 trials of DCV in combination with asunaprevir (ASV, NDA withdrawn due to Applicant business decision) and the phase 2 trials of DCV in combination with pegylated interferon and ribavirin (pegIFN/RBV). Both the DCV/ASV and DCV/pegIFN/RBV efficacy data were reviewed by the FDA statisticians in the original NDA review and are not included in this clinical review. Efficacy of DCV was established in DCV/ASV and DCV/ASV/pegIFN/RBV regimens and the efficacy data from these regimens are considered supportive to demonstrate the contribution of DCV in various treatment regimens and HCV genotypes. The ASV NDA was withdrawn and therefore, the applicant is not seeking approval of these regimens. Instead, this clinical review focuses on the efficacy findings from the ALLY-3 trial. Further details can be found in Dr. Zeng's statistical reviews.

The primary efficacy endpoint for ALLY-3 is the proportion of subjects with SVR12 (imputed), defined as HCV RNA below LLOQ Target Detected (TD) or Target Not Detected (TND) at follow up Week 12. Missing HCV RNA data were imputed using the next value carried backward (NVCB) approach.

HCV RNA levels were determined using the FDA-approved Roche COBAS[®] TaqMan[®] HCV v2.0 test, which has a reported lower limit of quantification (LLOQ) of 25 IU/mL, and a limit of detection (LOD) of approximately 10 IU/mL. The Abbott RealTime HCV

Genotype II assay was used for all genotype/subtype assessments. For samples with inconclusive results, the Versant HCV genotype 2.0 assay (LIPA) or viral sequence analysis was used. These analyses were conducted by [REDACTED] (b) (4)

6.1.2 Demographics

Demographic and baseline characteristics shown to predict lower SVR rates with standard of care treatment include a high viral load at baseline, advanced disease on histology (bridging fibrosis and cirrhosis), obesity, older age, and African American race. A genetic polymorphism near the IL28B gene is a strong predictor of SVR in patients receiving therapy with pegylated interferon and ribavirin. Numerous studies have demonstrated that patients who carry the variant alleles (C/T and T/T genotypes) historically have had lower SVR rates than individuals with the C/C genotype when administered IFN based regimens. With the development of the DAA based regimens, these historical factors remain important to evaluate to determine if they continue to influence SVR rates.

The overall baseline demographics and characteristics of ALLY-3 are highlighted in Table 4. The baseline demographics were generally comparable in the treatment-naïve and treatment-experienced cohorts. Overall, 59% of subjects were male. The median age was 55 years with 7% of subjects at or above age 65 years. The one difference between the cohorts was that the treatment-experienced cohort tended to be older (median age 58 years) compared with treatment-naïve subjects (median age 53 years). The trial population was predominantly white (90%) with only a small proportion of Asian (5%) and black/African American subjects (4%). The mean BMI was 27.1 kg/m². The trial was conducted in North America and 96% of subjects were from the US and 4% (6 subjects) were from Puerto Rico. Overall, 16% of subjects were Hispanic/Latino. The median baseline HCV RNA was 6.42 log₁₀ IU/mL and 71% of subjects had a baseline HCV RNA ≥ 800,000 IU/mL.

A total of 32 subjects (21%) had cirrhosis at baseline (19 treatment-naïve, 13 treatment-experienced); 109 subjects were non-cirrhotic, and 11 subjects did not have a cirrhosis status reported. In the 32 subjects with cirrhosis at baseline, cirrhosis was identified as follows: by liver biopsy (METAVIR F4) for 14 subjects, by FibroScan (> 14.6 kPa) for 11 and by FibroTest ≥ 0.75 with APRI > 2 for 7 subjects.

Fibrosis stage was determined by FibroTest scores as follows: F0: 0 to ≤0.27, F1: > 0.27 to ≤ 0.48, F2: > 0.48 to ≤ 0.58, F3: > 0.58 to ≤0.74, F4: > 0.74 to ≤ 1.00. A fibrosis stage of F0-F3 was reported for 78% of subjects; 20% of subjects had stage F4 fibrosis. Note that 3 subjects in ALLY-3 did not have FibroTest results; 2 of the 3 had biopsy data and the remaining subject had neither biopsy nor Fibroscan results prior to treatment.

The majority of subjects had IL-28B rs1297860 non-CC genotype (61%).

Table 4: Baseline Demographics and Baseline Characteristics of Subjects in ALLY-3

	Treatment-Naive N=101(%)	Treatment-Experienced N=51(%)	Total N=152 (%)
Age			
Median (years)	53	58	55
<65	95 (94)	47 (92)	142 (93)
≥65	6 (6)	4 (8)	10 (7)
Sex			
Male	58 (57)	32 (63)	90 (60)
Female	43 (43)	19 (37)	62 (41)
Race			
White	92 (91)	45 (88)	137 (90)
Black/African American	4 (4)	2 (4)	6 (4)
Asian	5 (3)	2 (4)	7 (5)
American Indian/Alaska Native	0	2 (4)	2 (1)
Ethnicity			
Hispanic/Latino	17 (17)	8 (16)	25 (16)
Not-Hispanic/Latino	84 (83)	43 (84)	127 (84)
Baseline HCV RNA (IU/mL)			
Median (log10)	6.27	6.54	6.42
< 800,000	31 (31)	13 (26)	44 (29)
≥ 800,000	70 (70)	38 (75)	108 (71)
Cirrhosis			
Absent	75 (74)	34 (67)	109 (72)
Present	19 (19)	13 (26)	32 (21)
Not Reported	7 (7)	4 (8)	11 (7)
Fibrosis Stage			
F0	35 (35)	10 (20)	45 (30)
F1	22 (22)	11 (22)	33 (22)
F2	5 (5)	9 (18)	14 (9)
F3	14 (14)	13 (26)	27 (18)
F4	22 (22)	8 (16)	30 (20)
Not reported	3 (3)	0	3 (2)
IL28B RS1297860 Genotype			
CC	40 (40)	20 (39)	60 (40)
CT	47 (47)	21 (41)	68 (45)
TT	14 (14)	10 (20)	24 (16)

Source: DM and ADSL datasets

Of the treatment-experienced subjects, most (84%; 43/51) had received a prior IFN-based HCV therapy, while 16% (8/51) had received HCV treatment other than an IFN-based regimen. Seven subjects (14%) received prior SOF/RBV and 2 subjects (4%) received prior cyclophilin –containing regimens (investigational agents: DEB025, alisporivir). (Note- 1 of the 2 subjects that received prior cyclophilin therapy had also received pegIFN and is included as having received prior IFN-based therapy). Predominantly, the treatment-experienced subjects were prior relapsers (61%; 31/51), but 14% (7/51) were null responders, 12% (6/51) were intolerant and the remainder had a partial response, virologic breakthrough, an indeterminate response or had never achieved HCV RNA < LLOQ, TND while on prior therapy.

6.1.3 Subject Disposition

In ALLY-3, 152 subjects in total were treated. Of the 152 subjects, 151 (99.3%) subjects completed the 12-week treatment period. One subject (ID 8-164) became pregnant and discontinued study drugs at on-treatment Week 8. This subject entered the follow-up period and achieved SVR12. At the time of database lock, all subjects had completed the follow-up Week 12 visit.

A total of 21 subjects enrolled but were not treated. The main reasons for not being treated were meeting exclusion criteria or exclusionary laboratory criteria.

6.1.4 Analysis of Primary Endpoint(s)

The overall SVR12 for ALLY-3 was 89% (135/152) with 95% confidence interval (CI) of (83%, 93%). The SVR12 rate for treatment-naïve cohort was 90% (91/101) with 95% CI of (83%, 95%), and 86% (44/51) with 95% CI of (74%, 94%) of the SVR12 in the treatment-experienced cohort. The SVR12 rates are comparable despite the limited number of treatment-experienced subjects compared to the treatment-naïve subjects.

The SVR12 rate for subjects with baseline cirrhosis was 63% (20/32) with 95% CI of (44%, 79%), and was 96% (115/120) with 95% CI of (91%, 99%) for subjects without baseline cirrhosis. The non-cirrhotic group includes 11 subjects with indeterminate or missing cirrhosis status; these subjects were included in the non-cirrhotic group as a more conservative clinical approach rather than excluding them from the analyses. Despite the small number of subjects with baseline cirrhosis, there was a compelling reduction in SVR12 rate in subjects with baseline cirrhosis compared to subjects without baseline cirrhosis; which suggests that the DCV/SOF 12 week regimen may not be the optimal duration and/or regimen for subjects with baseline cirrhosis. Additional data are needed to determine if the addition of RBV and/or a longer duration (e.g. up to 24 weeks) will improve the SVR12 rates for HCV genotype 3 patients with cirrhosis.

Table 5: SVR12 rates for ALLY-3

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

Source: modified from statistical review (Dr. Zeng)

The protocol for ALLY-3 did not define criteria for an efficacy claim. The current standard-of-care (SOC) for patients with genotype 3 HCV infection is SOF/RBV for 24 weeks. The statistical reviewer calculated the potential non-inferiority (NI) margins using historical data from SOF monotherapy, pegINF/RBV for 24 weeks, SOF/RBV 12 weeks and SOF/RBV 24 weeks. NI margins for the treatment-naïve, treatment-experienced cohorts and the overall combined populations were calculated using the various historical treatment arms to provide the comparisons. Depending on the selection of the comparator arm (putative placebo, using historical SVR data from the various other regimens) and the treatment cohort, an appropriate NI margin calculation ranged from a low of 17% to a high of 34% (M1), without regard to clinical considerations for a shorter duration or RBV-free regimen. The overall SVR12 rate difference between DCV/SOF for 12 weeks and the SOC (SOF/RBV for 24 weeks) is 3% with 95% CI of (-4%,9%). The lower bound of the 95% CI of -4% is less than the determined lowest NI margin of 17%. Therefore, even without clinical consideration for a shorter duration or RBV-free regimen, the results demonstrate that DCV/SOF for 12 weeks is non-inferior to SOF/RBV for 24 weeks duration.

As shown above, subjects with baseline cirrhosis had lower SVR12 rates in both the treatment-naïve and treatment-experienced cohorts in ALLY-3. The SVR12 rates from the currently approved SOC regimen of SOF/RBV for 24 weeks in HCV genotype 3 treatment-naïve subjects with cirrhosis was 92% (12/13 subjects) with a 95% CI of (64%, 100%) and 60% (27/45 subjects) with a 95% CI of (44%, 74%) in treatment-experienced subjects with cirrhosis. The treatment-naïve subjects with cirrhosis appear to have higher SVR12 rates with the SOF/RBV regimen for 24 weeks; however, these data are limited by the small sample size and resulting wide confidence interval. Overall, the ALLY-3 data in HCV genotype 3 subjects with baseline cirrhosis are comparable to currently approved SOF/RBV regimen and both are limited by small

sample sizes. Despite the limitation of reduced SVR rates in cirrhosis, efficacy has been demonstrated; and DCV/SOF for 12 weeks provides another treatment option for patients with genotype 3 HCV infection.

Please see the statistical review by Dr. Wen Zeng for the details and supporting data demonstrating the calculations of the NI margins and additional analyses of the efficacy results.

6.1.5 Analysis of Secondary Endpoints(s)

Impact of Resistance-Associated Substitutions

Resistance-associated substitutions are known to impact efficacy of DAA therapy. Analysis of 148 subjects with available baseline resistance data in ALLY-3, virus from 52% (77/148) of subjects had baseline NS5A polymorphisms at resistance associated positions (defined as any change from reference at NS5A amino acid positions 28, 30, 31, 58, 62, 92, or 93) identified by population sequencing. The Y93H polymorphism was detected in 9% (13/148) of subjects receiving DCV/SOF and was associated with reduced SVR12 rates (discussed further below). Polymorphisms at other NS5A positions were not associated with reduced SVR12 rates. Substitutions associated with SOF resistance or exposure (defined as any change from reference at NS5B positions L159, S282, C316, L320 or V321) were not detected in the baseline NS5B sequence of any subject (n=150) in ALLY-3 by population-based sequencing.

The SVR12 rate for subjects with a Y93H NS5A baseline polymorphism was 54% (7/13) with 95% CI of (25%, 81%), and 92% (128/139) with 95% CI of (86%, 96%) of the SVR12 for subjects without Y93H NS5A baseline polymorphism, respectively (Table 6). the Y93H NS5A baseline polymorphism has significant impact on the SVR12 rates for subjects with and without cirrhosis; albeit, based on a limited number of subjects.

Table 6: SVR12 Rates in Subjects with HCV Genotype 3 with/without the Baseline NS5A Y93H Polymorphism, by Cirrhosis Status in ALLY-3

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

^aIncludes 11 subjects with missing or inconclusive cirrhosis status

Source: Clinical Virology review by Dr. Patrick Harrington

Resistance associated substitutions were also evaluated for subjects who experienced virologic failure. Of 152 HCV genotype 3 subjects treated in ALLY-3, 17 subjects experienced virologic failure, of whom 12 had cirrhosis. Post-baseline NS5A and NS5B population nucleotide sequencing data were available from 17/17 and 16/17 subjects, respectively. Virus from all 17 subjects at the time of virologic failure harbored one or more of the NS5A resistance-associated polymorphisms A30K/S, L31I, S62A/L/P/T or Y93H. The most common substitution at failure was Y93H (15/17 subjects) which was observed at baseline in 6 subjects and emerged in 9 subjects. For NS5B, 1 of 16 subjects had virus with the emergent NS5B resistance-associated substitution S282T at failure.

In contrast to data previously observed in HCV genotype 1b infected subjects who failed DCV/ASV and developed multiple major DCV resistance-associated substitutions, clear emergence of additional major DCV resistance-associated substitutions was not observed among HCV GT3 infected subjects with the Y93H polymorphism who experienced virologic failure in ALLY-3. This difference likely reflects that in HCV GT3a, the Y93H polymorphism by itself confers a major and presumably clinically significant reduction in DCV susceptibility (>3,000-fold) in the absence of any other DCV resistance-associated polymorphisms or substitutions.

No data from ALLY-3 are available regarding the persistence of resistance-associated substitutions in HCV genotype 3 subjects. In a long term follow-up study of predominately HCV genotype 1 subjects treated with DCV-containing regimens from phase 2/3 clinical trials (A1444046; discussed in original NDA review), viral populations with treatment-emergent NS5A resistance-associated substitutions persisted at detectable levels for more than 1 year in most subjects.

Please refer to the clinical virology review by Dr. Patrick Harrington for further detailed discussion of the resistance analyses.

Reviewer Comment: The Y93H DCV resistance-associated polymorphism confers significant reduction in SVR rates for subjects both with and without cirrhosis. However, this polymorphism was prevalent in approximately 9% of the HCV GT3a subjects enrolled in ALLY-3, which represents a small fraction of the U.S. population of patients with HCV infection. Currently, there is no commercially available test to detect Y93H polymorphisms in genotype 3 subjects; however, if a test was available, screening for baseline NS5A polymorphism Y93H would be recommended in product labeling, not required, prior to initiating therapy due to the lower prevalence of this baseline polymorphism and lack of accumulation of multiple major DCV resistance-associated substitutions at failure. One advantage for identifying those with a baseline Y93H polymorphism by pre-screening is to provide additional important information to make an individual patient benefit/risk assessment with respect to treating now with DCV/SOF or wait for future treatment options. Additionally, because Y93H alone

without other associated polymorphisms confers a major reduction in DCV susceptibility for genotype 3, other emerging resistance polymorphisms have not been associated with failure to DCV/SOF. Therefore, the consequence of failure is different from what was observed in subjects with genotype 1b HCV who failed DCV/ASV therapy with development of multiple other resistance-associated polymorphisms observed at failure (see original NDA review). Regardless, DCV-associated resistance polymorphisms have been observed to remain present for > 1 year and could potentially limit future treatment options for the individuals that acquire them, as cross-resistance with the NS5A class is expected.

Currently, with SOF/RBV being the only other approved IFN-free treatment option available for genotype 3 patients, DCV/SOF provides an IFN and RBV-free treatment option with generally overall similar SVR rates (samples sizes are small for cirrhotic subjects with both regimens) and the advantage of a shorter treatment duration. Despite the reduction in SVR rates associated with the Y93H resistance-associated polymorphism, DCV/SOF provides an alternative shorter duration treatment option for patients, and may be the only treatment option for those who are unable to take RBV (e.g. patients with hereditary bleeding disorders, those with other significant anemia, or other medical contraindications to RBV).

6.1.6 Other Endpoints

Other secondary endpoints include on-treatment failure and virologic relapse. Of the 17 subjects who did not achieve SVR12 in ALLY-3, 1 subject (1%; 1/152) had virologic breakthrough and 16 subjects (11%; 16/152) had virologic relapse.

Please see the statistical review for full analyses of all secondary endpoints.

6.1.7 Subpopulations

As previously mentioned, a number of demographic and baseline characteristics have been shown to predict a lower SVR rates with the prior use of pegIFN/RBV-based therapy. These include a high HCV RNA at baseline ($\geq 800,000$ IU/mL), advanced disease on histology (bridging fibrosis and cirrhosis), male gender, older age, African American race and absence of the IL28B CC genetic polymorphism. With the use of direct acting antivirals, baseline resistance-associated substitutions have become important as baseline factors affecting outcome, and defines an additional subpopulation.

The impact of baseline cirrhosis and the Y93H resistance-associated substitution on SVR is discussed in Section 6.1.5. Additional analyses by baseline HCV RNA, gender, age, race and IL28B status did not show any statistically significant impacts on the SVR12 outcome. However, ALLY-3 was predominantly a white population (90%) and

therefore, the analyses by race are limited by under-representation of other non-white races. Please see the statistical review by Dr. Zeng for further details.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

DCV Dose Selection and Rationale

During the end of phase 2 review, results from the four phase 2a and 2b studies demonstrate similar antiviral activity among the doses evaluated 10, 20, or 60 mg DCV once daily in combination with pegIFN α -2a/RBV. The applicant also stated DCV 60 mg once daily may be a more appropriate dose for maintaining efficacy while compensating for extrinsic factors (food, poor compliance, strong CYP3A4 inducers) that could impact exposure.

Overall, the combined safety and efficacy analyses suggest 60 mg was an appropriate DCV dose to carry forward into phase 3 development. Furthermore, no exposure-response relationships between safety events and DCV exposure were identified during phase 2; suggesting doses of 60 mg would not lead to an increase in adverse events compared to lower DCV doses.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No long-term follow-up data from ALLY-3 are available to assess the durability of SVR12 for HCV GT3 infected subjects treated with DCV/SOF. As discussed in the original NDA review, in addition to other HCV DAA reviews, virologic relapse after achieving SVR12 is negligible. From the phase 3 DCV/ASV DUAL and QUAD (with pegIFN/RBV) trials, among subjects who achieved SVR12 with available data at follow-up Weeks 12 and 24, 5/1019 (0.5%) experienced virologic relapse between Weeks 12 and 24 of follow-up.

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy issues were identified.

7 Review of Safety

Safety Summary

DCV has been studied in a comprehensive clinical development program with > 7900 subjects exposed to DCV in phase 1, phase 2, and phase 3 studies. In addition, more than 4800 patients have been exposed to DCV under expanded access or compassionate use programs. The Applicant estimates 25,466 patients have been exposed to DCV, including 4051 global and 21,415 Japanese patients.

This resubmission NDA focuses the primary safety evaluation on data available from 868 subjects, of which a total of 363 subjects were exposed to DCV in combination with sofosbuvir (SOF) with or without ribavirin (RBV) for 12 to 24 weeks duration in AI444218 (ALLY-3) and AI444040, and another 505 subjects were exposed to DCV in combination with pegIFN/RBV. Both AI444040 and the DCV/pegIFN/RBV safety data were reviewed as part of the original NDA review cycle. In addition, the phase 3 safety database for DCV/ASV DUAL of 1265 subjects, also reviewed in the original NDA submission, is considered supportive to the overall safety profile of DCV. In total, 2133 subjects (868 + 1265) with chronic HCV infection have been treated with the recommended dose of DCV in combination with other anti-HCV drugs in the pivotal and supportive clinical trials for the original and resubmission DCV NDAs.

The most significant safety issue recently identified is a potential drug-drug interaction leading to life-threatening bradycardia with use of amiodarone in combination with sofosbuvir and another DAA, including DCV. This safety signal was identified in the DCV compassionate use population and investigated during the review cycle of this resubmission NDA. Warnings and Precautions language describing the risks, avoidance of the concomitant use of amiodarone and management of the combination of DCV/SOF and amiodarone when there are no other alternatives will be included in the product labeling for DCV. Similar Warnings and Precautions language is included in the sofosbuvir, ledipasvir/sofosbuvir and simeprevir labels. Other than the DDI with DCV/SOF and amiodarone, the available safety data from the compassionate use program in over 4,800 patients (DCV/SOF±RBV) supports the current safety profile of DCV and has not identified any new safety signals or trends.

Review of safety data from ALLY-3 did not identify any new safety signals associated with DCV use. The safety data are consistent with the prior safety findings for DCV included in the original NDA review. There were no deaths and no adverse events leading to discontinuation. Only one subject had an SAE of gastrointestinal hemorrhage due to varices, considered not related to DCV or other study therapy. Overall, the most common adverse reactions ($\geq 5\%$) were fatigue (n=21, 14%), headache (n=21, 14%), nausea (n=12, 8%) and diarrhea (n=7, 5%). Treatment-relatedness was considered for the regimen DCV/SOF and not for the individual drug components of the regimen. The only grade 3 and 4 (combined analysis) laboratory abnormality was increased lipase; there were no associated clinical pancreatitis or related AEs reported.

Generally, the proportions of subjects reporting AEs was similar between subjects with and without cirrhosis; however, headache and arthralgia were reported more frequently in subject with cirrhosis compared to those without cirrhosis (31% vs. 18% and 13% vs. 4%, respectively). While females have approximately a 30% higher exposure to DCV, there are no safety signals identified across the development program associated with the higher exposure in women. Additionally, there were no safety issues identified

regarding age, sex, race or region in ALLY-3; however, data are limited for race (predominately white) and region (study in US and Puerto Rico).

There are currently no known associations between DCV and poor pregnancy outcomes; however, data are limited. The safety and efficacy of DCV has not been established in the pediatric population.

7.1 Methods

The original NDA submission focused on the combination of DCV with asunaprevir (ASV) as the 'DUAL' regimen. The phase 3 safety database for DCV/ASV DUAL of 1265 subjects was reviewed in the original NDA submission and is considered supportive to the overall safety profile of DCV in this resubmission NDA. The phase 3 DUAL safety data are detailed in the original NDA clinical review and are only discussed where appropriate in this clinical review.

This resubmission NDA focuses the primary safety evaluation on data available from AI444218 (ALLY-3) and AI444040 with a total of 363 subjects who were exposed to DCV in combination with sofosbuvir (SOF) with or without ribavirin (RBV) for 12 to 24 weeks duration. Trial AI444040 data were also reviewed with the original NDA submission and are discussed in pertinent places in that clinical review. Additional supportive safety data from six phase 2 trials of DCV in combination with pegylated interferon (pegIFN) and RBV in 505 subjects were reviewed in the original NDA and clinical review. These data are considered supportive to the overall safety profile of DCV, in particular, because these DCV/pegIFN/RBV trials were all randomized, double-blind, placebo-controlled trials (please refer to Table 7 in the original NDA clinical review for a summary of the phase 2 trials). In total, the resubmission safety database focused on 868 subjects: 363 subjects from DCV/SOF +/- RBV and 505 subjects from DCV/pegIFN/RBV.

The Applicant also provided high level safety data from interim study reports from 2 compassionate use programs: the French Temporary Authorization of Use (ATU; AI444237) and the UK National Health System England Compassionate Use Programme (CUP; AI444237; cut-off date 09 Jan 2015). In the ATU, 639 physicians enrolled 4,111 patients for early access. All subjects had to have advanced liver disease (18% had F3 fibrosis and 70% had F4 fibrosis) or if they had a lower stage of fibrosis (F0-F2) they must have had extrahepatic complications of HCV (7%) to enroll. Additionally, 9% of subjects had prior liver transplantation. The CUP has provided access to a DCV containing regimen for 210 subjects as of January 2015. In addition, both these expanded access programs (EAP) include a majority of advanced liver disease patients with cirrhosis who have been exposed to 12 to 24 weeks duration of DCV and SOF with and without RBV. These data are considered supportive to the clinical trials data for DCV and are detailed in Section 7.7 of the review.

Safety data for the NDA resubmission are submitted by the Applicant as a clinical overview, summary of clinical safety, final clinical study reports, and electronic datasets. The Integrated Summary of Safety (ISS) includes information on deaths, SAEs, discontinuations due to AEs and other significant AEs. Narratives are provided for all subjects who died, developed an SAE, discontinued from the trial because of an AE or had other significant medical events (e.g. grade 3 or 4 liver-related events). In the datasets assessment of causality by the investigator as “drug-related” was generalized to all drugs in the treatment regimen and not specific to any one drug; however, narratives allowed for causality assessment for each drug in the regimen by both the Applicant and the Investigator. Case report forms are provided for all treated subjects who experienced death or discontinuations due to adverse events.

Summary results from ALLY-3 safety analyses are the focus of this section of the NDA resubmission. As stated above, the phase 2 safety data from AI444040 and the DCV/pegIFN/RBV trials were reviewed as part of the original NDA and are discussed where appropriate in that review. Similarly, the focus of this section is ALLY-3 with additional safety data included and highlighted from the phase 2 trials where appropriate.

Minor differences between the Applicant’s results and FDA’s results can be attributed to differences in the methods for conducting the analyses and do not significantly alter the final conclusions. Medical Dictionary for Regulatory Activities (MedDRA) terms is used in the analyses of AE tables in this review. The on-treatment period was defined as beginning on the first day of active study therapy and ended 7 days after the last dose of study therapy.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

DCV safety data derived from the phase 3 trial ALLY-3 constitute the main safety population used in FDA analyses of key safety signals for this resubmission NDA. The phase 2 data from both AI444040 and the DCV/pegIFN/RBV trials were also re-evaluated and included where appropriated.

Primary clinical safety data (n=152) to support the use of DCV 60 mg once daily in combination with sofosbuvir (SOF, Solvaldi™) 400 mg once daily for 12 weeks duration for subjects with genotype 3 HCV are provided from trial AI444218. This trial evaluated treatment-naïve and treatment-experienced subjects. Most treatment-experienced subjects had failed prior treatment with peg-interferon/ribavirin, but 7 subjects had been treated previously with a sofosbuvir regimen and 2 subjects with a regimen containing the investigational cyclophilin inhibitor, alisporivir. Previous exposure to NS5A inhibitors was prohibited. Subjects enrolled were generally otherwise healthy without evidence or history of cancer, organ transplant, suspected hepatocellular carcinoma, evidence of decompensated liver disease or other medical condition contributing to chronic liver disease other than HCV. Subjects must have tested negative for HIV and chronic

hepatitis B. Subjects with hemophilia or other genetic coagulopathy were excluded. Subjects with diabetes and/or hypertension must be well controlled. Subjects must not have a gastrointestinal disease or surgical procedure that could impact absorption of study drugs. Subjects could not have active substance abuse or severe psychiatric disorders. Subjects must have met the following laboratory parameters at screening to be enrolled in ALLY-3:

- ALT $\leq 10 \times$ the upper limit of normal (ULN)
- Total bilirubin ≤ 2.0 mg/dL unless due to history of Gilbert's disease
- Platelets $\geq 50 \times 10^3$ cells/ μ L
- HbA1c $\leq 8.5\%$
- ANC $> 0.75 \times 10^3$ cells/ μ L
- Creatinine clearance (CLcr) > 50 mL /min (as estimated by Cockcroft and Gault)
- Hemoglobin ≥ 10 g/dL
- Albumin ≥ 3.5 g/dL
- QTcF or QTcB > 500 mSec
- AFP > 100 ng/mL or AFP ≥ 50 and ≤ 100 ng/mL requires a liver ultrasound and any subject with suspicious findings for HCC were excluded.

***Reviewer Comment:** The safety analyses and conclusion in this review are primarily based upon the enrolled clinical trial population. The trial entry criteria may mitigate potential safety concerns that may be observed with wider use of DCV/SOF in the general population of patients with GT3 HCV.*

Safety data are included from the phase 2 trial AI444040 (n=211) that evaluated DCV in combination with SOF with or without RBV in HCV GT1, 2, and 3 patients, including subjects who had failed prior therapy with telaprevir or boceprevir in combination with pegIFN α /RBV.

Additionally, supportive safety data are provided from 6 double-blind, randomized, active-controlled phase 2 trials of DCV in combination with pegIFN α /RBV: AI444010, AI444011, AI444014, AI444021, AI444022 and AI444031. Collectively, these trials provide exposure data to the recommended dose of DCV 60 mg QD in combination with pegIFN α /RBV in 505 subjects with HCV GT1, 2, 3 and 4, including 53 subjects with compensated cirrhosis.

7.1.2 Categorization of Adverse Events

The Applicant coded AEs for the integrated analysis using MedDRA version 17.1. Some differences in reporting of AEs between the individual Clinical Study Reports and the Summary of Clinical Safety may occur due to different versions of MedDRA which were used for clinical study reports (e.g. 17.0 versus 17.1). However, an assessment of the Applicant's coding of events was performed to assure appropriate mapping of the

investigators' verbatim terms to the selected MedDRA Preferred Terms. Particular attention was given to serious adverse events, grade 3/4 adverse events, and adverse events that led to study drug discontinuation. Additionally, a random check of adverse events without respect to severity or causality of adverse events was performed. No issues of concern were identified.

Laboratory toxicities were graded according to the DAIDS US National Institutes of Health table for Grading the Severity of Adult and Pediatric Adverse Events (2004). The laboratory value during the study period with the highest toxicity grade was reported for each test.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant pooled the same treatment arms from trials ALLY-3 and AI444040 (DCV/SOF and DCV/SOF/RBV) and also pooled the DCV/pegIFN/RBV trials. Separate analyses of the individual trials were also completed. This clinical review focuses on display of the safety analyses from the phase 3 trial ALLY-3 and provides the main safety findings described in the product labeling. Data from ALLY-3 were generally not pooled with AI444040 for FDA analyses, because AI444040 cannot be used in the product label due to a lack of a right of reference to sofosbuvir. Additionally, AI444040 safety data were reviewed during the original NDA and the ALLY-3 data provide the basis of the safety data for display in the product label supporting the indication for treatment of HCV genotype 3. Data from the complete NDA resubmission were independently reviewed and confirmed with the results provided by the Applicant. The FDA results were consistent with the Applicant's findings.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The overall exposure for DCV at 60 mg once daily for 12 weeks or longer is 868 subjects for this NDA resubmission. Additionally, 1265 subjects were exposed to DCV 60 mg once daily for 24 weeks in the DUAL and QUAD regimens (DCV/ASV and DCV/ASV/pegIFN/RBV, respectively) in the original NDA. Therefore, overall the exposure is 2,133 subjects who have received DCV 60 mg for 12 weeks or longer in the pivotal and supportive clinical trials for the original and resubmission DCV NDAs. The total DCV safety database is > 7,900 DCV-exposed subjects in the clinical development program (includes all doses and durations). Additionally, more than 4,800 patients have been exposed to DCV 60 mg once daily under expanded access programs and an estimated 25,466 post-marketing patients have been exposed to DCV 60 mg once daily, predominately in Japan.

Please refer to Section 6.1.2 for a summary of participant demographics for ALLY-3 and to the original NDA clinical review for additional discussion of the demographics of the phase 3 DUAL trials supporting DCV.

7.2.2 Explorations for Dose Response

No additional explorations for dose response were conducted during the resubmission NDA review. Please see the original NDA clinical review for the dose response explorations.

7.2.3 Special Animal and/or In Vitro Testing

Appropriate nonclinical evaluation for DCV has been completed. Please see Section 4.3 and the original NDA Pharmacology/Toxicology review by Dr. Peyton Myers.

7.2.4 Routine Clinical Testing

Routine clinical evaluation and laboratory testing was performed at pre-specified regular intervals (i.e. Weeks 1, 2, 4, 6, 8, 10 and 12 etc.). The frequency and scope of this testing was deemed adequate. Safety assessments primarily included the following: physical examinations, measurement of vital signs, clinical laboratory testing, and ECG monitoring. Additional testing was performed as indicated or as deemed clinically necessary by the investigator during the trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolic, clearance and interaction workup was adequate. Please refer to Section 4.4 and to the Clinical Pharmacology Review for details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The first NS5A complex inhibitor approved was ledipasvir (LDV) in combination with SOF. The most common adverse reactions to LDV/SOF were fatigue and headache in subjects treated with 8, 12 or 24 weeks. Nausea, diarrhea and insomnia were also observed in $\geq 5\%$ of subjects receiving LDV/SOF for 8, 12 or 24 weeks in clinical trials.

Postmarketing cases of serious symptomatic bradycardia, including fatal cardiac arrest and cases requiring pacemaker intervention were reported when amiodarone was co-administered with SOF in combination with another DAA including LDV, DCV and simeprevir (SMV). Currently the mechanism for this effect remains unknown. Bradycardia generally occurred within hours to days, but a few cases were observed up to 2 weeks after initiating HCV therapy. Patients also receiving beta blockers or those

with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. No subjects in the ALLY-3 or AI444040 databases received amiodarone and all cases involving DCV were ex-US. Of note, in Europe DCV is approved for use with SOF and several large compassionate use programs are ongoing; and several bradycardia cases were identified from the compassionate use program. Please see Section 7.3.5 for additional analysis and discussion of cardiac issues associated with DCV.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths during the on-treatment or follow-up periods in ALLY-3 or in AI444040 (DCV/SOF with and without RBV).

Two deaths were reported in subjects treated with DCV/pegIFN/RBV during the follow-up period. Subject AI444011-16-81 died due to, sepsis, hemorrhagic shock, liver and renal failure during follow-up (83 days after last-dose of DCV, but subject had continued pegIFN/RBV for another 38 days), which was considered related to study therapy (all study therapy including DCV, pegIFN and RBV) by the investigator. Subject AI444011-58-69 died due to hemoperitoneum as a complication of hepatocellular carcinoma 232 days after the last dose of DCV. This event was considered unrelated by the investigator. In addition, one subject exposed to placebo + pegIFN/RBV also died. These deaths are unlikely to be related to use of DCV, because of both the nature of the events, the comorbidities of the target population (e.g. hepatocellular carcinoma), the timing of the events (mostly during follow up period) and the concomitant use of pegIFN/RBV. Please see the original NDA clinical review for more details.

Reviewer Comment: No new clinical safety concerns for DCV are raised based on re-analysis of the deaths observed in the clinical database. However, multiple post-marketing cases including a fatality (related to SOF + another NS5A inhibitor + amiodarone) outside of the clinical safety database raised the safety signal of a drug-drug interaction between DCV/SOF with concomitant amiodarone. These safety events contributed to the overall concerns regarding life-threatening cardiac arrhythmias, including significant bradycardia and the DDI between SOF+ other DAA containing regimens and amiodarone. Please see section 7.3.5 for additional details regarding evaluation of this safety issue.

7.3.2 Nonfatal Serious Adverse Events

In ALLY-3, one subject (AI444218-1-105) reported a SAE of grade 3 GI hemorrhage on Day 15 of treatment. This 58 year old female was reported as non-cirrhotic at

enrollment; however, she did have a baseline FibroTest stage F3 fibrosis and thrombocytopenia at baseline. On Day 15 she presented to the ER vomiting blood and had a 1 day history of melena. An EGD revealed bleeding esophageal and gastric varices. Banding was unsuccessful and the patient underwent a TIPS procedure. Study drugs were interrupted for 6 days. Her hospitalization was complicated by a grade 2 jugular vein thrombosis and the patient was subsequently anticoagulated. By Day 38 the GI bleed resolved and the patient was discharged. Study drugs were restarted during the hospitalization and the patient completed therapy and achieved SVR12. The investigator considered the GI bleeding as unrelated to study drugs.

Reviewer Comment: This was the only SAE reported on treatment or during follow-up in ALLY-3. I agree with the investigator assessment that the episode of GI bleeding was likely unrelated to study drugs and more likely related to underlying cirrhosis and/or portal hypertension with varices that were undiagnosed at the time of enrollment.

No new SAE data were presented in this resubmission for trials AI444040 or for the DCV/pegIFN/RBV phase 2 trials. Please see the original clinical review for additional details. Briefly in summary:

- In AI444040, on-treatment SAEs were reported for 7% (n=15) of subjects overall. A higher proportion of subjects in the 24-week duration groups reported SAEs compared to the 12-week duration groups (9-12% vs 2%).
- Overall, on-treatment SAEs regardless of causality were comparable between DCV/pegIFN/RBV and placebo/pegIFN/RBV (29 subjects (6%) on DCV/pegIFN/RBV and 12 subjects (7%) on placebo/pegIFN/RBV). The proportion of subjects with drug-related SAEs for subjects exposed to DCV/pegIFN/RBV was 3% compared to 2% in the placebo/pegIFN/RBV group. Anemia was the only drug-related SAE reported in more than 1 subject (1 DCV/pegIFN/RBV subject and 3 placebo/pegIFN/RBV subjects).

7.3.3 Dropouts and/or Discontinuations

No subjects in ALLY-3 experienced adverse events leading to discontinuation. One subject discontinued at Week 8 due to pregnancy and subsequently achieved SVR12.

For subjects exposed to DCV/pegIFN/RBV in phase 2, AEs leading to discontinuation occurred in 7% (33/505) of subjects compared to 9% (15/174) of placebo/pegIFN/RBV subjects. The AEs leading to discontinuation were consistent with the known profile of pegIFN/RBV. Additionally, two subjects (<1%) had an AE leading to discontinuation of study therapy in AI444040 evaluating DCV/SOF with and without RBV. One subject had a grade 2 cerebrovascular accident and one subject had grade 3 fibromyalgia; neither event was considered related to study therapy. Additional details are provided in the original NDA review.

7.3.4 Significant Adverse Events

The majority of AEs reported on-treatment in ALLY-3 were grade 1 or 2 and none were grade 4. Grade 3 AEs were reported in 3 (2%) subjects:

1. **Subject AI444218-1-105:** 58 year old female had a grade 3 GI hemorrhage on Day 15 considered unrelated to study drugs (also a SAE, see Section 7.3.2).
2. **Subject AI444218-24-29:** 55 year old male who experience grade 3 food poisoning, nausea and vomiting and grade 1 abdominal pain on Day 11. The AEs resolved the same day with treatment with ondansetron and morphine. The AEs were considered unrelated to study drugs
3. **Subject AI444218-33-76:** 60 year old male who developed grade 3 arthralgia on Day 29 considered unrelated to study drugs by the investigator. The subject was treated with ibuprofen and the AE resolved in 22 days.

No grade 3 or 4 AEs were reported during the follow-up period.

In total, 7 subjects (3%) reported grade 3 or 4 AEs in AI444040; of which, 2 subjects received 12 weeks duration and the remaining 5 subjects received 24 weeks of DCV/SOF with and without RBV. None of the grade 3 or 4 events were considered related. Analysis of the DCV/pegIFN/RBV regimen showed that overall rates of grade 3 or 4 AEs were lower in the DCV/pegIFN/RBV (16%) compared to the placebo/pegIFN/RBV (25%) cohort. The most frequently reported grade 3/4 treatment-related AE was neutropenia in both the DCV/pegIFN/RBV and placebo/pegIFN/RBV cohorts (6% compared to 9%, respectively). The grade 3 and 4 AEs reflect the known AE profile of pegIFN/RBV and no additional safety signal attributable to DCV was identified.

7.3.5 Submission Specific Primary Safety Concerns

Cardiac Events Related to DCV/SOF

There were no cardiac disorders or chest pain AEs reported in ALLY-3. A small proportion of subjects treated with DCV/SOF±RBV in AI444040 reported cardiac disorders or chest pain (7/211; 3%); however, subjects also receiving RBV had a higher proportion of cardiac disorders/chest pain than those not receiving RBV: 6% (5/90) vs. 2% (2/121). All events were grade 1 or 2 and most had pre-existing conditions which may contribute to the reported events. Three reports (Angina pectoris grade 1, diastolic dysfunction grade 2 and palpitations grade 1) were considered related to the study regimen.

European postmarket safety surveillance identified cases of severe cardiac arrhythmia associated with amiodarone use co-administered with SOF in combination with other DAAs, including ledipasvir, DCV and simeprevir. The Applicant conducted a detailed

review of cardiac arrhythmias associated with DCV/SOF use in response to a request from the European Pharmacovigilance Risk Assessment Committee (PRAC). To address the potential for cardiac arrhythmia associated with the use of DCV/SOF, the Applicant submitted in the resubmission NDA an EMA report in response to PRAC request as above, DCV safety database evaluation for cardiac failure and cardiomyopathy, ECGs from patients with potential amiodarone drug-drug interactions with DCV/SOF and an evaluation of phase 3 data in subjects who were taking calcium channel blockers and/or beta blockers while on DCV/SOF. In addition to consideration of the nonclinical cardiac evaluations, the overall DCV safety database was evaluated for any events related cardiac arrhythmia, cardiomyopathy and cardiac failure. The following subsection summarizes the overall findings from the preclinical evaluations, the cardiac arrhythmia events (including the events signaling a potential DDI with amiodarone) and the cardiomyopathy and cardiac failure analyses. The finding of severe symptomatic bradycardia associated with amiodarone use co-administered with SOF in combination with another DAA, including DCV is detailed below. Despite a lack of a clear understanding of the underlying mechanism for this safety finding, the potential DDI leading to severe bradycardia warrants labeling under Warnings and Precautions.

Preclinical Cardiac Summary

There was no cardiac safety signal for DCV in toxicology studies or in the thorough QTc (TQT) study. In brief, preclinical cardiac safety evaluation of daclatasvir revealed the following:

- Daclatasvir (IC₅₀ 29 µM) exhibited weak inhibition of hERG/I_{kr}, and sodium and L-type calcium currents (> 214x RHD free [unbound] C_{max}) but no effects on any Purkinje fiber action potential parameters.
- In anesthetized rabbits given 30 mg/kg intravenously (C_p = 159 µg/mL, 92x RHD C_{max}), QRS, PR, AH and HV intervals were moderately increased.
 - DCV also produced a small increase (7%) in mean arterial blood pressure.
 - The NOEL was 10 mg/kg (C_p = 72.9 µg/mL, 42x RHD C_{max}).
- In telemetered dogs, a single dose of 100 mg/kg (C_p = 10.9 µg/mL) induced reversible increases in systemic pressures and small decreases in an index of cardiac contractility, whereas 15 mg/kg (2.2x RHD C_{max}) was the NOEL.
- There were no cardiovascular system effects identified in repeat-dose single-agent (< 9 months) or combination (< 3 months) toxicity studies in rats, dogs, or monkeys at the highest doses tested.

A thorough QT (TQT) study for daclatasvir was negative at the suprathreshold dose (180 mg), selected to target concentrations 2.5-fold what is obtained at the highest therapeutic dose (60 mg). In their review of the TQT study, the interdisciplinary review team noted that “no clinically relevant effects on vital signs, ECGs, physical examinations, clinical laboratory values, or adverse event profiles have been noted.”

Specifically, no clinically relevant effect on heart rate, PR or QRS was observed at the supratherapeutic dose.

DCV Evaluation for Cardiac Arrhythmia

DCV has been evaluated in 90 clinical trials in multiple regimens in approximately 7,900 subjects and has been administered as combination therapy via a large Early Access Program (EAP) including more than 4,800 patients. The majority of the DCV EAP patients are enrolled in the French cohort Authorisation Temporaire d'Utilisation (ATU), receiving DCV/SOF with and without RBV. As of December 3, 2014, a total of 4,111 patients have been treated in the ATU, the majority of who are treatment-experienced and have advanced hepatic fibrosis or cirrhosis. This population is considered to have no other treatment options for HCV and is considered a 'sicker' population than the DCV clinical trials populations. The ATU is predominantly male with an average age of 56 years. The cohort includes those who have had or are awaiting liver transplantation, have extra-hepatic manifestations of HCV, are co-infected with HIV and/or have other co-morbid conditions or concomitant medications generally excluded from clinical trials.

Based on the postmarket signal of a potential for cardiac arrhythmia, BMS conducted a cumulative search of their safety database to identify all DCV AE reports including serious interventional clinical trials reports, all serious and non-serious spontaneous AE reports, EAP and literature adverse events. This search was then reviewed to identify all cases related to cardiac arrhythmias. Overall, 30 individuals were identified who reported 31 Cardiac Arrhythmia events. In total, 15 events occurred in patients receiving DCV/SOF and 2 events occurred in patients receiving DCV/SOF/RBV. The remaining events occurred with the following regimens: DCV and asunaprevir (ASV) (7), DCV/ASV and beclabuvir (2), DCV/ASV/pegIFN/RBV (1), DCV/pegIFN/RBV (1), DCV/Lambda-interferon/RBV (2) and DCV and an unknown combination therapy (1).

Reviewer Comment: This clinical review focuses on the DCV/SOF containing regimens; however the events occurring with all the DCV regimens were reviewed in full and considered in the totality of the DCV cardiac safety assessment, including the FDA cardio-renal consult. The cases of cardiac arrhythmia and cardiac-related fatalities in other DCV containing regimens are confounded by underlying comorbidities including advanced chronic HCV, use of concomitant medications and in many cases, pre-existing cardiac abnormalities.

A brief summary of the cardiac arrhythmia cases associated with use of DCV/SOF are provided here. As stated above, there were 17 reports in which patients experienced cardiac events while receiving DCV in combination with SOF (15 reports) or SOF/RBV (2 reports). These reports included 1 clinical trial report (cardiac arrest with fatal outcome) and 1 spontaneous report (atrioventricular block complete), 9 reports from the French ATU, and 6 reports from other EAPs. The French ATU reports included single

cases of sinus arrhythmia, bradycardia, atrioventricular block complete, tachycardia, atrial flutter, sinus bradycardia, bundle branch block, atrial fibrillation and sudden death. Reports from other EAPs included atrial fibrillation (5) and a single report of bradycardia.

Among the 17 cardiac arrhythmia reports 5 reports occurred in patients also receiving amiodarone; 4 cases described severe bradycardia, while 1 described atrial flutter (see Table 7). Amiodarone was excluded from use in most of the clinical trials evaluating DCV; however, use of amiodarone was not prohibited in the EAPs, which included patients with multiple comorbidities and advanced hepatic disease. In the French ATU, 30 patients (<1%) were receiving amiodarone and 3 of the 5 reports of arrhythmia in patients receiving amiodarone were from the French ATU program. One of the cases provided detailed dechallenge/rechallenge information supporting a potential drug-drug interaction between amiodarone and DCV/SOF (see Case 21349394 details below). Additionally, 3 of the 5 patients with reported arrhythmia were also receiving propranolol. In the 4 reports of bradycardia while receiving stable dosing of amiodarone, the events occurred 3 hours to 10 days following initiation of a DCV/SOF regimen. In one case (21582184), the patient, who was on amiodarone and propranolol, fell and was hospitalized with 3rd degree heart block one day after DCV/SOF was initiated. Amiodarone was then discontinued. An amiodarone level was reported as 1.09 μM , within normal therapeutic range (0.77-3.87 μM), but the timing of the test in relation to the last amiodarone dose was not clear. No amiodarone exposure data are available for the other three subjects.

Case 21349394 was a 50 year old male with history of ascites, hepatic encephalopathy, diabetes, bradycardia, portal vein thrombosis, portal hypertension, obesity, varices, tobacco use, cardiac arrhythmia, alcoholism, hepatic cirrhosis with fibrosis stage F4 registered on liver transplantation list and paroxysmal atrial fibrillation on amiodarone who was treated with DCV/SOF. Three hours after initiating therapy, he developed sinus bradycardia to 25 beats per minute and syncope which spontaneously resolved. He was monitored and after another 3 days, he developed bradycardia to 30 - 35 beats per minute. Therapy with DCV/SOF, amiodarone and propranolol were stopped. Eight days later, he was rechallenged with DCV/SOF, and he developed sinus bradycardia at 30 beats per minute that lasted approximately two hours. Both the reporter and the Applicant assessed the event of sinus bradycardia as possibly related to DCV/SOF, amiodarone, and propranolol. Seven weeks later, after washout of amiodarone, another trial of DCV/SOF resulted in a negative rechallenge and was tolerated without arrhythmia. The reporter and the Company considered sinus bradycardia was possibly related to a potential drug interaction between amiodarone and anti-HCV treatment (also see case 21349394 in Table 7).

***Reviewer Comment:** This case provides strong evidence of the potential drug-drug interaction between amiodarone and SOF, plus another DAA, in this case, DCV. The rapid onset of bradycardia with syncope, the positive dechallenge, positive rechallenge*

(8 days after amiodarone was stopped but due to the long half-life is expected to still be present) and successful reintroduction of DCV/SOF after a longer washout of amiodarone provides strong evidence of amiodarone coadministration with DCV/SOF lead to this event, rather than other drugs such as the beta-blocker propranolol.

Table 7: Cases of Arrhythmia Associated with DCV/SOF with and without RBV and Concomitant Amiodarone

Case #	Event	Concomitant Medications	Onset	Age/ Sex	Outcome	Past Medical History
21582184	3 rd degree AV block, Bradycardia, Syncope, Convulsion	Amiodarone, propranolol Therapeutic levels of amiodarone at 1.09 micromol/L	Day 1	74 yo M	D/C amiodarone, Pacemaker inserted (unknown date) "favorable" 7 days later (after pacemaker) Con't HCV therapy	ventricular extrasystole, cirrhosis with esophageal varices
21349394	Sinus bradycardia (25 bpm), Syncope	Amiodarone, propranolol, Lactulose, spironolactone, Actrapid, Lantus, norfloxacin and Normix	3 hours	50 yo M	(+)rechallenge x 3 days; D/C HCV meds and amiodarone, propranolol Day 5 (+)dechallenge; (+)rechallenge ~8 days later; (-) rechallenge ~ 8 weeks later (off cardiac medications ~9 weeks)	decompensated cirrhosis, bradycardia, atrial fibrillation, diabetes, ascites, liver encephalopathy, alcoholism, tobacco user, esophageal varices, obesity
20786414	Bradycardia, Sinus node dysfunction, Syncope	Amiodarone Propranolol Digoxin Digoxin level 1.4-1.5 (wnl)	Day 12	51 yo F	D/C HCV and antiarrhythmic therapy. Plan to have antiarrhythmics restarted	cardiomyopathy, atrial fibrillation, RBBB, s/p AVR, breast cancer.
21678149	Bradycardia	Amiodarone	Day 2	70 yo F	D/C HCV therapy, (+) dechallenge 'Later on' d/c amiodarone	extrasystoles, decompensated cirrhosis awaiting transplant, RI, cardiac insufficiency
21288246	Atrial Flutter	Amiodarone Ramipril Furosemide Aldactone tamsulosine	Day 18	53 yo M	No action taken with medications; patient recovered	cardiac disorder valvular, transplant aortic valve, cardiac failure, hepatocellular

carcinoma,
prostatic disorder,
anemia

Source: modified from PRAC Query DDI Amiodarone Report

In addition, a case of cardiac arrest in a patient receiving DCV/SOF and amiodarone was reported after the database lock used for the EMA cardiac arrhythmia response report. Case BMS-2015-003146 was a 61 year old female with hypertension, atrial fibrillation after acute coronary syndrome, coronary arterial disease, ischemic stroke and intra-ventricular hemorrhage among other comorbidities who developed sudden cardio-respiratory arrest 30 minutes after the first doses of DCV/SOF for treatment of chronic HCV. The patient was resuscitated by emergency responders with external cardiac massage, intubation and adrenalin and was stabilized with bradycardia during her hospitalization. The life-threatening cardio-pulmonary arrest and drug interaction were considered related to DCV/SOF and amiodarone by the reporter and the Applicant.

***Reviewer Comment:** Based on the rapid onset and the severity and seriousness of this drug-interaction, this additional case provides strong evidence and support for the Warnings and Precautions statement regarding the potential DDI with amiodarone and SOF, with another DAA, including DCV to be included in package insert.*

The Applicant received and reviewed ECGs for 4 of the 5 patients with potential amiodarone drug-drug interactions with DCV/SOF. These ECGs were reviewed by the FDA internal Cardio-Renal consultant. In general, the consultant agreed with some, but not all of the interpretations of the ECGs; overall, they agreed that some of the cardiac rhythm abnormalities are consistent with amiodarone's effect but that the ECGs did not further explain the temporal relationship between DCV/SOF administration and the abnormalities. Therefore, the assessment of the potential for a DDI was not changed by the available ECGs. Lastly, the Applicant provided an assessment of their ongoing clinical trials of DCV/SOF±RBV (n=468; ALLY-1, -2, and -3) to further evaluate for any evidence of significant or serious bradycardia in subjects on stable beta blocker or calcium channel blocker regimens, without amiodarone use. In total, 15% (71/468) of subjects were on a stable beta blocker regimen and 10% (47/468) were on a stable calcium channel blocker regimen. Overall, no clinically relevant differences were observed evaluating vital signs for subjects on a stable beta blocker or calcium channel blocker compared to those who were not.

***Reviewer Comment:** Analyses by FDA and the Applicant of anti-HCV regimens of DCV without SOF and without amiodarone were completed to evaluate for any DCV-related signal for bradycardia in the available data. No trends or safety signals for bradycardia or significant cardiac arrhythmia were identified for DCV without concomitant SOF and amiodarone use. FDA and the Applicant will continue monitoring for cardiac arrhythmia associated with DCV use.*

It is known that amiodarone slows heart rate, and excessive dosage of amiodarone may lead to severe bradycardia. As there does not appear to be a direct mechanism for DCV to cause the observed pharmacodynamic effect, a more plausible hypothesis from the Applicant regarding the clinical observations is that coadministration with DCV/SOF increases amiodarone exposure in these subjects, although it is not yet confirmed by PK/PD data. The Applicant asserts that a CYP-mediated DDI with DCV is not likely as DCV did not affect exposure of midazolam, a sensitive CYP3A4 substrate in humans and did not inhibit other major CYP enzymes *in vitro*. The Applicant believes the most plausible mechanism for the presumed amiodarone exposure increase in humans would be through the inhibition of gut efflux and/or hepatic uptake. The Applicant continues to explore possible mechanisms for this drug-drug interaction.

The focus of the mechanism exploration has been on amiodarone as the driver of the safety findings with DAAs (SOF in combination with other antiviral agents, including DCV) exacerbating the effect via pharmacokinetic interactions or potentially through direct pharmacodynamic effects. The Applicant conducted a series of *in vitro* studies to evaluate transporter evaluation in amiodarone disposition. The following summarizes the results:

- Amiodarone is a substrate of human P-gp, but not of BCRP
- Hepatic uptake of amiodarone was primarily via active transport process that may involve NTCP and other unidentified uptake transporters, but not OATP1B1, OATP1B3, OCT1, or OAT2

The data regarding amiodarone and P-gp transport stated above provides a plausible mechanism through which co-administered drugs could provoke a pharmacokinetic interaction with amiodarone. All three non-nucleotide DAAs, ledipasvir (LDV), simeprevir (SMV), and DCV, have demonstrated to be *in vitro* inhibitors of P-gp so these DAAs have the potential to increase amiodarone exposure as well.

Other possible mechanism may include:

- All three non-nucleotide DAAs (SMV, LDV and DCV) increased SOF exposure in the clinic, which is proposed to be via P-gp/BCRP inhibition. Given that amiodarone is also a P-gp inhibitor, the combined P-gp inhibition effect by amiodarone and the non-nucleotide DAA has the potential to lead to a greater increase in SOF exposure. However, this may not be clinically relevant as exposure for the major circulating metabolite of SOF (GS-331007) was not affected.
- PK interactions with amiodarone through either inhibition of CYP3A4 or protein binding displacement. However, simeprevir shows a weak clinical interaction with midazolam, a sensitive CYP3A4 probe substrate and LDV and DCV show no clinically meaningful interaction with CYP3A4 substrates.

The applicant is planning to evaluate the direct interaction of one of the DAAs with cardiomyocytes which exacerbates the pharmacodynamic effect of amiodarone.

Further evaluation of the feasibility of conducting multielectrode array electrophysiology studies (b) (4)

Reviewer Comment: The temporal relationship between initiating DCV/SOF against a background of amiodarone (and, in some instances, a beta-blocker, often prescribed for varices, or a calcium channel blocker), the rapid onset of symptomatic bradycardia and evidence of positive dechallenge and rechallenge cumulatively lend support to a causal relationship between use of DCV/SOF and amiodarone. This reviewer is in agreement with the Applicant that the concomitant administration of amiodarone with DCV/SOF may result in severe or life threatening bradycardia. Despite a lack of a clear understanding of the underlying mechanism for this interaction, these safety findings warrant labeling under Warnings and Precautions (See Section 9.2 for Labeling Recommendations).

Additionally, review of the other cases of cardiac arrhythmias reported without concomitant use of amiodarone did not reveal any causal association with DCV or DCV/SOF±RBV. These patients had pre-existing comorbid conditions, risk factors or concomitant medications or other confounding factors which makes clear attribution to DCV or other drugs in the HCV treatment regimen difficult.

Cardiac Failure and Cardiomyopathy Analyses

To further explore potential signals for cardiac toxicity, on March 4, 2015, the Applicant conducted a cumulative search of their safety database with a cut-off date of February 20, 2015. The search included in Standardized MedDRA queries (SMQ) “Cardiac Failure” or “Cardiomyopathy”. The search included serious interventional clinical trial reports and all serious and non-serious spontaneous, expanded access programs and literature adverse events.

This search identified 39 reports of cardiac failure or cardiomyopathy-related events associated with the use of DCV. Of these 39 cases, 13 were excluded from additional discussion because the subjects were administered BMS-986094 which was discontinued from development due to associated cardiotoxicity. The remaining 26 cases were all considered serious and 7 cases had a fatal outcome. The time to onset (provided in 17 cases) ranged from 9 to 185 days (median 51 days) after initiation of daclatasvir combination therapy.

Of the 26 cases, 2 were reported from interventional clinical trials, 17 from the DCV EAP (including 7 from the French cohort ATU), 2 from the German Registry of HCV and 5 were spontaneous reports (4 from Japan and 1 from France).

Of the 26 reports, 18 reported the Preferred Terms “cardiac failure” or “cardiac failure congestive”: 10 received DCV/SOF with (4) or without (6) RBV. Another 2 patients from

the EAP received DCV/SOF with or without RBV but the full regimen was not reported. There were 5 patients that received DCV/ASV with (2) or without (3) pegIFN/RBV. One patient received DCV/pegIFN/RBV.

There were 4 reports with the Preferred Term “pulmonary edema”, 2 of which received DCV/SOF and had a fatal outcome, both attributed to advance or end-stage liver disease. The remaining 4 reports were 1 report of cardiopulmonary failure (DCV/SOF), 1 report of congestive cardiomyopathy (DCV/SOF), 1 report of cardiac failure congestive, cardiomyopathy and systolic dysfunction (DCV/SOF/RBV) and 1 report of left ventricular failure and ischemic cardiomyopathy (DCV/ASV).

Reviewer Comment: All cases were reviewed and assessed based on the information available. Overall, the available safety data does not provide a causal association between DCV and cardiac failure and/or cardiomyopathy. Several cases lack enough detail for appropriate classification, particularly because edema, ascites and fluid retention, observed in right-sided heart failure, can also occur with cirrhosis. These reports also occurred in middle-aged and elderly patients where the incidence of risk factors for these conditions are higher and may occur spontaneously. Lastly, the reports are confounded by pre-existing cardiac disease and/or comorbid conditions which may cause or exacerbate heart failure.

Internal consultation to the Division of Cardiovascular and Renal Products was completed by Dr. Shari Targum, regarding the risk of DCV/SOF associated cardiac dysrhythmias or symptomatic bradycardias, with and without the administration of amiodarone therapy. The submitted safety reports, ECGs and summary of subjects taking Beta-Blockers and Calcium Channel Blockers were reviewed. The overall assessment of the consult supported a potential for a DDI with DCV/SOF with concomitant use of amiodarone. Based on the available information, the consultant did not identify a signal for cardiac dysrhythmia or dysfunction for DCV/SOF in the absence of amiodarone therapy. My independent clinical review of the available data also supports these conclusions. Regardless, post-marketing vigilance for cardiac related events will continue as a focus of ongoing safety assessment for DCV containing regimens.

Hepatic Safety

The original NDA review safety evaluation focused predominately on hepatic safety related to the combination of DCV and ASV, a HCV NS3 protease inhibitor. The hepatic safety findings were primarily from the phase 3 DCV/ASV DUAL program. Overall, ASV appeared to be related to a higher proportion of liver-related events, particularly in subjects of Japanese ancestry. The following points summarize the findings that are discussed in detail in the original NDA review regarding liver-related safety and the role of DCV from both the phase 2 and phase 3 data.

- Nonclinical data for DCV showed the major nonclinical organs of toxicity were the liver and adrenal gland. No significant findings were associated with the adrenal changes. The liver changes (rat and monkey; increased drug concentration in the liver, hypertrophy/hyperplasia with AST/ALT increases, portal/periportal hepatic lesions at high doses) were considered reversible and monitorable in the clinic (*Reviewer Comment: These nonclinical liver findings are consistent with findings from other liver-concentrated HCV drugs. Hepatic necrosis was not reported.*).
- Nonclinical data for ASV showed the major nonclinical organs of toxicity were the gastrointestinal tract and liver. Liver findings (rat and dogs) were increased drug concentration in the liver, increase in weight of the liver, increase in hepatic enzymes (roughly doubling for all: ALT, ALP, TBIL, GGT) with minimal/slight hepatocellular coagulative necrosis.
- Results from a phase 2 dose finding trial (AI447016) of ASV in combination with PegIFN/RBV in treatment-naïve subjects with genotypes 1 and 4 HCV infection demonstrated a trend in the frequency and magnitude of ALT and AST elevations, and occasionally bilirubin elevations, in the ASV treated groups, most frequently at doses > 200 mg BID.
- The phase 2 evaluation of ASV/pegIFN/RBV demonstrated a higher proportion of liver related discontinuations compared to DCV/pegIFN/RBV.
- The overall incidence of hepatic AEs was low in DCV/pegIFN/RBV treated subjects (19/505; 4%) and comparable with placebo/pegIFN/RBV (8/174; 5%).
- The rate of discontinuation due to hepatic AE was low for DCV/pegIFN/RBV (0.4%) and comparable to placebo/pegIFN/RBV (1%), and occurred in subjects with cirrhosis with decompensation, which was likely attributable to pegIFN/RBV exposure.
- The proportion of subjects with grade 3/4 ALT elevations was the same for DCV/pegIFN/RBV and placebo/pegIFN/RBV (2%, respectively).
- No DCV/pegIFN/RBV subjects met the predefined criteria for potential drug-induced liver injury (DILI); however, 5/505 (1%) subjects met the laboratory criteria for Hy's Law. These cases were confounded by comorbid conditions, underlying cirrhosis with progression of liver disease while on treatment, or had virologic breakthrough leading to elevation of liver biochemistries. DCV was not clearly associated with liver-related toxicity in these cases.
- The phase 2 data from AI444040 evaluating DCV/SOF±RBV did not reveal any cases of increased liver biochemistries (ALT, AST or bilirubin) or evidence of hepatotoxicity.
- The Applicant convened an external panel of experts to review the totality of the DCV/ASV DUAL hepatic safety data. The overall opinion of the expert panel was that DCV/ASV containing regimens are capable of rarely causing hepatocellular injury and that this liver injury can cause liver dysfunction. While liver failure was not observed in the phase 2/3 clinical trials, the risk for liver failure remains

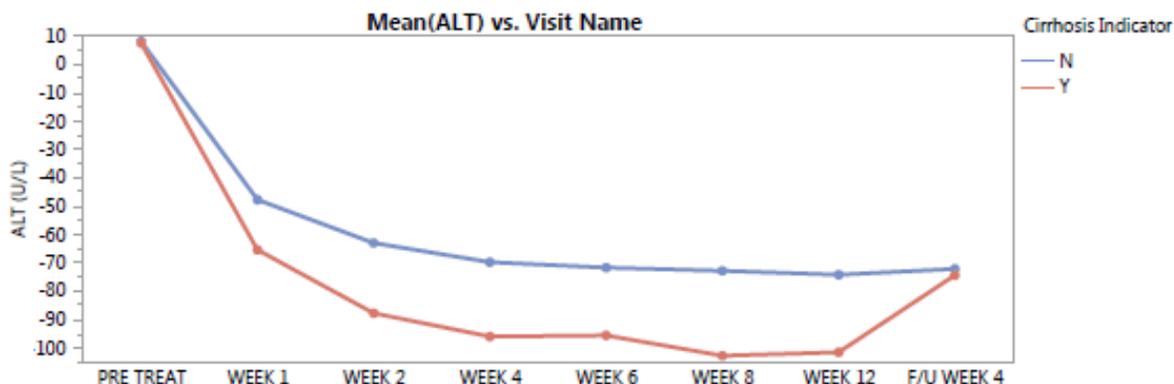
possible. Additionally, the panel had consensus that the issue of hepatotoxicity appeared related to ASV and not DCV.

Based on the totality of the available hepatic safety data from the DCV/ASV DUAL program, and by evaluating DCV in regimens without ASV (comparison to placebo with the pegIFN/RBV background and DCV/SOF), the data suggests that the increased risk for hepatic toxicity appears most-likely related to ASV, rather than DCV. However, it should be noted that any hepatic concentrated drug may have the potential to cause liver abnormalities in a broad population, particularly one with underlying comorbidities such as chronic HCV.

Overall evaluation of hepatic events for DCV/SOF±RBV from both ALLY-3 and AI444040 did not reveal any new risks or safety signals for liver toxicity. There were no hepatic SAEs, no discontinuations due to serious or nonserious hepatic AEs, no grade 3 or 4 hepatic events and no subjects met Hy's Law laboratory or clinical criteria. No subjects in ALLY-3 reported hepatic AEs and 3 subjects from AI444040 reported nonserious hepatic AEs of liver palpable subcostal (AI444040-20-312), hepatic pain (AI444040-18-83) and hepatomegaly (AI444040-20-313).

Analysis of liver biochemistry results from subjects in ALLY-3 showed that overwhelmingly, subjects treated with DCV/SOF rapidly normalized their liver biochemistries while on-therapy. Figure 1 shows the mean ALT by study week on treatment. Both cirrhotic and non-cirrhotic subjects had improvement in the mean ALT measurements while on therapy.

Figure 1: Mean ALT (U/L) by Visit for ALLY-3



Source: Laboratory datasets ALLY-3

Figure 2 provides results for liver biochemistries for all subjects in the trial by Study Day. The dotted lines represent the cut points for the peak liver biochemistries according to Hy's Law laboratory criteria (AST and ALT 3x ULN, Total Bilirubin 2xULN and ALP 2.5xULN). Overall, 71 (47%) subjects had at least 1 aminotransferase value above 3x ULN during ALLY-3. The majority of these subjects had elevation of ALT and AST above 3x ULN in the pretreatment phase through approximately Week 2 on treatment. By Week 2, the liver biochemistries improved below the cut points for all subjects on treatment. Elevations in ALT and AST beyond 3x ULN occurred in a few subjects who developed HCV viral relapse after end of treatment, during the follow-up phase (beyond Day 84). There were no significant abnormal trends for ALP or Total Bilirubin.

Figure 2: Liver Biochemistries from ALLY-3 by Study Day



Source: Laboratory datasets ALLY-3

Rash-related Events

In order to determine if a DCV-combination regimen may increase the frequency and/or severity of rash events known to be associated with either pegIFN or RBV or other DAAs, further analyses were completed. The rash composite analysis included the following MedDRA preferred terms: dermatitis allergic, vasculitic rash, eczema, purpura, petechiae, dermatitis acneiform, ecchymosis, gingival disorder, cheilitis, pemphigoid, acute generalized exanthematous pustulosis, dermatitis, dermatitis bullous, dermatitis exfoliative, dermatitis exfoliative generalised, drug eruption, drug rash with eosinophilia and systemic symptoms, erythema multiforme, exfoliative rash, fixed eruption, genital rash, haemorrhagic urticaria, idiopathic urticaria, mucocutaneous rash, oral mucosal eruption, rash, rash erythematous, rash follicular, urticaria, rash generalised, rash macular, rash maculo-papular, rash maculovesicular, rash morbilliform, rash papular, rash papulosquamous, rash pruritic, rash pustular, rash vesicular, septic rash, Stevens-Johnson syndrome, tongue eruption, toxic epidermal necrolysis, toxic skin eruption, and urticaria papular.

Rash related AEs occurred at a low frequency with DCV/SOF±RBV, with more events in subjects who received RBV as part of their regimen, which is consistent with the known AE profile of RBV. Only 1 additional case of rash (rash maculo-papular, mild and resolved on treatment) was reported from ALLY-3. However, there was also one case of treatment-related erythema of moderate severity which also resolved on treatment. There were 19 additional subjects with rash (composite PT search) from AI444040, all except 1 case were considered grade 1 or 2, and all resolved; none were serious or led to discontinuation of treatment. A higher proportion of subjects who were treated with DCV/SOF/RBV had any grade rash (composite) compared with the subjects who did not receive RBV: 13.3% (12/90) versus 2.9% (8/273), supporting the contribution of RBV to the development of rash.

In the pegIFN/RBV phase 2 regimens, the incidence of rash (composite) was comparable between DCV/pegIFN/RBV and placebo/pegIFN/RBV subjects (34% and 40%, respectively). Grade 3 or 4 rash AEs were reported in 7 (1%) DCV/pegIFN/RBV subjects compared to none in the placebo group. None of the rash events were serious, however rash led to discontinuation in 6 of the DCV/pegIFN/RBV treated subjects and none in the placebo group.

Overall, DCV did not appear to increase the frequency and/or severity of rash-related events.

Psychiatric Disorders

Psychiatric AEs have been commonly reported in HCV clinical trials, in particular due to the use of pegIFN/RBV. Psychiatric AE were observed much less frequently in subjects

treated with DCV/SOF±RBV than in those treated with pegIFN/RBV, with and without DCV, which is consistent with the known AE profile of pegIFN/RBV.

In ALLY-3, 15 subjects (10%) reported psychiatric AEs during the treatment-period. All the AEs were grade 1 or 2, none were serious or led to discontinuation of treatment. The most frequently reported event was insomnia (9 subjects, 6%), followed by anxiety (4 subjects, 3%). Irritability was reported by 2 subjects (1%) and abnormal dreams and panic attack by one subject each.

Overall, based on the totality of the data there is no psychiatric safety signal associated with DCV/SOF. Generally, higher incidences of psychiatric AEs have been observed with the addition of RBV to DCV/SOF and in pegIFN/RBV based regimens.

Hypersensitivity; Pyrexia and Eosinophilia

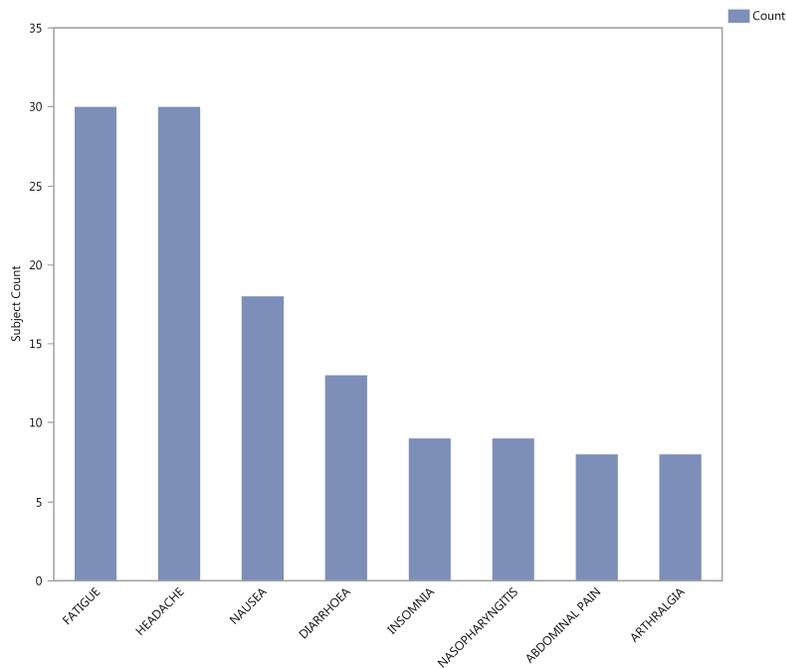
Clinical review of the original NDA identified hypersensitivity and pyrexia with eosinophilia in association with DCV/ASV use. The data supports ASV as the likely drug contributing to the risk of hypersensitivity and pyrexia/eosinophilia observed in the DUAL DCV/ASV phase 3 data, in particular in Japanese subjects. Therefore, analyses were completed evaluating subjects who received DCV/SOF in ALLY-3 for potential hypersensitivity and/or pyrexia and eosinophilia. No subjects met criteria for hypersensitivity or had reported pyrexia or evidence of significant eosinophilia.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Overall in ALLY-3, 70% of subjects (107/152) reported at least 1 AE (all grades). The majority of treatment-emergent AEs were mild or moderate in intensity and none led to discontinuation. Overall, the most common AEs (≥5%) regardless of causality were fatigue (n=30; 20%), headache (n=30; 20%), nausea (n=18; 12%), diarrhea (n=13, 9%), insomnia (n=9; 6%), nasopharyngitis (n=9, 6%), abdominal pain and arthralgia (both n=8, 5%) (Figure 3). Generally, the proportions of subjects reporting AEs was similar between subjects with and without cirrhosis; however, headache and arthralgia were reported more frequently in subject with cirrhosis compared to those without cirrhosis (31% vs. 18% and 13% vs. 4%, respectively). However, the cirrhotic group is small (n=32) so interpretation of these data are limited by the small size of this cohort.

Figure 3: Most Common On-Treatment AEs in $\geq 5\%$ of Subjects in ALLY-3



Dictionary-Derived Term ordered by Total Count (descending)

Where(Percent Occurrence \geq 5.009 & Percent Occurrence \leq 19.7)

Source: AE dataset ALLY-3

The most common AEs ($\geq 5\%$) treatment-related to study drugs were fatigue (n=21, 14%), headache (n=21, 14%), nausea (n=12, 8%) and diarrhea (n=7, 5%). Relatedness was considered for the regimen DCV/ SOF and not for the individual drug components of the regimen.

The ALLY-3 treatment-related AEs are similar to the overall findings from AI444040. Fatigue, headache, nausea and diarrhea were also the most-common treatment-related AEs ($\geq 5\%$) reported in AI444040. Overall, the safety profile was very similar between the DCV/SOF subjects in ALLY-3 and the DCV/SOF \pm RBV subjects from AI444040.

7.4.2 Laboratory Findings

Analyses of laboratory findings from ALLY-3 did not reveal any clinically relevant trends. Most laboratory abnormalities were grade 1 or 2. In total, on-treatment grade 3 or 4 laboratory abnormalities were reported in 10 subjects (7%). One subject reported a grade 4 lipase elevation; however, the subject had no clinical AEs related to pancreatitis. Nine subjects reported grade 3 events: two subjects each reported increase ALT, increased INR, decreased platelets and increase lipase and one subject reported decreased lymphocytes. The 2 subjects with grade 3 ALT were both non-

cirrhotic and had grade 3 ALT pre-treatment and on-treatment at Week 1 (ALTs were in the low 200s). The ALT normalized to grade 0 by Week 2 or 4 and remained grade 0 for the duration of treatment. Two subjects (one subject F4 and the other F1 at baseline) had grade 3 INR increases. Both were single, isolated events without associated bleeding (INR values were 2.53 and 2.75). Two subjects reported grade 3 decreased platelets; both had baseline cirrhosis. One subject had a grade 2 decreased platelets at baseline and a single grade 3 value at Week 6 (47×10^9 /L); the other subject also had baseline portal hypertension and had grade 3 values at Weeks 2 and 12 (46 and 47×10^9 /L). Three subjects had grade 3 lipase elevations, but none had clinical pancreatitis or other associated AEs reported.

Table 8 provides analyses of selected on-treatment worst grade clinical laboratory test abnormalities from ALLY-3. No grade 3 or 4 laboratory abnormalities occurred in greater than 2% of subjects; however, if grade 3 and 4 laboratory abnormalities are pooled together, >2% of subjects had increased total lipase. All other laboratory abnormalities were grade 1 and 2. Analyses of ALT and AST laboratories are discussed in Section 7.3.5 under Hepatic Safety. In Table 8, only the toxicity grades with reported events are included for the individual laboratory tests (for example, no grade 3 or higher events were reported for AST and therefore they are not included).

Table 8: Selected On-Treatment Worst Grade Laboratory Tests for ALLY-3

Laboratory Test	Standard Toxicity Grade	AI444218 N=152
Alanine Aminotransferase (ALT)	1	53 (35%)
	2	16 (11%)
	3	2 (1%)
Aspartate Aminotransferase (AST)	1	41 (27%)
	2	6 (4%)
Lipase, Total (colorimetric assay)	1	44 (29%)
	2	29 (19%)
	3	3 (2%)
	4	1 (1%)
Platelet Count	1	27 (18%)
	2	19 (13%)
	3	2 (1%)
Creatinine	1	21 (14%)
	2	3 (2%)
Intl Normalized Ratio (INR)	1	11 (7%)
	2	1 (1%)
	3	2 (1%)
Bilirubin, Total	1	9 (6%)
	2	3 (2%)

Alkaline Phosphatase (ALP)	1	6 (4%)
Glucose, Serum	1	6 (4%)
	2	1 (1%)
Hemoglobin	1	4 (3%)
	2	1 (1%)
Albumin	1	4 (3%)
	2	1 (1%)
Creatine Kinase (CK)	1	1 (1%)
	3	1 (1%)

Source: laboratory datasets ALLY-3

7.4.3 Vital Signs

Analyses of ALLY-3 data were completed for changes in mean heart rate, systolic blood pressure and diastolic blood pressure for the on-treatment period. There were no trends observed for clinically meaningful increases or decreases for these vital sign parameters and no adverse events related to blood pressure abnormalities.

7.4.4 Electrocardiograms (ECGs)

In comparing end-of-treatment Week 12 to baseline ECG parameters, there were no clinically significant ECG abnormalities observed in ALLY-3. Please see Section 7.3.5 for the discussion of cardiac arrhythmia observed with DCV/SOF and concomitant use of amiodarone.

7.4.5 Special Safety Studies/Clinical Trials

A thorough QT (TQT) was completed for DCV. Fifty-six subjects received daclatasvir 60 mg, 180 mg, placebo and moxifloxacin 400 mg. No significant QTc prolongation effects of daclatasvir doses of 60 mg and 180 mg) were detected in the TQT trial. The largest upper bounds of the 2-sided 90% CI for the mean differences between DCV 60 mg and placebo, and between DCV 180 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, indicating that assay sensitivity was established.

7.4.6 Immunogenicity

Because both DCV is a small molecule and is not a peptide, immunogenicity effects were not anticipated and therefore not specifically assessed during the clinical trials.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Only DCV 60 mg once daily dosing was used in all pivotal clinical trials. This is the proposed dose for use if the marketing application is approved. Dose adjustment for DCV for 30 mg and 90 mg are proposed for DDI. Please see Section 7.5.5.

7.5.2 Time Dependency for Adverse Events

The duration for ALLY-3 was 12 weeks as is proposed in the dosing indication; therefore no duration dependency evaluation for AEs was performed.

However, in the original NDA the duration for the phase 3 trials for the DCV/ASV DUAL regimen was 24 weeks. Analyses of the reported AEs in phase 3 DUAL trials showed majority of AEs during the DUAL trials occurred in the first 12 weeks of the regimen. Overall, less than 13% of subjects reported AEs occurring between Weeks 12 and 24 on-treatment in the phase 3 DUAL trials. No additional safety risks have been identified for DCV with dosing durations up to 24 weeks.

7.5.3 Drug-Demographic Interactions

The exposure of DCV in females is approximately 30% higher compared to males. However, no clinically relevant trends in clinical adverse events or laboratory findings have been identified across the development program. Analyses by sex, age, race and country did not reveal any clinically significant differences or trends in AE reporting or laboratory findings in ALLY-3. However, analyses by race were limited due to the small numbers of non-white subjects enrolled. Similarly, ALLY-3 was conducted solely in the U.S. and Puerto Rico; therefore, analyses by region are limited. Females were well-represented in ALLY-3 with 41% of the population identified as female.

Also see the Clinical Pharmacodynamics review for discussion of the FDA exposure response analyses.

7.5.4 Drug-Disease Interactions

Multiple analyses were completed to evaluate AEs for any patterns where subjects with baseline cirrhosis may have increased risk for particular safety events in ALLY-3. Generally, AE events were similar in frequency and intensity in subjects with baseline cirrhosis compared to those without cirrhosis. The proportions of subjects with AEs of headache and arthralgia tended to be higher in subjects with cirrhosis in ALLY-3 (31% and 13% in cirrhotics vs 18% and 4% in noncirrhotics, respectively). Additional analyses also focused on liver-related AEs and laboratory abnormalities, again no difference was

found for subjects with or without baseline cirrhosis which is consistent with the Applicant's findings.

Evaluation of both DCV in subjects with hepatic and renal impairment was completed. See Section 4.4.3 in the original NDA clinical review for details.

7.5.5 Drug-Drug Interactions

Please refer to the Clinical Pharmacology Review of the original NDA for detailed assessment of the phase 1 drug-drug interaction (DDI) trials and labeling considerations.

In this NDA resubmission, the major DDI issues were related to labeling for use of DCV with strong CYP3A inhibitors (decrease DCV dose to 30 mg QD), moderate CYP3A inhibitors (monitor for DCV related adverse events), and moderate CYP3A inducers (increase DCV dose to 90 mg QD). In addition, strong CYP3A inducers are contraindicated.

(b) (4)



7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The maximum study duration of the DCV clinical trials (majority of data at 12-24 weeks duration and limited 48 weeks duration) limits the assessment for oncologic events. Most of the reported malignancies are those consistent with the patient population (e.g. hepatocellular carcinoma) and no clustering of any particular events was noted.

In addition, there is no signal for drug-related increase in tumor incidence in the 2 year and 6 month nonclinical carcinogenicity studies.

7.6.2 Human Reproduction and Pregnancy Data

In nonclinical data, there was no evidence of selective developmental toxicity associated with DCV across the standard battery of reproductive toxicity studies.

Developmental toxicities were observed in both rats and rabbits exposed to DCV (in the presence of maternal toxicity). DCV was shown to cross the placenta in limited amounts and was excreted into milk in rodent studies. These results suggest that both the fetus and nursing infants of women receiving DCV may be exposed to DCV and its metabolites.

There are no clinical trials of DCV in pregnant and lactating women. While pregnant and lactating women were excluded from DCV clinical trials, a total of 35 pregnancies of study subjects or female partners were reported as of December 23, 2014, 3 of which have occurred since the 32 pregnancies reported in the DCV Safety Update Report with the original NDA. One additional spontaneous abortion was reported for a subject that was previously reported as “not provided”. In the majority of cases, DCV was administered with RBV, a known teratogen.

Overall of the 35 pregnancies reported, 28 were in subjects treated with DCV. Known pregnancy outcomes for these 28 cases are as follows: 12 healthy infants, 4 elective terminations, 4 spontaneous abortions, 1 fetal malformation (unviable renal agenesis), and 6 outcomes were either not provided or unavailable due to ongoing pregnancy at the time of database lock. Post-database lock, 1 male infant was born with an unspecified infection due to placental abruption in a female subject (subject AI444218-8-164).

There are currently no known associations between DCV and poor pregnancy outcomes; however, data are limited.

7.6.3 Pediatrics and Assessment of Effects on Growth

No clinical trials of DCV in pediatric subjects have been conducted to date; and therefore, the safety and efficacy of DCV has not been established in the pediatric population.

Waiver Request for Children < 3 years of age (FDA agreed)

FDA has agreed to a full waiver in children < 3 years of age (FDA correspondence October 10, 2013). The rationale for the waiver in children < 3 years of age is that chronic HCV in this age group is relatively benign and spontaneous clearance is possible (24% by age 3 years).

Pediatric Study Plans for DCV

The Applicant included a proposed pediatric study plan (PSP) for DCV and for ASV with the original NDA submission. However, due to the business decision by the Applicant to withdraw ASV from development, the PSP is no longer pertinent to the indication sought for DCV with this current NDA resubmission. However, an appropriate pediatric plan has been submitted which supports the proposed PREA PMR for DCV in combination with other DAAs for treatment of chronic HCV in pediatric patients from 3 years to <18 years of age.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Experience regarding the effects of DCV overdose in humans is limited. Events typically represented inadvertent single extra doses of study medication and did not result in clinical symptoms or require treatment intervention.

The potential for drug abuse, withdrawal or rebound for DCV/SOF therapy was not studied. Risk for abuse or dependent potential or withdrawal or rebound is not anticipated.

7.7 Additional Submissions / Safety Issues

The Applicant provided summary safety data from 2 expanded access programs, the ATU cohort and the UK CUP. Summaries of high level safety data are provided below.

French Authorization for Temporary Use (ATU) Cohort (AI444258)

The French National Agency for Medicines and Health Products Safety (ANSM) granted on March 4, 2014, a temporary authorization for use (ATU) so-called “cohort” for BMS DCV 60 mg and 30 mg (b)(4) tablets for treatment of chronic hepatitis C infection for AI444258. This ATU cohort procedure allows for early availability of a drug product that does not have marketing authorization when it is intended for the treatment, prevention, or diagnosis of serious or rare diseases in the absence of other marketed suitable treatments.

For participation in this cohort, patients must have presented with advanced hepatic disease (hepatic fibrosis F3/F4 or with HCV extra-hepatic manifestations) without appropriate therapeutic alternatives, or were on a waiting list for hepatic or renal transplantation, or had undergone hepatic transplantation and presented with recurrence of hepatitis C infection.

As of the data cutoff for these interim data (December 3, 2014), approximately 4111 patients were enrolled, which included 15% (601/4026) patients with HCV genotype 3, 9% (371/4111) liver transplant patients, and 6% (262/4109) patients with an indication

for liver or kidney transplantation. Approximately 84% (3365/4023) received DCV/SOF and 16% (658/4023) received DCV/SOF/RBV.

Overall, the enrolled population of the ATU cohort is much “sicker” than DCV clinical trials populations; the majority of patients have complex comorbid conditions and concomitant medications which were excluded from use in clinical trials. The population is predominantly male (67%, 2714/4022) with an average age of 56 years. Approximately 93% (3796/4069) had advanced fibrosis (METAVIR stage F3/F4) and/or extrahepatic manifestations of chronic HCV infection; 69.5% (2827/4069) of patients had a diagnosis of cirrhosis (fibrosis stage F4). Approximately 9% (371/4111) were post liver transplant patients, 6% (262/4109) had an indication for liver or kidney transplant, 18% (733/4111) were HIV/HCV co-infected, and 82% (3281/4029) were previously treated with HCV antiviral agents.

As of December 3, 2014, the company has received a total of 490 initial AE reports including 1050 events; of the 490 initial reports, 120 were considered serious. Of the 1050 AEs, 191 were serious, with 53 considered related to DCV by the reporter. Cumulatively there have been 18 cases with fatal outcome; 3 were considered possibly related by the reporter (cardiac failure/hemorrhagic stroke; hepatic encephalopathy; hepatic cirrhosis), but all were considered not related/not likely related by the Company.

Reviewer comment: The fatal cases were reviewed and I support the assessment that DCV is not causally related in these events. All are confounded by underlying disease, comorbid conditions and concomitant medications including other DAAs.

The most significant finding from the interim safety review was the evaluation of the 11 cardiac events, including 7 reports of arrhythmias. Overall, 0.5% of subjects were also receiving concomitant amiodarone. Evaluation of these cardiac events led to the suggestion of a possible drug-drug interaction between DCV/SOF and amiodarone, resulting in significant bradycardia. Discussions of these findings are detailed in Section 7.3.5.

Other than the DDI between DCV/SOF and amiodarone, review of the MedDRA SOCs, and reported AEs did not reveal any new safety signals associated with use of DCV in this ATU cohort. There were 11 events in “Hepatobiliary Disorders” SOC, including single reports of hepatic function abnormal, hypertransaminasemia, and jaundice. Considering the advance stage of liver disease in this cohort, hepatic related events were relatively uncommonly reported in this population. Overall, the current safety profile of DCV in this population with advanced liver disease and comorbid conditions is consistent with that established for DCV from the available clinical trials data. The ATU is ongoing with most patients still receiving treatment at this time of this analysis; close safety monitoring of this cohort will continue.

United Kingdom (UK) Compassionate Use Program (CUP) Cohort

The CUP for DCV was established to provide UK patients with chronic HCV who are at high risk of liver decompensation or death within 12 months if left untreated, and who have no available treatment options. In the UK CUP, patients receive DCV/SOF±RBV for 12 weeks, with a possible extension to 24 weeks (to date, only 3 patients received 24 weeks).

As of January 20, 2015, the interim data showed 210 patients received therapy. Most had HCV genotype 3 (62%); the majority (89%) was treated with DCV/SOF/RBV. Similar to the ATU cohort, the enrolled population had advanced liver disease and significant comorbidities. The majority had cirrhosis (89%), most of whom had prior decompensation events; 16 were HIV-1 coinfecting; 17 had liver transplantation, with an additional 4 patients receiving transplants while on HCV treatment and another 21 were on the transplant waiting list; 18 had been diagnosed with hepatocellular carcinoma. Almost 50% had Model for End-Stage Liver Disease (MELD) scores >10.

The Applicant searched their AWARE safety database to identify all spontaneous and literature AE reports received for this cohort from July 1, 2014 through January 20, 2015. Overall, 24 reports including 37 events were identified for this interim report. Of these 24 reports, 20 were serious (including 29 serious AEs), and 4 had a fatal outcome (all in patients with cirrhosis). These reports occurred in 10 males and 14 females ranging in age from 33 to 72 years (N = 23) with a median age of 53 years.

The most frequently reported AEs occurred in the MedDRA SOCs of “Nervous System Disorders” (encephalopathy/hepatic encephalopathy) and “Gastrointestinal Disorders.” Overall, 17 of the 37 reported events described complications of underlying hepatic disease. No cardiac AEs were reported. Cause of death was provided for 3 of the 4 cases with fatal outcome: multi-organ failure (concomitant RBV; time to onset 64 days), upper gastrointestinal hemorrhage (time to onset 47 days), and sepsis (concomitant RBV; death occurred 19 days after last dose of HCV therapy); the fourth patient had been hospitalized with severe electrolyte disturbances (time to onset 102 days) and subsequently expired. The events were considered unrelated to HCV therapy in all cases. No new safety signal or trends were identified from this interim safety report.

Reviewer Comment: The CIOMS adverse event reporting forms were submitted and reviewed. The fatal events were complicated by progression of underlying serious liver disease, infection, comorbid conditions and concomitant medications. I agree with the assessment that the deaths were not causally related to use of DCV. Additionally, review of the non-fatal reports generally showed complications of cirrhosis (jaundice, encephalopathy, upper GI bleeding etc.) or infection leading to decompensation or other acute changes. There was no identifiable new safety signal or trend for DCV in this interim report.

8 Postmarket Experience

There is no U.S. postmarket experience. Please see section 7.7 which describes the overall safety profiles provided in the expanded access programs which have been ongoing post-approval in Europe. The Applicant has estimated based on internal shipment data, that approximately 25,466 patients have been exposed to DCV, which includes 4051 global and 21,415 Japanese patients.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Labeling negotiations are ongoing. Below are general clinical recommendations for proposed labeling.

- **Indications and Usage (1):** DCV will specifically be indicated for use with sofosbuvir for the treatment of patients with genotype 3 HCV infection. A Limitations of Use statement regarding reduced rates of SVR in patients with cirrhosis will be included.
- **Recommended Dosage (2.1):** The recommended dosage of DCV is 60mg taken orally once daily in combination with sofosbuvir. The recommended duration will be 12 weeks. A statement is included regarding the optimal duration of DCV/SOF for patients with cirrhosis has not been established and refers to Clinical Studies (14).
- **Dosage Modification Due to Drug Interactions (2.2):** This section discusses the need to reduce the dose of DCV to 30 mg once daily when coadministered with strong CYP3A inhibitors and to increase the dosage to 90 mg once daily when coadministered with moderate CYP3A inducers. DCV is contraindicated with strong CYP3a inducers.
- **Warnings and Precautions, Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions (5.1):** This section will describe known and potential drug-drug interactions (DDI) that may lead to loss of therapeutic effect and possible development of resistance, need for dosage adjustments of concomitant medications or DCV and possible increased exposures leading to adverse reactions for concomitant drugs or DCV; and refers to Tables 1 and 3.
- **Serious Symptomatic Bradycardia When Coadministered with Sofosbuvir and Amiodarone (5.2):** This section details the postmarketing cases of symptomatic bradycardia and provides details about the cases resulting in bradycardia and requiring pacemaker. Coadministration of amiodarone with

SOF in combination with another DAA, including DCV is not recommended; however, guidance for coadministration in patients with no alternative treatment options will be provided. Patients should be counseled about the risk of serious symptomatic bradycardia and cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended followed by outpatient self-monitoring of heart rate on a daily basis for 2 weeks.

- **Clinical Trials Experience (6.1):** This section will provide the safety database for the approval (n=868) based on this resubmission. However, FDA took under consideration the comprehensive clinical development program with > 7900 subjects exposed to DCV in phase 1, phase 2, and phase 3 studies during the review of the original and resubmission NDA review. This section provides the safety findings from the ALLY-3 trial. The most common adverse reactions were headache and fatigue. Table 2 in this section provides the ADRs reported in ≥ 5 % of subjects in ALLY-3 (e.g. headache, fatigue, nausea and diarrhea). The only grade 3 and 4 (at least $>3 \times \text{ULN}$) laboratory abnormalities that were reported at a frequency of 2% or higher were transient, asymptomatic lipase elevations.
- **Postmarketing Experience (6.2):** DCV is approved in the EU and Japan. This section describes the Cardiac Disorder of serious symptomatic bradycardia in patients taking amiodarone who initiate treatment with SOF in combination with another DAA, including DCV, and refers to Warnings and Precautions (5.2) and Drug Interactions (7.3).
- **Pregnancy and Lactation (8.1 and 8.2):** Labeling in this section is updated in the PPLR format.
- **Clinical Studies (14):** This section will describe demographics and baseline characteristics of the phase 3 trial ALLY-3 and provide a table of the SVR results by subjects with and without cirrhosis and the outcomes of subjects who did not achieve SVR12. Additionally, a reference is included to the Microbiology Section 12.4 for display of outcome data related to baseline NS5A Y93H polymorphism. .

9.3 Advisory Committee Meeting

No advisory committee meeting was held for this application.

9.4 Clinical Investigator Financial Disclosure Review Template

Application Number: 206843

Submission Date(s): February 13, 2015

Applicant: BMS

Product: Daclatasvir

Reviewer: Wendy Carter, DO

Date of Review: February 28, 2015

Covered Clinical Study (Name and/or Number): AI444218 (ALLY-3)

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>212 unique individual served as either PIs or Sub-Is in the covered trial</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>none</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>none</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation

reason:		from applicant)
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BMS has adequately disclosed financial interests/arrangements with clinical investigators in accordance with 21CFR Part 54. The Applicant provided certification (Form 3454) which indicates that the investigators and sub-investigators who participated in ALLY-3 had no financial arrangements with the Applicant. No subjects had disclosable financial information. Only one sub-investigator was listed with an outstanding financial disclosure; however, based on a note to file dated 10-Feb-14, this person was listed on the initial 1572 but was no longer participating at the time the site was activated. Therefore, this sub-investigator was not included in my assessment of outstanding financial disclosures and no other investigators or sub-investigators met that criterion.

Based on the lack of any investigators with a financial interest and the objective nature of the trial design including a central laboratory HCV RNA PCR based efficacy endpoint, the likelihood that the trial results were substantively biased based on financial interest is minimal.

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/s/

WENDY W CARTER
06/29/2015

KIMBERLY A STRUBLE
06/29/2015

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	John Farley, M.D.,M.P.H.
Subject	Deputy Office Director Decisional Memo
NDA #	206843
Applicant Name	Bristol Myers Squibb (BMS)
Date of Submission	March 31, 2014
PDUFA Goal Date	November 28, 2014
Proprietary Name / Established (USAN) Name	Daklinza/ daclatasvir
Dosage Forms / Strength	30 mg and 60 mg tablets
Proposed Indication	Treatment of chronic hepatitis C infection
Action:	<i>Complete Response</i>

Daclatasvir (DCV) is a new molecular entity NS5A replication inhibitor submitted for the proposed indication of treatment of chronic hepatitis C infection. The dosage form is a tablet in strengths of 30 mg and 60 mg. The proposed adult dosage is 60 mg once daily (with dose adjustments to 30 mg or 90 mg once daily when co-administered with certain interacting drugs). NDA 206843 for DCV was submitted by the applicant with NDA 206844 for asunaprevir (ASV) as the two products had been studied together in clinical trials. On October 6, 2014, the applicant withdrew NDA 206844 for ASV.

The adequate and well-controlled trials to support NDA 206843 for DCV were two clinical trials, AI447026 and AI447028, evaluating the combination of DCV with ASV in genotype 1b subjects and one trial, AI447029, evaluating the combination of DCV, ASV, pegylated interferon, and ribavirin in genotype 1a, 1b and 4 subjects. As NDA 206844 was withdrawn, NDA 206843 does not contain sufficient evidence of the safety and efficacy of DCV without ASV for the indication proposed. There are supportive Phase 2 clinical trials submitted which studied DCV in combination with pegylated interferon and/or ribavirin without ASV in patients with chronic hepatitis C. However, the applicant is not seeking an indication for DCV in combination with pegylated interferon/ribavirin, the data were not reviewed for this purpose, and such a regimen would no longer be considered appropriate care in the U.S. Thus, the NDA does not contain substantial evidence of efficacy.

Dr. Wendy Carter reviewed the clinical safety of DCV. The safety database for this NDA included over 6,000 patients exposed to DCV, with 3,415 exposed to the proposed DCV dose of 60 mg once daily. There were no on-treatment deaths in the Phase 3 DCV clinical trials. The proportion of subjects with AEs considered related to study drugs that led to discontinuation was low ranging from 1-5%. Headache, pyrexia, fatigue, diarrhea and naso-pharyngitis were the most common AEs reported by more subjects exposed to DCV containing regimens compared to placebo subjects.

Safety findings during the review of this NDA prompted a targeted review of hepatic safety. One particularly concerning case was a subject from trial AI447026 who presented with pyrexia, peripheral eosinophilia and elevated liver tests who had biopsy confirmed liver damage with eosinophils present. Nine additional subjects from the clinical program were identified who appeared to meet laboratory criteria for Hy's Law, including one subject exposed to placebo. Higher proportions of DCV/ASV exposed Japanese subjects reported liver-related AEs and laboratory abnormalities when compared to non-Japanese subjects. Rash and lymphadenopathy or other symptoms associated with hypersensitivity reactions did not appear to be associated with this clinical presentation. Consultations with experts in drug induced liver injury were obtained and an Advisory Committee meeting focused on this issue and overall risk benefit was planned at the time NDA 206844 was withdrawn. Following the withdrawal of NDA 206844, the planned Advisory Committee meeting was cancelled. Dr. Senior, an Agency drug-induced liver injury consultant, assessed five of the ten cases meeting laboratory Hy's Law criteria as drug-related, but opined that overall risk benefit was favorable. It remains unclear whether only ASV or the combination of DCV and ASV is associated with these events, but both non-clinical and clinical data suggest ASV as the likely cause. For example, hepatocellular necrosis was observed in a 1 month dog study of ASV at the highest dose of 300 mg/kg as well as increased liver weights in a 6 month rat study, and this was not observed in DCV animal studies. In addition, liver test abnormalities were noted in Phase 2 ASV trials and were dose limiting. It remains unclear whether there is a possible increased risk associated with demographic factors as the trial with most of the concerning events included only Japanese patients. The hepatic safety of DCV will need to be further considered in a future review cycle.

The CMC Review was completed by Drs. Rajiv Agarwal and Chunchun Zhang. They concluded that there was sufficient information to assure the identity, strength, purity, and quality of the drug product. All manufacturing sites were acceptable. The Biopharmaceutics Reviewer, Dr. Sandra Suarez Sharp, found the NDA acceptable.

The Pharmacology Toxicology Reviewer, Dr. L. Peyton Myers, found that the submitted studies represented a complete nonclinical toxicology package for DCV and found the NDA acceptable.

Drs. Stanley Au, Eric Zhang, Fang Li, and Jeffrey Kraft provided Clinical Pharmacology reviews and found the NDA acceptable. DCV is mainly metabolized by CYP3A and is a P-gp substrate. There are potential drug interactions which will need to be addressed in future labeling. The Reviewers recommended administration with or without food and no dose adjustment for renal impairment. A thorough QT trial was completed for DCV. There was no association of DCV with QT_c prolongation or clinically meaningful effects on other ECG intervals.

Virology reviews were provided by Dr. Patrick Harrington and Dr. Lalji Mishra. Both found the NDA to be acceptable. Among virologic failure subjects in the clinical trials, the most common treatment-emergent substitutions in NS5A were L31M, L31V, and

Y93H. When present at baseline, these polymorphisms were associated with reduced efficacy of the DCV/ASV regimen in clinical trials.

In summary, I concur with the CDTL, Dr. Kimberly Struble, and the Division Director, Dr. Debra Birnkrant, that the NDA does not contain substantial evidence of efficacy of DCV for the indication proposed and the appropriate regulatory action is a Complete Response. To address this deficiency, the applicant will need to provide clinical data to support the safety and efficacy of DCV in combination with other antiviral agents for the treatment of chronic hepatitis C virus infection. This additional clinical data will be helpful in further evaluation of the hepatic safety of DCV.

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/s/

JOHN J FARLEY
11/25/2014

Joint Cross-Discipline Team Leader and Division Director Memo

Date	October 22, 2014
From	Kimberly Struble, PharmD and Debra Birnkrant, MD
NDA/BLA # Supplement#	NDA 206843 (daclatasvir)
Applicant	Bristol Myers Squibb (BMS)
Date of Submission	March 31, 2014
PDUFA Goal Date	November 28, 2014
Proprietary Name / Established (USAN) names	Daklinza (daclatasvir)
Dosage forms / Strength	Daclatasvir 30 mg and 60 mg tablets
Proposed Indication(s)	Treatment of chronic hepatitis C infection
Recommended:	Complete Response

Rationale for Recommended Regulatory Action:

The Applicant, BMS, submitted two NDAs; NDA 206843 for daclatasvir and NDA 206844 for asunaprevir. The proposed indication for both NDAs was the treatment of chronic hepatitis C virus infection. The pivotal data to support safety and efficacy for each drug came from three Phase 3 trials which evaluated the combination of daclatasvir and asunaprevir or the combination of daclatasvir and asunaprevir in combination with pegylated interferon alpha and ribavirin (PR). Thus, both NDA's shared the same three pivotal phase 3 trials. On October 6, 2014, BMS withdrew the asunaprevir NDA 206844. As a result, the daclatasvir NDA does not contain adequate evidence to establish the safety and efficacy of daclatasvir without asunaprevir for an indication for the treatment of chronic hepatitis C virus infection in combination with other HCV antivirals. While the daclatasvir NDA did contain supportive data for daclatasvir in combination with PR, BMS is not seeking an indication for this combination and a daclatasvir/PR regimen would not be a useful treatment regimen today because HCV treatment has evolved past PR based regimens for the majority of patients.

Before the application can be approved, BMS must provide additional clinical trial data to support the safety and efficacy of daclatasvir in combination with other direct acting HCV antiviral agents for the treatment of chronic hepatitis C virus infection. A meeting will be held with BMS to discuss the contents of a resubmission. Currently, BMS proposed to include the ALLY 3 trial to demonstrate the safety and efficacy of daclatasvir in combination with sofosbuvir for genotype 3 HCV-infected patients. The ALLY 3 trial includes 152 subjects (101 treatment-naïve and 51 treatment-experienced patients). To date, only SVR4 data are available and show an overall SVR12 rate of 89% with lower SVR12 rates in both treatment-naïve and treatment-experienced cirrhotics compared to non-cirrhotics. Therefore, the optimal treatment and duration for cirrhotics is not known and additional trials are needed to determine if extending the duration to 24 weeks and/or the addition of ribavirin will improve SVR12 rates. Results from the ALLY 3 trial alone are not sufficient to support a broad indication for treatment of genotype 3 chronic hepatitis C virus infection. Evidence from other daclatasvir containing regimens is needed.

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/s/

KIMBERLY A STRUBLE
10/23/2014

DEBRA B BIRNKRANT
10/23/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206-843 and 206-844
Priority or Standard	P
Submit Date(s)	February 28, 2014 and March 31, 2014
Received Date(s)	March 31, 2014
PDUFA Goal Date	November 28, 2014
Division / Office	DAVP/OAP
Reviewer Name(s)	Wendy Carter, D.O.
Review Completion Date	August 29, 2014
Established Name	Daclatasvir (DCV) and Asunaprevir (ASV)
(Proposed) Trade Name	Daklinza (b) (4)
Therapeutic Class	DCV: NS5A replication inhibitor; ASV: Protease inhibitor
Applicant	Bristol-Myers Squibb Company
Formulation(s)	DCV 30 mg and 60 mg tablets; (b) (4)
Dosing Regimen	DCV 60 mg once daily by oral route; (b) (4)

Indication(s)	Treatment of chronic hepatitis C in adults
Intended Population(s)	Adult patients (18 years and older) with genotype (b) (4) chronic hepatitis C virus infection

Template Version: March 6, 2009

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NDA 206-843 and NDA 206-844
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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

A recommendation for regulatory action for daclatasvir (DCV) and asunaprevir (ASV) cannot be determined at the time of this primary clinical review because a full risk benefit assessment remains ongoing.

Hepatotoxicity was identified as a primary safety issue and, at present, can be categorized based on the currently available safety data as the following:

- **Dose-related liver toxicity:** Based on phase 2 data of ASV in combination with pegylated interferon and ribavirin, there is a dose-related risk of liver toxicity associated with use ASV, both in severity and frequency of liver biochemistry abnormalities and adverse events. Across the phase 3 data, evaluating the combination of ASV and DCV, drug associated increases in ALT and AST were also observed, most frequently without elevations of bilirubin. However, cases were reported that did have increases in bilirubin and met protocol defined criteria associated with drug-induced liver injury (DILI).
- **Liver toxicity associated with eosinophilia:** An initial presentation of a case of pyrexia, peripheral eosinophilia and significant biopsy proven liver toxicity with eosinophils occurred during a phase 3 trial (AI447026) conducted in Japan of the oral combination of daclatasvir (DCV) and asunaprevir (ASV), referred to as the DUAL regimen. Further assessment of the totality of safety data reveals a particular pattern of transient elevation of eosinophils in some Japanese subjects within the first month of exposure to the DUAL regimen which is generally not identified in non-Japanese subjects. Predominately, subjects with pyrexia and transient eosinophilia were not symptomatic and did not have associated liver abnormalities; however, five subjects were identified from trial AI447026 who also had grade 2 or higher increases in ALT. Additionally, higher proportions of DUAL exposed Japanese subjects reported liver-related AEs and laboratory abnormalities when compared to non-Japanese subjects. Rash and lymphadenopathy, other symptoms associated with hypersensitivity type-reactions, do not appear to be associated with this clinical presentation.

FDA clinical safety analysis of pyrexia and eosinophilia was based on a broader exploration of any subjects who reported an AE of pyrexia and elevation of eosinophils from laboratory results. Based on this analysis, more cases of pyrexia and eosinophilia with and without liver involvement were identified compared to what was identified by the Applicant based on their more stringent hypersensitivity definition (see Section 7.3.5

Submission Specific Primary Safety Concerns for additional details). At the time of filing of the NDAs, no Advisory Committee was planned; however, based on the

additional pyrexia/eosinophilia findings and the overall hepatic safety analyses, senior management decided to pursue expert opinion through internal FDA consultation as well as through an Advisory Committee Meeting late in the review cycle (planned for November 17, 2014). We are seeking input on the overall hepatotoxicity signal and how the observed eosinophilia findings (with and without pyrexia and with and without liver-involvement) relate to the demonstrated dose-related hepatotoxicity observed in phase 2 development of ASV. It remains unclear whether these safety findings represent a single clinical syndrome, or distinct events and whether only ASV or the combination of DCV and ASV are associated with these events. Additionally, it remains unclear whether there is a possible increased risk associated with demographic factors (i.e., race). Because unanswered safety concerns remain for these New Drug Applications and a full risk benefit assessment cannot be made, no recommendation for regulatory action is made at this time. An addendum to this primary clinical review will be made after the Advisory Committee meeting in November to address the regulatory recommendation and the full risk-benefit assessment.

1.2 Risk Benefit Assessment

As discussed above, a full risk benefit assessment cannot be made at this time because of ongoing further safety investigations surrounding liver toxicity. Summaries of the efficacy data and the safety data are provided in sections 6 and 7, respectively. A future addendum to this review will address the full risk benefit assessment.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are currently no recommendations for Postmarket Risk Evaluation and Mitigation Strategies related to these NDA submissions. Safety assessments are ongoing and will take into account the ongoing internal FDA consultation and the Advisory Committee meeting.

1.4 Recommendations for Postmarket Requirements and Commitments

Expert consultation and Advisory Committee Recommendations have not yet been completed; therefore, at this time, there are no clinical recommendations for postmarket requirements and commitments.

(b) (4)



2 Introduction and Regulatory Background

Globally it is estimated that approximately 170 million people are infected with HCV, including approximately 3 million people in the United States (US) (<http://www.epidemic.org/thefacts/theepidemic/worldPrevalence/>). The most common HCV GT in the US is GT 1 (70-80%), followed by GT 2 and GT 3. The natural history of chronic HCV infection (CHC) involves progression to cirrhosis, hepatocellular carcinoma, liver failure, and death. In the US, CHC is currently the most common reason for liver transplantation and there are more yearly deaths related to HCV than human immunodeficiency virus (HIV) infection (Ly 2012).

The ultimate goal of HCV treatment is to reduce the occurrence of end-stage liver disease and its related complications, and achieving sustained HCV viral eradication through successful HCV treatment is associated with improvements in clinical outcomes such as decreased development of hepatocellular carcinoma, hepatic events, fibrosis, and all-cause mortality (van der Meer 2012; Backus 2011; Singal 2010; Veldt 2007). Several host and viral baseline factors have been identified which are more likely to result in treatment failure in HCV GT 1 patients treated with pegylated interferon and ribavirin-containing regimens, including high baseline viral load, significant fibrosis (Metavir fibrosis score F3 or F4), older age and IL28B non-C/C genotype (Ge 2009; Ghany 2009; Jacobson 2011; Poordad 2012).

The current NDA applications request approval of daclatasvir and asunaprevir for the proposed indication for treatment of chronic hepatitis C (CHC) in adults.

2.1 Product Information

Table 1 summarizes the pertinent product information for both NDAs.

Table 1: Product Information

	NDA 206843	NDA 206844
Generic Name	Daclatasvir	Asunaprevir
Trade Name	Daklinza	(b) (4)
Chemical Class	New molecular entities	New molecular entities
Pharmacological Class	NS5A replication inhibitor	NS3 protease inhibitor
Proposed indication	Treatment of hepatitis C	Treatment of hepatitis C
Dosage	60 mg once daily (dose adjustments to 30 or 90 mg once daily based on drug-drug interactions)	(b) (4)
Dosage form	Oral tablet	(b) (4)
Age Groups	Adults	(b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

HCV is a small positive-strand ribonucleic acid (RNA) virus in the Flaviviridae family. At least 6 viral HCV GTs have been identified, numbered 1 to 6, and most GTs have been divided into multiple subtypes (e.g., GT 1 subtypes 1a and 1b). In the US, GT 1 is the most common, accounting for 70 to 80 percent of infections. The selection of treatment for chronic HCV GT 1 infection depends upon factors such as prior HCV treatment history and eligibility to receive interferon.

The currently approved drugs for the treatment of HCV infection are listed in Table 2.

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

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

Table 2: Currently US Approved Agents for Treatment of Chronic HCV Genotype 1 Infection

Drug Class	Generic Name	Trade Name
Pegylated interferons	Peginterferon alfa-2a	Pegasys®
	Peginterferon alfa-2b	PegIntron®
Interferons	Interferon alfa-2a	Roferon-A®*
	Interferon alfa-2b	Intron-A®
Nucleoside Analogue	Ribavirin	Rebetol®, Copegus®
NS3/4A Protease Inhibitors	Boceprevir	Victrelis®
	Telaprevir	Incivek®
	Simeprevir	Olysio™
NS5B Inhibitor	Sofosbuvir	Sovaldi™

* Voluntarily withdrawn from U.S. market 10/1/2007; not due to safety or efficacy concerns

2.3 Availability of Proposed Active Ingredient in the United States

Daclatasvir and asunaprevir are not currently available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

The QUAD regimen combines DCV and ASV with pegylated interferon and ribavirin. Therefore, the safety profile of pegylated interferon and ribavirin is discussed briefly in this section.

Pegylated Interferon and Ribavirin (pegIFN/RBV or P/R):

Almost all patients treated with pegylated interferons and ribavirin experience one or more adverse events during the course of therapy. The most commonly reported adverse events are influenza-like side effects such as fatigue, headache, myalgia, fever and rigors. Other common adverse events include anorexia, nausea, vomiting, diarrhea, arthralgias, injection site reactions, alopecia, and pruritus. Neuropsychiatric side effects include depression, anxiety, insomnia, emotional lability, mood disorders, frank psychosis, suicidal ideation, completed suicide, and homicide. The currently approved alpha-interferon product labels carry Warnings and Precautions regarding potential toxicities in a substantial number of organ systems as shown in the table below. All the approved interferon products carry a Pregnancy Category rating of C.

Table 3: Class Effect of Alpha-Interferons in Combination with Ribavirin

Adverse Events (Warnings and Precautions)	
Neuropsychiatric	Suicide, suicidal/homicidal ideation, depression, relapse of drug addiction, drug overdose
Infections	Serious and severe infections (bacterial, viral, or fungal)
Bone marrow toxicity	Neutropenia, anemia, thrombocytopenia
Cardiovascular disorders	Hypotension, hypertension, supraventricular arrhythmias, chest pain, myocardial infarction
Cerebrovascular disorders	Ischemic and hemorrhagic cerebrovascular events
Hepatic failure and hepatitis exacerbations	Risk of hepatic decompensation in patients with cirrhosis
Hypersensitivity	Severe acute reactions, serious skin reactions (Stevens Johnson Syndrome, exfoliative dermatitis)
Endocrine disorders	Hypo- or hyperthyroidism, hypo- or hyperglycemia, diabetes mellitus
Autoimmune disorders	Myositis, hepatitis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, interstitial nephritis, thyroiditis
Pulmonary disorders	Dyspnea, pulmonary infiltrates, interstitial pneumonitis, bronchiolitis obliterans, pneumonia, pulmonary hypertension, sarcoidosis
Colitis	Ulcerative colitis, hemorrhagic/ischemic colitis
Ophthalmologic disorders	Macular edema, retinal artery/vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, papilledema, serous retinal detachment
Pancreatitis	Fatal and nonfatal pancreatitis

Source: US Package Inserts: Pegasys® and PegIntron®

The most common and concerning adverse events related to ribavirin are hemolytic anemia and rash. Ribavirin is genotoxic and teratogenic and is classified as Pregnancy Category X.

Safety issues with approved NS3/4A protease inhibitors:

Boceprevir:

In clinical trials, the most commonly reported adverse reactions (more than 35% of subjects regardless of investigator's causality assessment) in adult subjects were fatigue, anemia, nausea, headache, and dysgeusia when boceprevir was used in combination with PegIntron and Rebetol.

Anemia was a significant adverse event which occurred in 49% of subjects in the boceprevir treatment arms and 30% in the control arm. Dose modifications due to anemia occurred twice as often in boceprevir exposed subjects compared to control, 26% versus 13%, respectively. However, discontinuation due to anemia was the same for both boceprevir subjects and control subjects at 1%.

Other notable adverse events and laboratory abnormalities from clinical trials experience include anemia, neutropenia, thrombocytopenia, serious acute hypersensitivity reactions and dysgeusia (alteration of taste).

The following ADRs were identified during post-approval use: mouth ulceration, stomatitis, angioedema, urticaria, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, exfoliative rash, exfoliative dermatitis, Stevens-Johnson syndrome, toxic skin eruption, and toxicoderma.

Telaprevir:

The most common adverse drug reactions to telaprevir (incidence at least 5% higher with telaprevir than in controls) were rash, pruritus, anemia, nausea, hemorrhoids, diarrhea, anorectal discomfort, dysgeusia, fatigue, vomiting, and anal pruritus. The most frequent adverse drug reactions leading to discontinuation of telaprevir were rash, anemia, fatigue, pruritus, nausea, and vomiting.

Other notable adverse events and laboratory abnormalities from clinical trials experience include anemia, anorectal symptoms, lymphopenia, thrombocytopenia, elevated bilirubin, elevated uric acid and serious skin reactions/rash.

In clinical trials, serious skin reactions, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Stevens Johnson Syndrome (SJS) were reported in less than 1% of subjects who received telaprevir combination treatment compared to none who received peginterferon alfa and ribavirin alone. These serious skin reactions

required hospitalization, and all subjects recovered. The presenting signs of DRESS may include rash, fever, facial edema, and evidence of internal organ involvement (e.g., hepatitis, nephritis). Eosinophilia may or may not be present. The presenting signs of SJS may include fever, target lesions, and mucosal erosions or ulcerations (e.g., conjunctivae, lips).

Rash events (all grades) developed in 56% of subjects who received telaprevir combination treatment and in 34% of subjects who received peginterferon alfa and ribavirin. Rash most frequently began during the first 4 weeks, but could occur at any time during telaprevir combination treatment. Rash events led to discontinuation of telaprevir alone in 6% of subjects and discontinuation of telaprevir combination treatment in 1% of subjects. Severe rash (e.g., a generalized rash or rash with vesicles or bullae or ulcerations other than SJS) was reported in 4% of subjects who received telaprevir combination treatment compared to less than 1% who received peginterferon alfa and ribavirin alone. The severe rash may have a prominent eczematous component.

During post-approval use Toxic Epidermal Necrolysis (TEN) and Erythema Multiforme (EM) were reported. Due to these events, the following information was added post-approval as a boxed warning for telaprevir (Incivek®):

Fatal and non-fatal serious skin reactions, including Stevens Johnson Syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with telaprevir combination treatment. Fatal cases have been reported in patients with progressive rash and systemic symptoms who continued to receive telaprevir combination treatment after a serious skin reaction was identified.

Simeprevir

In clinical trials adverse reactions that occurred with at least a 3% higher frequency among simeprevir subjects compared to controls, were rash, pruritus, nausea, myalgia and dyspnea. The most frequent reason for discontinuation was due to skin-related AEs.

Photosensitivity was reported in 5% of the simeprevir subjects compared to 1% of the Control group. No discontinuations of simeprevir due to photosensitivity were reported, but two photosensitivity related SAEs (both requiring hospitalization and one requiring systemic steroids) occurred in the simeprevir treatment group during the first 12 weeks of treatment while no SAEs occurred in the Control group.

Rash (excluding photosensitivity events) occurred in 25% of subjects in the simeprevir group and 19% of subjects in the Control group during the first 12 weeks of treatment. The majority of rash events occurred during the first 4 weeks of treatment with

simeprevir. Grade 3 rash AEs occurred in 1% of subjects in the simeprevir group and no subjects in the Control group.

Other notable adverse events and laboratory abnormalities from clinical trials experience include increased bilirubin (due to inhibition of hepatic transporters) and increased alkaline phosphatase (grades 1 and 2 only).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The clinical development of DCV and ASV to support the DCV/ASV (DUAL) and QUAD regimens for the treatment of CHC was conducted under IND 79,599 (DCV, originally submitted 18-Oct-2007), 100,932 (ASV, originally submitted on November 19, 2007) and (b) (4) (DCV/ASV (DUAL) combination, originally submitted 05-Apr-2012). Fast Track designation was granted to DCV and ASV on 08-Sep-2008 and 31-Dec-2009, respectively. Breakthrough Therapy designation was granted to DCV/ASV (DUAL) combination therapy for the treatment of genotype 1b, chronic hepatitis C virus infection on 03-Feb-2014.

End of Phase 1 Meeting for DCV on December 2, 2008

- Agreement on the general design of phase 2 trials which included agreement to assess data from the phase 2a cohorts prior to initiation of phase 2b in treatment-naïve and treatment experienced populations

End of Phase 1 Meeting for ASV planned for (b) (4)

- (b) (4)
- (b) (4)

Type C Meeting for DCV/ASV on July 29, 2010

- Agreement on development of DUAL and QUAD regimens
- General agreement on designs of the phase 3 DCV/PegIFN/RBV vs. TVR/PegIFN/RBV trial
- Agreement that the DCV/PegIFN/RBV vs. TVR/PegIFN/RBV trial, the 2 phase 2b trials (naïve and nonresponders) and the 2 special population trials (African Americans/Hispanics and HIV/HCV coinfecting) may support filing of an NDA for DCV/PegIFN/RBV

- Guidance was provided regarding some clinical pharmacology studies: renal impairment, OATP1B1 DDI

Type C Meeting for DUAL and QUAD on July 7, 2011

- FDA discussed diminishing window of opportunity for using PegIFN/RBV control arms in GT1 subjects; acknowledgement that evolving phase 2 QUAD regimen in null responders remained promising, and agreed with plans to proceed to phase 3
- FDA requested review of data to support partial responders with QUAD
- Discussed plans for phase 3 DUAL combination in GT1b partial/null responders and intolerant/excluded subjects
- Total safety database numbers were discussed but any final decision were dependent on the order of filings (DCV/PegIFN/RBV vs DUAL vs QUAD)
- SVR12 was decided to be the primary endpoint for the DCV and ASV trials

End of Phase 2 meeting for DUAL and QUAD on February 27, 2012

- Prior to this meeting on December 7, 2011 drafts of the 2 phase 3 trials AI447028 and AI447029 were submitted for review
- Agreement was reached that the ASV 100 mg BID (b) (4) could be dosed as the new (b) (4) formulation without regard to meals and was acceptable to move forward into the phase 3 trials
- Agreement that the DUAL trial need to wait for SVR4 data from AI447011 prior to dosing in the US
- Agreement to include the 12 week placebo control arm in AI447028 for the treatment naïve population
- Agreement that GT4 subjects could be included in the QUAD trial
- BMS inquired whether the Japanese trial AI447026 may be used to support the US DCV and ASV filing. FDA was agreeable to consider this trial in the filing as long as adequate US data would also be included.

PreNDA meeting on January 31, 2014

- Agreement regarding the content of NDAs for DCV and ASV
- Agreement that no REMS would be required for DCV or ASV based upon available data, but that NDA review would determine the final need for potential REMS
- Agreement that Applicant could provide (b) (4) of the original NDA application.

2.6 Other Relevant Background Information

The Applicant submitted phase 2 safety and efficacy data from trial AI444040 evaluating the combination of daclatasvir and sofosbuvir (DCV/SOF) with and without RBV for genotype 1, 2 and 3 subjects, who were treatment-naïve or prior telaprevir or boceprevir failures. However, the Applicant did not provide a right of reference to sofosbuvir and therefore, only the safety data supporting DCV was reviewed from this Application.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Site audits by Division of Scientific Investigations (DSI) were conducted for these NDAs and the results currently remain pending.

3.2 Compliance with Good Clinical Practices

The Applicant certified that their clinical trials were conducted in accordance with ICH Good Clinical Practice guidelines. The trial protocols and amendments were reviewed and approved by Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs). Written informed consent was obtained from all subjects prior to any trial-related procedures. Inspections of selected clinical sites by DSI are currently ongoing (refer to section 3.1 for additional detail).

3.3 Financial Disclosures

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators in accordance with 21CFR Part 54. The Applicant provided certification (Form 3454) which indicates that the vast majority of investigators and sub-investigators who participated in BMS studies had no financial arrangements with the Applicant. There were a very small number of BMS employees (5; 1 as a Principal Investigator and 4 as sub-Investigators) who participated in phase 1 studies at a BMS Clinical Pharmacology Unit prior to it being closed and only 1 investigator with disclosable financial information; however, the financial amount was \$1,600 which does not exceed the \$25,000 category, and it was reported due to his institution's [REDACTED] (b) (6) requirement that any interaction regardless of compensation amount be recorded.

Based on the low proportion of investigators with a financial interest and the objective nature of the pivotal and supportive trial designs (randomized and placebo controlled or open label with central laboratory HCV RNA PCR based efficacy endpoints), the likelihood that trial results were substantively biased based on financial interest is

minimal. Please see detailed Financial Disclosure Templates for both DCV and ASV in Appendix A.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Daclatasvir dihydrochloride (b) (4) tablets, 30 mg and 60 mg (as the free base), contain daclatasvir dihydrochloride drug substance. The drug substance is a white to yellow powder with the 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-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate dihydrochloride.

The clinical formulation of DCV used during phase 3 clinical trials was oral film-coated tablets containing daclatasvir dihydrochloride, anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, silicon dioxide and magnesium stearate. Opadry® Green is used as the (b) (4)



Please refer to the CMC Review for further details on manufacturing processes, process controls, formulation specifications, and the adequacy of data provided to assure drug stability, strength, purity and quality for both DCV and ASV. The inspections of the production facilities are currently ongoing.

4.2 Clinical Microbiology

This section includes a brief summary of key DCV and ASV nonclinical virology characteristics to support the clinical trial evaluating the DUAL and QUAD regimens.

Please refer to the Clinical Virology Reviews by Dr. Lalji Mishra for DCV and Dr. Patrick Harrington for ASV for additional details.

Daclatasvir (DCV)

Mechanism of Action and Antiviral Activity in Cell Culture

DCV is an NS5A inhibitor. The mechanism of action of DCV has been characterized in HCV replicon resistance selection studies, (b) (4), biochemical assays evaluating phosphorylation of NS5A, and NS5A binding studies, although the precise mechanism of NS5A inhibition and the resulting inhibition of HCV replication is unclear. Based on drug resistance mapping, NS5A inhibitors like DCV appear to target primarily the N-terminus of the protein. Inhibition of HCV replicons with picomolar EC₅₀ values indicates that DCV targeting of NS5A results in inhibition of HCV RNA replication.

Antiviral Activity in Cell Culture

(b) (4)

Effect of Individual Amino Acid Substitutions on DCV Anti-HCV Activity

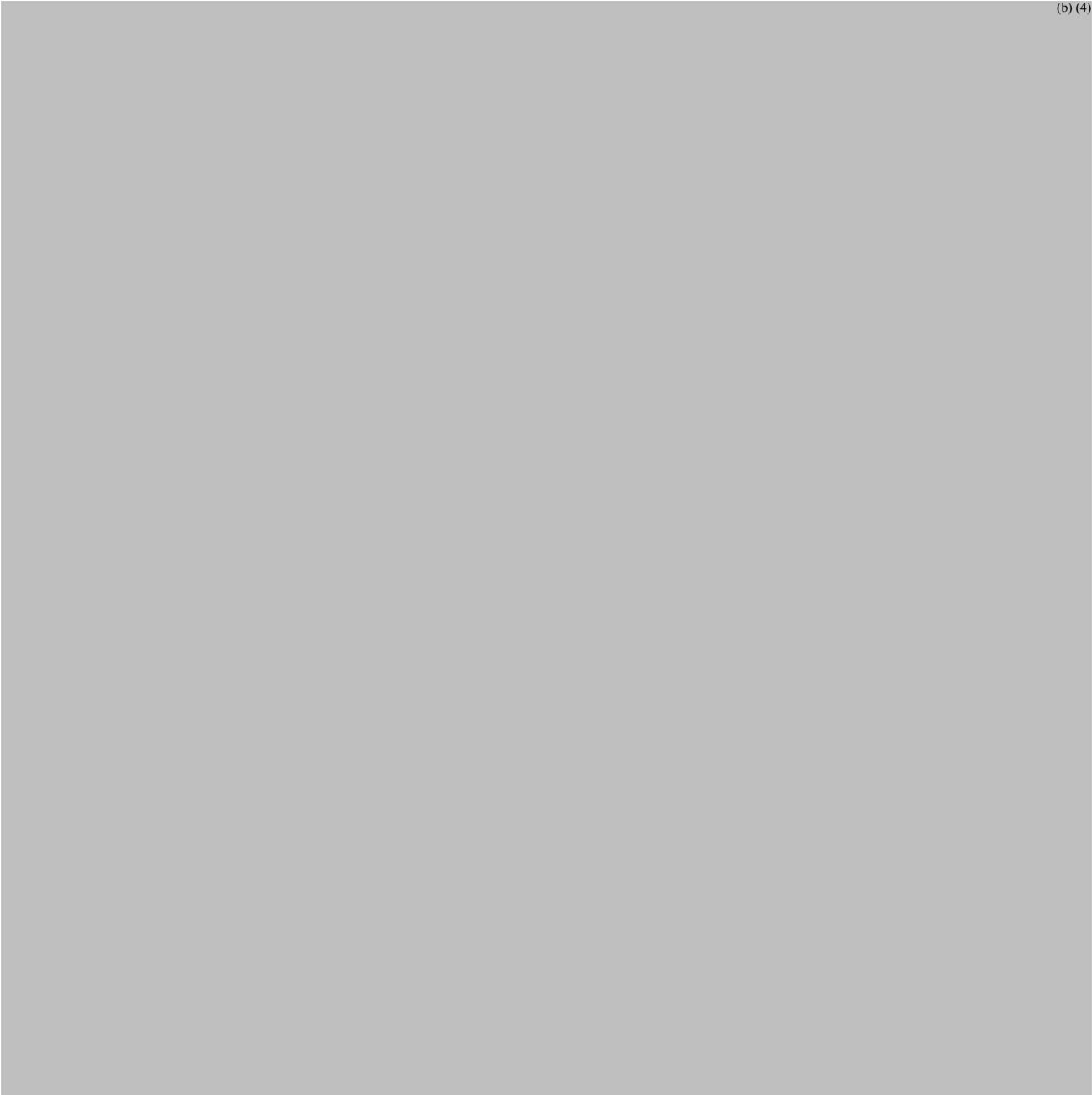
In general, DCV has a low resistance barrier, although the resistance barrier likely varies by HCV genotype and subtype.

(b) (4)

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Asunaprevir (ASV)

(b) (4)



4.3 Preclinical Pharmacology/Toxicology

Please refer to the Pharmacology/Toxicology Review by Dr. Peyton Myers for a full assessment for DCV and ASV.

A brief summary of nonclinical toxicology findings are presented below for DCV and ASV, respectively.

Daclatasvir (DCV)

The toxicity profile of DCV was evaluated in mouse, rat, dog, and monkey in repeat dose toxicity studies with longer exposures (up to 9 months) in rats and (6 months) in monkeys. Human safety margins were calculated based on the toxicity findings from the repeat dose toxicity studies for DCV. Safety margins for DCV for human exposure were not substantial in the repeat dose toxicity studies (ranging from 0.2-1.5). Safety margins = (animal AUC at the lowest dose with no adverse effects (NOAEL)/Human AUC at the proposed daily dose). Safety Margin values of more than 10 are considered substantial, whereas values less than 10 are considered not substantial.

Toxicities noted from the nonclinical studies with DCV are considered monitorable in humans; thus, appropriate clinical and laboratory monitoring was established during the clinical trials. There were no significant findings relating to reproductive toxicity or carcinogenicity. The NOAELs and safety margins for the pivotal toxicology studies for DCV are summarized in Table 4.

Key findings in the nonclinical species:

- Adrenal Glands (rat and monkey): Vacuolation with increased adrenal weights and discoloration.
- Urine output (rat): Increased with increased water consumption (no kidney changes on histology or related adverse events).
- Liver (rat and monkey): Increased drug concentration in the liver. Hypertrophy/hyperplasia with AST/ALT increases. Hepatic lesions (portal/periportal) at high doses.

Table 4: DCV Safety Margins for Pivotal Toxicology Studies Based on Overall Study NOAELs

Species	Study	NOAEL (mg/kg)	AUC (µg*h/ml)	Exposure Multiple AUC*
Rat	4-week	10 mg/kg	5.07	0.5
Dog	4-week	3 mg/kg	1.80	0.2
Monkey	4-week	10 mg/kg	1.98	0.2
Rat	6 Month	25 mg/kg	16.4	1.5
Monkey	4 Month	15 mg/kg	2.31	0.2
Monkey	9 Month	15 mg/kg	3.26	0.3
Rat	Embryofetal	Maternal 50 mg/kg Fetal 50 mg/kg	70.1 70.1	6.5 6.5
Rabbit	Embryofetal	Maternal 40/20 mg/kg Fetal 40/20 mg/kg	245 245	22.7 22.7
Rat	Peri-, Post-natal	Maternal 50 mg/kg Fetal 50 mg/kg	39.5 39.5	3.7 3.7
Rat	2-yr Carcinogenicity	M 50 mg/kg F 50 mg/kg	70.2 70.3	6.5 6.5
Mouse	6 month Transgenic	M 300 mg/kg F 300 mg/kg	131 131	12.1 12.1

*60 mg QD in HCV patients, median AUC 10.783 µg*h/mL.
Source: table provided by Pharmacology/Toxicology reviewer Dr. Peyton Myers

Asunaprevir (ASV)

(b) (4)

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4.4 Clinical Pharmacology

Brief summaries of the key clinical pharmacology findings are provided in this section. Please see the clinical pharmacology review by Dr. Stanley Au for additional details.

4.4.1 Mechanism of Action

Daclatasvir is an NS5A replication inhibitor. Asunaprevir is a specific inhibitor of the HCV NS3/4A protease.

4.4.2 Pharmacodynamics

(b) (4) Because DCV is a CYP3A substrate, DCV has proposed dose adjustments with strong inducers and inhibitors. For further discussion on the CYP450 and transporters as well as drug-drug interactions and dose adjustments see Section 7.5.5 Drug-Drug Interactions.

Daclatasvir Pharmacodynamics

Based on the in vitro study results, DCV is a P-gp substrate but not an OATP1B1 or OATP1B3 substrate and does not appear to be a BCRP substrate, though BCRP inhibitors were not evaluated in the in vitro study. The in vitro studies also indicate that DCV potentially inhibits P-gp, BCRP, OATP1B1 and OATP1B3. Inhibitory effects on digoxin exposure, a P-gp substrate, and rosuvastatin (OATP and BCRP substrate), were observed in drug-drug interaction trials with DCV (b) (4).

Asunaprevir Pharmacodynamics

(b) (4)

4.4.3 Pharmacokinetics

The pharmacokinetics of the coadministration of DCV and ASV were evaluated in trial AI447009. The trial results from AI447009 do not permit a definitive conclusion to be made regarding whether a dose adjustment for either DCV or ASV is necessary when coadministered together. However, the coadministration of DCV and ASV in the phase 3 trials did not result in any clinically significant exposure-related efficacy or safety issues.

The pharmacokinetic properties of DCV and ASV were each evaluated in healthy adult subjects and in subjects with chronic HCV.

- Following multiple oral doses of DCV 60 mg once daily in combination with pegIFN/RBV in HCV-infected subjects, the geometric mean (CV%) daclatasvir C_{max} was 1534 (58) ng/mL, $AUC_{0-24hour}$ was 14122 (70) ng•h/mL, and C_{min} was 232 (83) ng/mL.

-  (b) (4)

Absorption and Bioavailability:

DCV:

- In HCV-infected subjects, DCV peak plasma concentrations occurred between 1 and 2 hours
- Daclatasvir C_{max} , AUC, and C_{min} increased in a dose-proportional manner.
- Steady state was achieved after 4 days of once-daily administration.
- At the 60 mg dose, exposure to daclatasvir was similar between healthy and HCV-infected subjects.
- The absolute bioavailability of the tablet formulation is 67%.
- In healthy subjects, DCV 60 mg after a high-fat meal (approximately 1000kcal, 50% from fat) decreased C_{max} and AUC by 28% and 23%, respectively compared to under fasting conditions. Administration after a light meal (275 kcal, 15% from fat) did not reduce DCV exposure.

ASV:

-  (b) (4)

-

(b) (4)

Reviewer Comment: The phase 3 trials were conducted without regard to food. Administration with or without food is acceptable based on the exposure-efficacy and exposure-safety analysis of the phase 3 population PK data (b) (4).

Distribution

The protein binding of (b) (4) DCV is >99% in humans and is concentration independent based on the *in vitro* studies. Based on the data from the absolute bioavailability trials, the volume of distribution for DCV is 47.1 liters (b) (4).

Metabolism

In plasma, DCV parent drug was the major contributor to total radioactivity. (b) (4)

The *in vitro* study results indicate that CYP3A is the primary cytochrome P450 enzyme system responsible for DCV (b) (4) metabolism and in a drug-drug interaction trial, (b) (4) DCV exposure were (b) (4) increased with concomitant use of ketoconazole (b) (4) DCV AUC_[0-inf] increased by 200%).

Excretion

Based on results of the mass balance trial, the majority of the dose (88%) of DCV was eliminated through the fecal route with 7% eliminated renally. (b) (4)

For DCV, approximately half of the total dose (53%) in feces was identified as daclatasvir parent drug and virtually the entire total dose in urine (6%) was identified as daclatasvir parent drug; (b) (4)

Hepatic Impairment

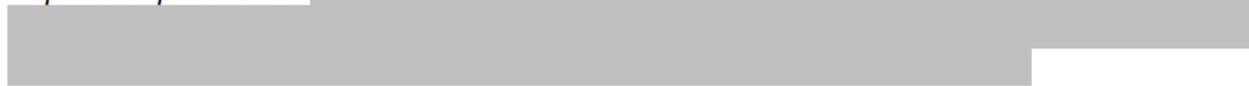
The pharmacokinetics of DCV (b) (4) were studied in non-HCV-infected subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment compared with unimpaired subjects.

DCV: The C_{max} and AUC of total daclatasvir (free and protein-bound drug) were lower in subjects with hepatic impairment; however, hepatic impairment did not have a clinically significant effect on the free drug concentrations of daclatasvir.

ASV: (b) (4)



Reviewer Comment: Based on the data from the hepatic impairment trials, DCV does not require dose adjustment and can be given to subjects with mild, moderate or severe hepatic impairment. (b) (4)



Renal Impairment

(b) (4) evaluated in non-HCV infected subjects with ESRD and on dialysis. Additionally a population pharmacokinetic analysis of HCV-infected subjects with mild to moderate renal impairment was done for comparison. Dialysis and impaired creatinine clearance did not affect the pharmacokinetic parameters of DCV (b) (4) in a clinically significant way. Dosage adjustments are not necessary to compensate for the changes in DCV (b) (4) exposure with renal impairment.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The phase 3 data to support use of DCV and ASV are from 2 clinical trials AI447026 (7026) and AI447028 (7028) evaluating the DUAL regimen in genotype 1b subjects and one trial AI447029 (7029) evaluating the QUAD regimen in genotype 1a, 1b and 4 subjects. Table 6 below provides a brief summary of the phase 3 trials.

Table 6: Summary of Phase 3 Trials

Trial	Country	Population	Study Design/Type of Control	Treatment Regimen	Number of Subjects
AI447026	Japan	Japanese subjects with Chronic HCV Genotype 1b (Non-responder, IFN therapy ineligible naive/intolerant) Cirrhosis: 10% (n=22)	Non-randomized, open-label, 2 parallel group	24 weeks ASV: 100 mg* BID DCV: 60 mg QD If Rescue, 48 weeks	222
AI447028	Argentina; Australia; Austria; Canada; France; Germany; Ireland; Israel; Italy; Korea; Netherlands; New Zealand; Poland; Russia; Spain; Taiwan; United Kingdom; United States	Chronic HCV Genotype 1b (Null / partial responders, and IFN therapy ineligible naive/intolerant)	Non-randomized, open-label	24 weeks ASV: 100 mg* BID DCV: 60 mg QD If Rescue, up to 48 weeks	440
		<i>and</i> Chronic HCV Genotype 1b (Treatment-naive) Cirrhosis: 30% n=207 DUAL, n=16 PBO	Randomized, placebo-controlled (treatment-naïve cohort)	12 weeks; then enrolled in open label treatment trial	307
AI447029	Argentina; Canada; Denmark; France; Germany; Italy; Korea; Mexico; Netherlands; Russia; Spain; Sweden; Switzerland; Taiwan; United States	Chronic HCV Genotype 1a, 1b, and 4 (Null / partial responders) Cirrhosis: 23% N=93	Non-randomized, open-label	24 weeks ASV: 100 mg* BID DCV: 60 mg QD pegIFNα2a/RBV	398

Source: Adapted from tabular listing of Clinical Trials in NDAs 206843 and 206844

Supportive clinical data for DCV and ASV are from 10 phase 2 trials. The trials are organized by the treatment regimen as either supportive of both DCV and ASV, or DCV alone or ASV alone. The phase 2 trials have inclusion of subjects only from particular treatment arms that are supportive of the proposed dose and duration for DCV and ASV, respectively; these numbers are highlighted in bold in the following table.

Table 7: Summary of Supportive Phase 2 Trials

Trial	Country	Population	Study Design/Type of Control	Treatment Regimen	Number of Subjects
Phase 2 data supportive of DCV and ASV (DUAL or QUAD)					
AI447011	France; United States	Genotype 1 null responders	Randomized, open-label, parallel group	DCV: 60 mg QD ASV:200 mg BID with or without peg IFN/RBV; 24 weeks	N=122; N=18 for DUAL and N=20 (arm B1) for QUAD are included for analyses
AI447017	Japan	Genotype 1 Null responder, IFN therapy ineligible naive/ intolerant	Non-randomized, open-label, 2 parallel groups, 2 parts	ASV: 200, 600 mg BID DCV: 60 mg QD 24 weeks	N=43 N=33 for DUAL are included for analyses
Phase 2 data supportive of DCV (DCV + pegIFN/RBV; DCV/SOF*)					
AI444010	Australia; Canada; Denmark; Egypt; France; Germany; Italy; Mexico; Sweden; United States, including Puerto Rico	Genotype 1 and 4 Treatment- naive	Randomized, double-blind, placebo-controlled, multinational	DCV: 0, 20, 60 mg with pegIFN α - 2a/RBV 24 or 48 weeks	N=395 (GT-1:365; GT-4:30) N=158 included for analyses; N=78 PBO
AI444011	Argentina; Australia; Canada; Denmark; France; Germany; Italy; Mexico; Sweden; United States, including Puerto Rico	Genotype 1 Null or partial responders	Randomized, double-blind, placebo-controlled, multinational	DCV: 0, 20, 60 mg with pegIFN α - 2a/RBV 24 or 48 weeks	N=419 N=199 included for analyses; N=17 PBO

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AI444014	France, United States	Genotype 1 Treatment-naive	Randomized, double-blind, placebo-controlled	DCV: 0, 3, 10, 60 mg with pegIFN α - 2a/RBV 48 weeks	N=48 N=12 included for analyses; N=12 PBO
AI444021	Japan	Genotype 1	Randomized, double-blind, placebo-controlled	DCV: 0, 3, 10, 60 mg with pegIFN α - 2a/RBV 24 or 48 weeks	N=45 N=19 included for analyses; N=8 PBO
AI444022	Japan	Genotype 1	Randomized, double-blind, placebo-controlled	DCV: 0, 3, 10, 60 mg with pegIFN α - 2a/RBV 24 or 48 weeks	N=42 N=17 included for analyses; N=8 PBO
AI444031	Australia; Canada; Denmark; France; Italy; United States	Genotype 2 and 3 Treatment-naive	Randomized, double-blinded, placebo-controlled	DCV: 0, 60 mg with pegIFN- 2a/RBV	N=151 N= 100 included for analyses; N=51 PBO
AI444040*	United States, including Puerto Rico	Genotype 1, 2, and 3 Treatment-naive or telaprevir or boceprevir treatment failure	Randomized, open label, parallel treatment group	DCV: 60 mg QD SOF: 400 mg QD RBV: 200 mg BID	N=211

(b) (4)

*AI444040 (DCV/SOF) data are included for safety analyses only; the Applicant did not provide a right of reference to sofosbuvir (SOF) which is owned by Gilead Sciences
Source: Adapted from tabular listing of Clinical Trials in NDAs 206843 and 206844

Lastly, Trial AI444046 is an ongoing observational long-term follow-up trial to evaluate the durability of efficacy (SVR), resistance and characterization of progression of liver disease. A total of 1000 subjects are planned for enrollment; however 756 had enrolled at the time of the interim clinical study report. Eligible subjects must have chronic HCV previously treated with DCV and/or ASV.

The total number of subjects with clinical data from phase 2 and 3 supporting the DCV and the ASV NDAs is 2,052 and 1,525 subjects, respectively. However, 1,336 subjects received either the DUAL or QUAD regimens and are common to both NDAs (three phase 3 trials N=1265 subjects plus N=71 subjects from phase 2 trials AI447011 and AI447017). Table 8 below provides a summary of the enrolled subjects by trial and the various totals for support of both the DCV and ASV NDAs.

Table 8: Summary of Subject Numbers in Support of DCV and ASV NDAs

	DUAL DCV/ASV	QUAD DCV/ASV/P/R	DCV/P/R	PBO/P/R	ASV/P/R	DCV/SOF ±RBV	Total DCV	Total ASV	Total DUAL + QUAD common to both NDAs	Total Phase 3 safety	Total Phase 2 safety from ISS database
Phase 3 Trials											
AI447028	645 (PBO n=102)						645	645	645	645	
AI447026	222						222	222	222	222	
AI447029		398 (GT1: 354; GT4: 44)					398	398	398	398	
Phase 2 Trials											
AI447011	18	20					38	38	38		18
AI447017	33						33	33	33		33
AI444040						211	211				
AI444010			158	78			158				236
AI444011			199	17			199				216

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	DUAL DCV/ASV	QUAD DCV/ASV/P/R	DCV/P/R	PBO/P/R	ASV/P/R	DCV/SOF ±RBV	Total DCV	Total ASV	Total DUAL + QUAD common to both NDAs	Total Phase 3 safety	Total Phase 2 safety from ISS database
AI444014			12	12			12				24
AI444031			100	51			100				151
AI444021			19	8			19				27
AI444022			17	8			17				25
(b) (4)											
TOTALS	918	418	505	174	189	211	2,052	1,525	1,336	1,265	991 (745 w/o PBO)

Source: demographic and ADSL datasets

5.2 Review Strategy

This reviewer, Dr. Wendy Carter, is the primary clinical reviewer for these NDAs. The clinical, statistical and clinical virology reviewers collaborated extensively during the review process and a number of the analyses included in this review were performed by the FDA statistical reviewer, Dr. Wen Zeng and the FDA clinical virology reviewer Dr. Patrick Harrington. In addition, there were significant interactions with the FDA clinical pharmacology, pharmacology/toxicology, and chemistry manufacturing and controls reviewers. Their assessments are summarized in this document in the relevant sections, but complete descriptions of their findings are available in their respective discipline reviews.

This NDA application was part of a pilot project “JumpStart” being undertaken by Computational Science Center (CSC) at Center for Drug Evaluation and Research (CDER). The data quality fitness and some of the analyses outputs for the pivotal trials were provided by the project team and the CSC staff.

The clinical review for these 2 NDAs is based primarily on the pivotal phase 3 trials: AI447026 (7026), AI447028 (7028) and AI447029 (7029). In addition, data from the 10 phase 2 trials as highlighted in Table 7 above, were reviewed for key safety analyses. These supportive phase 2 trials include subjects in the safety analyses that were exposed to DCV or ASV or the combination DCV/ASV at the proposed dose and duration for marketing. Other phase 2 subjects from these trials, while contributing to the overall safety database presented by the Applicant, were not included in the specific data analyses because of the different doses of DCV or ASV that these subjects were exposed to in the particular trial arms. Additionally, the phase 2 efficacy data provides support to the phase 3 efficacy analyses; however, the clinical review focuses only on the phase 3 efficacy data. Please see the Biometrics review by Dr. Wen Zeng for discussion of the key efficacy findings from the phase 2 trials. Overall, the safety profile from the supporting phase 2 data is similar to that of the pivotal phase 3 data; any important safety differences compared to the pivotal data are highlighted in the appropriate places throughout the review.

5.3 Discussion of Individual Studies/Clinical Trials

The pivotal phase 3 trials are summarized individually in this section. Please see the table in Section 5.1 for the 10 supportive phase 2 trial descriptions.

Title

AI447026, “A Phase 3 Japanese Study of BMS-790052 plus BMS-650032 Combination Therapy in Chronic Hepatitis C Genotype 1b Infected Subjects Who Are Non-Response to Interferon plus Ribavirin and Interferon Based Therapy Ineligible Naïve/Intolerant”

Study Location

24 sites in Japan

Summary of Trial Design

Clinical trial AI447026 was an open-label, phase 3 study of subjects with chronic HCV genotype 1b infection, conducted in Japan. The trial included two parallel groups of study populations: prior IFN/RBV non-responders (which could include IFN α or IFN β) and IFN-based therapy ineligible-naïve/intolerant subjects. Approximately 200 subjects were to receive ASV 100 mg BID and DCV 60 mg QD (DCV/ASV DUAL therapy) for 24 weeks. Subjects in the non-responder group who experienced on-treatment virologic failure were eligible to receive “rescue” therapy with DCV/ASV + P/R (QUAD) for an additional 24 weeks, at investigator discretion.

The study population consisted of males and females 20 – 75 years of age with GT1b chronic HCV infection. Chronic HCV was documented by:

- positive anti-HCV Ab, HCV RNA, or positive HCV genotype (GT) test at least 6 months prior to enrollment, and positive for HCV RNA and anti-HCV Ab at Screening OR
- positive for anti-HCV Ab and HCV RNA at Screening with a liver biopsy (within 36 months prior to enrollment) consistent with chronic HCV (evidence of chronic HCV, such as presence of fibrosis)

Patients with compensated cirrhosis (Child-Pugh A) were allowed to enroll but were capped at 10%. Cirrhosis had to be documented by a liver biopsy or laparoscopy (regardless of time performed) or discriminated by the following function:

$$Z = 0.124 \times (\gamma\text{-globulin } (\%)) + 0.001 \times (\text{hyaluronate}) (\mu\text{g } 1^{-1}) - 0.075 \times (\text{platelet } (\times 10^4 \text{ counts per mm}^3)) - 0.413 \times \text{gender (male, 1; female, 2)} - 2.005$$

Positive result indicates cirrhosis, negative result indicates chronic hepatitis.

The primary efficacy endpoint was the proportion of subjects who achieved SVR24, defined as HCV RNA <LLOQ (Target Detected [TD] or Target Not Detected [TND]) at Follow-up Week 24 (SVR24). For consistency across different trials and HCV DAA development programs, SVR12 was considered the primary efficacy outcome in AI447026 for FDA review.

Virologic failure was defined by the sponsor as follows:

- Virologic breakthrough: confirmed >1 log₁₀ IU/mL increase in HCV RNA over nadir or confirmed HCV RNA \geq LLOQ after confirmed undetectable (presumably referring to TND) HCV RNA
- Relapse: HCV RNA <LLOQ/TND at end-of-treatment followed by HCV RNA \geq LLOQ during follow-up
- Null response: <1 log₁₀ IU/mL decrease in HCV RNA at Treatment Week 4

- EOT detectable: HCV RNA \geq LLOQ or $<$ LLOQ/TD at end of treatment, including early discontinuation

HCV RNA levels were determined using the Roche COBAS[®] TaqMan[®] HCV Auto assay, which has a reported LLOQ of 15 IU/mL. Population nucleotide sequence analyses were to be conducted on Baseline samples for all subjects, and during or following treatment for subjects who experienced virologic failure and had HCV RNA \geq 1,000 IU/mL.

This trial was not conducted under IND, and therefore not FDA reviewed prior to initiation; however, the trial was conducted in accordance with Good Clinical Practice.

Title

AI447028, “A Phase 3 Study with Asunaprevir and Daclatasvir (DUAL) for Null or Partial Responders to Peginterferon Alfa and Ribavirin (P/R), Intolerant or Ineligible to P/R Subjects and Treatment-Naive Subjects with Chronic Hepatitis C Genotype 1b Infection”

Study Location

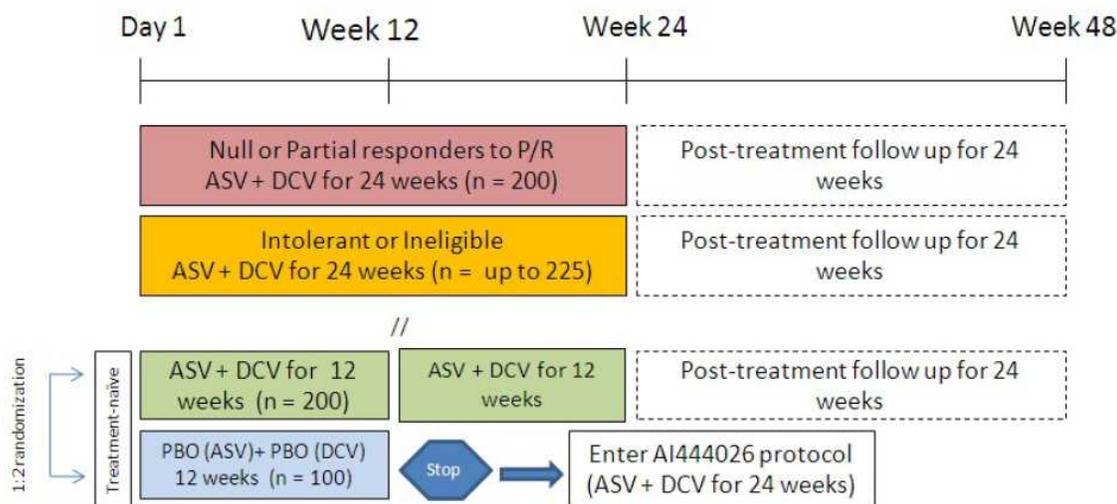
116 sites in 18 different countries, including the United States

Summary of Trial Design

Clinical trial AI447028 was a phase 3 study of subjects with chronic HCV genotype 1b infection. The trial included three groups of study populations: P/R null and partial responders, P/R ineligible/ intolerant subjects, and treatment-naïve subjects. Approximately 625 subjects were to receive ASV 100 mg BID and DCV 60 mg QD (DCV/ASV DUAL therapy) for 24 weeks, and another ~100 treatment-naïve subjects were to receive placebo for 12 weeks before rolling over to another protocol (AI444026) where they received DCV/ASV treatment for 24 weeks. The placebo group served to characterize the safety profile of DCV/ ASV treatment. The null/partial responder and the Intolerant/ineligible cohorts were open-label and not randomized; however, the placebo-controlled treatment-naïve portion of the trial was randomized 2:1 (DCV/ASV: placebo) and blinded through Week 12. Randomization was stratified by cirrhosis status (absent or present).

Subjects in the null/partial responder and treatment-naïve cohorts who experienced on-treatment virologic failure (breakthrough or futility) were eligible to receive “rescue” therapy with DCV/ ASV + P/R (QUAD) for an additional 24 or 48 weeks at investigator discretion.

Figure 1: AI447028 Study Design Schema



Abbreviations: ASV = asunaprevir; DCV = daclatasvir; P/R = peginterferon/ribavirin; PBO = placebo

Source: Clinical Study Report AI447028

Study subjects were males and females at or above 18 years of age and infected with chronic HCV genotype 1b. Chronic HCV was defined as positive HCV RNA and anti-HCV antibody at screening and either positive anti-HCV Ab, HCV RNA or HCV genotype 6 months prior or liver biopsy consistent with chronic HCV (cirrhosis or evidence of fibrosis and/or inflammation).

Subjects with compensated cirrhosis were permitted. If a patient did not have cirrhosis at enrollment, then a liver biopsy within 3 year prior to enrollment was required to demonstrate the absence of cirrhosis; however, if cirrhosis was present any prior liver biopsy was sufficient. For countries where liver biopsy is not required prior to treatment, non-invasive imaging tests (Fibroscan[®] ultrasound; ≥ 14.6 kPa considered cirrhosis (Metavir F4); Metavir F3 = ≥ 9.6 kPa to < 14.6 kPa) were allowed to assess the extent to liver disease.

Subjects had to meet the one of the following categories to enroll:

Null or partial responders: Subjects chronically infected with HCV Genotype 1b who previously failed treatment with P/R, classified as previous null or partial responders based on previous therapy, OR;

Treatment-naïve: No previous exposure to an interferon formulation (i.e. IFN α , pegIFN α), RBV, or HCV direct acting antiviral (protease, polymerase inhibitor, etc.), OR;

Intolerant to or Ineligible for P/R: Subjects must meet at least one of the depression, anemia, neutropenia, or thrombocytopenia with fibrosis/cirrhosis criteria described below:

- Depression
 - Previously excluded from P/R therapy due to a prior history of clinical depression (documented), OR
 - Previously discontinued from P/R due to depression during treatment (documented), OR;
 - Subjects with mild to moderate (stable) depression at the time of study enrollment.

OR,

- Anemia - Subjects who were previously treated with P/R therapy and had a decline in hemoglobin to < 10.0 g/dL during therapy (documented) or have a baseline hemoglobin < 12.0 g/dL (female), < 13.0 g/dL (male) and ≥ 8.5 g/dL

OR,

- Neutropenia - Subjects who were previously treated with P/R therapy and had a decline in ANC to < 0.75×10^9 cells/L during therapy (documented) or have a baseline ANC < 1.5×10^9 cells/L and $\geq 0.5 \times 10^9$ cells/L.

OR,

- Thrombocytopenia - Subjects with compensated advanced fibrosis/cirrhosis (F3/F4) who were previously treated with P/R therapy and had a decline in platelet counts < 50×10^9 cells/L during therapy (documented) or have a screening platelet count < 90×10^9 cells/L and $\geq 50 \times 10^9$ cells/L;

The primary efficacy endpoint was the proportion of treated subjects who achieved SVR12, defined as HCV RNA <LLOQ (Target Detected [TD] or Target Not Detected [TND]) at Follow-up Week 12.

Virologic failure was defined by the sponsor as follows:

- Virologic breakthrough: confirmed >1 log₁₀ IU/mL increase in HCV RNA over nadir or confirmed HCV RNA \geq LLOQ after confirmed undetectable (presumably referring to TND) HCV RNA
- Treatment futility: confirmed HCV RNA \geq LLOQ at Week 8
- Relapse: HCV RNA <LLOQ/TND at end-of-treatment followed by confirmed HCV RNA \geq LLOQ during follow-up
- Other non-responder (end-of-treatment HCV RNA detected, missing SVR, etc.): Non-SVR subjects who did not meet the relapse criteria during follow-up, or did not meet the futility or virologic breakthrough criteria during treatment. This category included subjects such as those with HCV RNA detected at the end of treatment (without breakthrough), or those with missing data in the follow-up Week 12 window.

HCV RNA levels were determined using the Roche COBAS® TaqMan® HCV v2.0 test, which has a reported LLOQ of 25 IU/mL. Population nucleotide sequence analyses were to be conducted on Baseline samples for all subjects, and during or following

treatment for subjects who experienced virologic failure and had HCV RNA $\geq 1,000$ IU/mL.

Title

AI447029, “A Phase 3, Open-Label Study with Asunaprevir and Daclatasvir plus Peginterferon Alfa-2a (Pegasys™) and Ribavirin (Copegus™) (P/R) (QUAD) for Subjects Who Are Null or Partial Responders to Peginterferon Alfa 2a or 2b plus Ribavirin with Chronic Hepatitis C Genotypes 1 or 4 Infection”

Study Location

79 sites in 15 different countries, including the United States

Summary of Trial Design

Clinical trial AI447029 was an open-label, single-arm, phase 3 study of subjects with chronic HCV genotype 1 or 4 infection. Eligible study subjects included prior P/R null or partial responders. Approximately 390 subjects (350 genotype 1, 40 genotype 4) were to be enrolled. All subjects were to be treated for 24 weeks with the “QUAD” regimen of DCV/ASV + P/R.

Study subjects were males and females ≥ 18 years of age chronically infected with HCV GT-1 only (minimum 40% of either GT-1a or non GT-1a) or GT-4 only (capped at 10%) with a HCV RNA viral load of $\geq 10^4$ IU/mL (10,000 IU/mL) at screening, and who had previously failed treatment with pegIFN α /RBV (classified as previous null and partial responders based on previous therapy). Subjects with compensated cirrhosis were eligible for enrollment, but were capped at approximately 25% of the treated population. AI447029 used the same criteria as AI447028 to define chronic HCV and compensated cirrhosis for the study population.

The primary efficacy endpoint was the proportion of subjects who achieved SVR12, defined as HCV RNA $< \text{LLOQ}$ (Target Detected [TD] or Target Not Detected [TND]) at Follow-up Week 12.

Virologic failure was defined by the sponsor as follows:

- Virologic breakthrough: confirmed >1 log₁₀ IU/mL increase in HCV RNA over nadir or confirmed HCV RNA $\geq \text{LLOQ}$ after previously declined to $< \text{LLOQ}/\text{TD}$ or TND
- Treatment futility: confirmed HCV RNA $\geq \text{LLOQ}$ at Week 8
- Relapse: HCV RNA $< \text{LLOQ}/\text{TND}$ at end-of-treatment followed by HCV RNA $\geq \text{LLOQ}$ during follow-up

HCV RNA levels were determined using the Roche COBAS® TaqMan® HCV v2.0 test, which has a reported LLOQ of 25 IU/mL. Population nucleotide sequence analyses were to be conducted on Baseline samples for all subjects, and during or following

treatment for subjects who experienced virologic failure and had HCV RNA $\geq 1,000$ IU/mL.

6 Review of Efficacy

Efficacy Summary

The Applicant's proposed indication for the treatment of chronic HCV infection is based primarily on the SVR12 results from the phase 3 pivotal trials: AI447026, AI447028 and AI447029. The overall SVR12 results from the DUAL trials (7026 and 7028) combined was 85% with a range of 80-90%, depending on prior-treatment status of the population. The overall SVR12 rate from trial 7026 was 85% (189/222) with 95% confidence interval (CI) of (80%, 90%). The SVR12 rates for prior non-responders and Intolerant/Ineligible cohorts in trial 7026 were 80% (70/87) with 95% CI of (71%, 88%) and 81% (119/135) with 95% CI of (81%, 93%), respectively. For Trial 7028 the overall SVR12 was 84% (542/643) with 95% confidence interval (CI) of (81%, 87%). The SVR12 rates for prior non-responders, intolerant/ineligible and treatment-naïve (TN) cohorts in trial 7028 were 82% (168/205) with 95% CI of (76%, 87%), 82% (192/235) with 95% CI of (76%, 86%) and 90% (182/203) with 95% CI of (85%, 94%), respectively.

The overall SVR12 rate for the QUAD regimen was 94% (372/398) with 95% CI (91%, 96%).; however, genotype 1a subjects achieved lower rates of SVR12 at 87% compared to 99% of genotype 1b and 98% of genotype 4 subjects. Overall, the SVR12 rates observed across the three trials were all higher than the determined historic thresholds of the standard of care for the studied populations.

Concordance between the SVR24 and SVR12 data was 99.5% based on available data for both the DUAL and QUAD regimens. The concordance rate is similar to the 98% concordance between SVR24 and SVR12 previously demonstrated for interferon-based regimens (Chen, et al, 2013). The DUAL regimen has a concordance rate of SVR24 to SVR12 of approximately 99.7% (only 2 subjects of 662 subjects with available data had relapse between Follow-up Weeks 12 and 24). This represents one of the first all-oral DAA regimens to provide evidence of high concordance between SVR24 and SVR12.

Subpopulation analyses did not reveal any historic baseline characteristics leading to lower SVR12 rates, including sex, age, race, IL28B subtype, baseline HCV RNA or cirrhosis status for both the DUAL and QUAD regimens. Additionally, the pivotal trials included large proportions of IFN/RBV treatment-experienced subjects, females, IL28B non-CC genotype, high baseline HCV RNA, Asian subjects and older adults (above age 65). However, as noted above, in subjects treated with the QUAD regimen, SVR12 rates were lower for subjects with baseline subtype GT1a compared to subtype 1b or genotype 4.

Most significant to the efficacy of the DUAL regimen, is the effect of naturally occurring baseline NS5A resistance-associated polymorphisms on response rates in genotype 1b subjects. Based on analyses of NS5A sequence data there was a clear association between the detection of certain DCV resistance-associated polymorphisms and treatment outcome, particularly L31 polymorphisms (including F, I, M, or V) and Y93H (see section 6.1.7 for more details). These NS5A positions are known to be key sites for the emergence of DCV resistance. Approximately 10% of U.S. subjects had the L31F/I/M/V or Y93H polymorphism(s) naturally at baseline. Based on these results, to optimize treatment efficacy this reviewer recommends that HCV GT1b patients considering treatment with the ASV/DCV DUAL regimen should be screened for the presence of NS5A L31F/I/M/V or Y93H polymorphisms, and those with the polymorphisms should consider alternative treatments. Of concern, at the present time the NS5A sequencing assays have been only available for clinical research and there are currently no commercially available NS5A sequencing assays for routine clinical use.

Reviewer Comment: At the time of this review, the Applicant has notified FDA that they have had discussions with 2 diagnostic companies, (b) (4) to ensure an appropriate NS5A sequencing assay is available pending an approval action. (b) (4)

These baseline NS5A resistance-associated polymorphisms did not affect the efficacy of the QUAD regimen.

Overall, DCV and ASV are 2 DAAs that used in combination, with or without other drugs (e.g. pegIFN/RBV) have demonstrated high rates of SVR12. In particular, the DUAL regimen represents an all-oral ribavirin-free regimen that provides an additional treatment option for genotype 1b patients.

6.1 Indication

Daclatasvir

The Applicant has requested an indication for DCV, in combination with other agents for the treatment of chronic hepatitis C (b) (4)

6.1.1 Methods

The efficacy data from the phase 3 trials AI447026 and AI447028 were reviewed in support of the use of DCV in combination with ASV (DUAL regimen) for 24 weeks for treatment of genotype 1b chronic HCV infection. The phase 3 trial AI447029 was reviewed in support of the use of DCV and ASV in combination with pegylated interferon alfa and ribavirin (QUAD regimen) for 24 weeks duration for treatment of genotype 1a, 1b and 4 chronic HCV infection. Supportive efficacy data are available from the phase 2 trials that support the activity for both DCV and ASV as single agents added to a pegIFN/RBV backbone. These supportive efficacy data were reviewed by the FDA statisticians but are not included in this clinical review. Further details can be found in Dr. Zeng's statistical review.

The primary efficacy endpoint for the pivotal trials is the proportion of subjects with SVR12, defined as HCV RNA below LLOQ Target Detected (TD) or Target Not Detected (TND) at follow up Week 12.

In clinical trial AI447026 conducted in Japan, HCV RNA levels were measured in a central laboratory ((b) (4)) using the Roche COBAS® TaqMan® HCV Auto assay, which has a reported LLOQ of 15 IU/mL.

In clinical trials AI447028 and AI447029, HCV RNA levels were determined using the FDA-approved Roche COBAS® TaqMan® HCV v2.0 test, which has a reported lower limit of quantification (LLOQ) of 25 IU/mL, and a limit of detection (LOD) of approximately 10 IU/mL. These analyses were conducted by (b) (4)

6.1.2 Demographics

Demographic and baseline characteristics that have been shown to predict a lower SVR rate with standard of care treatment include a high viral load at baseline, advanced disease on histology (bridging fibrosis and cirrhosis), obesity, older age, and African American race¹. A genetic polymorphism near the IL28B gene is a strong predictor of SVR in patients receiving therapy with pegylated interferon and ribavirin. Numerous studies have demonstrated that patients who carry the variant alleles (C/T and T/T

genotypes) historically have had lower SVR rates than individuals with the C/C genotype when administered IFN based regimens. With the development of the DAA based regimens, these historical factors remain important to evaluate to determine if they continue to influence SVR rates.

The overall baseline demographics and characteristics of the phase 3 trials are highlighted below in Table 9. There are some important differences to note in the enrolled populations across the phase 3 trials. In trial 7026, all subjects were Japanese, 65% were female, 40% were age 65 or older and only 10% were classified as cirrhotic at Baseline. Comparatively, in the global trial 7028, the majority of subjects were Caucasian (68%) while 24% of subjects were Asian, of these only 2 subjects (<1%) were Japanese. However, 51% of subjects overall were female, 21% were age 65 or older and 32% of DUAL exposed subjects in 7028 were cirrhotic. Similarly, in the QUAD trial 7029, the majority of subjects were Caucasian (76%) with fewer Asian subjects (12%), even fewer subjects were 65 years or older (9%) and 23% were cirrhotic at Baseline.

Reviewer Comment: The phase 3 trials generally enrolled a large proportion of subjects historically considered 'hard-to-treat' including those above age 65, those with high HCV RNAs and those with IL28B non-CC genotypes. Females were enrolled in high numbers across the phase 3 program; however, African Americans/Blacks made up less than 10% of the overall phase 3 trials population.

Table 9: Baseline Demographic and Characteristics of the Phase 3 Trials

	AI447026	AI1447028		AI447029
	DCV + ASV N=222	DCV + ASV N=645	PBO N=102	DCV+ ASV + PegIFN + RBV N=398
Gender n (%)				
Male	77 (35)	310 (48)	54 (53)	273 (69)
Female	145 (65)	335 (52)	48 (47)	125 (31)
Race n (%)				
Caucasian		452 (70)	59 (58)	304 (76)
Black		34 (5)	8 (8)	37 (9)
Asian	222 (100)	153 (24)	33 (32)	48 (12)
Other		6 (<1)	2 (2)	9 (2)
Age				
Median (years)	62.5	57		53
<40 years	8 (4)	60 (9)	16 (16)	39 (10)
40-64 years	125 (56)	452 (70)	68 (67)	322 (81)
>=65 years	89 (40)	133 (21)	18 (18)	37 (9)

	AI447026	AI1447028		AI447029
	DCV + ASV N=222	DCV + ASV N=645	PBO N=102	DCV+ ASV + PegIFN + RBV N=398
Geographical Region n (%)				
North America		156 (24)	31 (30)	141 (35)
Asia	222 (100)	142 (22)	28 (27)	42 (11)
Europe		277 (43)	32 (31)	204 (51)
South America		12 (2)	1 (1)	11 (3)
Australia		58 (9)		
Baseline Cirrhosis				
No	200 (90)	438 (68)	86 (84)	305 (77)
Yes	22 (10)	207 (32)	16 (16)	93 (23)
IL28B				
Missing			98 (96)	
CC	110 (50)	187 (29)		36 (9)
CT	106 (48)	326 (51)	4 (4)	262 (66)
TT	6 (3)	119 (18)		100 (25)
Baseline HCV RNA				
≥ 800,000 IU/mL	189 (85)	517 (80)	76 (75)	336 (68)
< 800,000 IU/mL	33 (15)	128 (20)	26 (25)	62 (13)

Source: Demographics and Subject-level Analysis Datasets

Discussion of pertinent differences in baseline demographics and characteristics by the treatment arms in the phase 3 trials are summarized by trial below.

Trial 7026

Trial 7026 had 2 parallel arms: Non-responders (N=87) and IFN ineligible-naïve/intolerant (N=135). All subjects were Japanese; for the non-responder and the IFN ineligible Naïve/Intolerant arms the median age was 60 years and 64 years, the proportion with age ≥ 65 years was 31% and 46% and female gender was 55% and 72%, respectively.

All subjects had HCV genotype 1b infection. Generally, the treatment arms were well balanced with respect to most demographic and baseline characteristics. Most (85%) subjects had high baseline viral loads (>800,000 IU/mL): 92% of prior non-responders and 81% of IFN ineligible-naïve/intolerant subjects. The proportion of subjects with cirrhosis at baseline was 10%. Overall 50% of subjects had IL28B rs12979860 CC genotype, while 50% had non-CC genotype (~47% CT and~ 3% TT). However, as expected, more subjects with CC genotype were in the IFN ineligible-naïve/intolerant group and more non-CC genotype subjects were in the prior non-responder group, which reflects the natural distribution of these populations.

Prior non-responders were defined as subject who never attained undetectable HCV RNA levels after a minimum of 12 weeks of therapy. Of the 87 prior non-responders, 48 (55%) were prior null responders, 36 (42%) were partial responders to prior IFN based therapy, and 3 subjects (3%) were prior non-responders whose prior treatment history could not be verified.

IFN-based therapy ineligible naïve subjects (n=100) were those who have never received IFN-based therapy due to meeting any of the following criteria: depression (10%), anemia, neutropenia, thrombocytopenia (44%); a current or previous history of diseases requiring medications (e.g. hypertension, diabetes mellitus, autoimmune disease, abnormal thyroid function) (34%); or advance age (12%).

IFN-based therapy intolerant subjects (n=35) were those who received IFN-based therapy for <12 weeks and discontinued due to the IFN/RBV related toxicities.

Trial 7028

Overall a total of 747 subjects were treated in AI447028 in the following 4 treatment arms: Prior null or partial responders (N=205); Intolerant/Ineligible n=235; Treatment-naïve N=205; and Treatment-naïve placebo (N=102). Overall baseline demographics were balanced across cohorts. However, there were a slightly higher proportion of females (58%) in the intolerant/ineligible cohort. The median age was 57 years and there was a higher proportion of subjects at or above 65 years of age in the prior null or partial responder (22%) and ineligible/intolerant (26%) group compared to the treatment-naïve (14%) and placebo (18%) cohorts.

Of the 205 subjects in the null/partial responder cohort, the majority (58%; 119/205 subjects) were prior null responders (meeting the null responder 12-week definition of achieving < 2 log₁₀ HCV RNA decline), and 41% (84/205 subjects) were prior partial responders. The null/partial responder cohort had fewer subjects with IL28B CC genotype than other cohorts, as expected given prior IFN-based treatment failure.

Two subjects enrolled in the null/partial responder cohort were prior relapsers on IFN-based therapy (AI447028-46-80068 and AI447028-55-80056).

In the intolerant/ineligible cohort, 61% of subjects were ineligible for IFN-based therapy and 72% were intolerant of IFN-based therapy; and total of 34% of subjects were both intolerant and ineligible for IFN-based therapy.

The HCV disease characteristics were comparable across cohorts. Overall, 30% of subjects had cirrhosis at baseline; however, cirrhosis was reported most frequently in the intolerant/ineligible cohort (47%) which enrolled a cohort of subjects with

compensated advanced fibrosis/cirrhosis. All subjects had HCV GT1b infection. Overall, 25.0% of subjects had IL-28B rs12979860 CC genotype and 80% of subjects had HCV RNA \geq 800,000 IU/mL.

Trial 7029

Overall, 398 subjects were treated with the QUAD regimen in AI447029; of these, 354 subjects were HCV GT1 (50% each GT1a and GT1b) and 44 subjects were HCV GT4 (20 subjects GT4; 20 subtype GT4a/c/d; 3 subject GT4e; 1 subject GT4h). The demographics were comparable between GT1 and GT4 cohorts, except there were fewer Asian GT4 subjects.

Overall, 23% of subjects had compensated cirrhosis at baseline (21% GT1; 46% GT4).

Null responders comprised 67% (66% with GT-1 and 77% with GT-4) and partial responders comprised 33% (34% with GT-1 and 23% with GT-4) of the treated study population, respectively. Most (84%) subjects had a high baseline viral load (\geq 800,000 IU/mL): 87% of subjects with GT-1 and 66% with GT-4. A total of 9% of subjects had IL-28B rs12979860 CC genotype, while 66% and 25% had IL-28B rs12979860 CT and TT genotypes, respectively.

6.1.3 Subject Disposition

Table 10, Table 11 and

Table 12 describe subject disposition for the phase 3 trials based on disposition datasets. Overall, the majority of subjects completed therapy. Across all three phase 3 trials, the main reason for not completing treatment was due to lack of efficacy with 7%, 8% and 3% of subjects having this reason from trials 7026, 7028 and 7029, respectively. Adverse Events led to discontinuation in 2% of subjects from 7028 and 7029, and 5% of subjects from 7026.

Table 10: Disposition for AI447026

	Non-responder N=87 (n%)	IFN Ineligible Naïve/Intolerant N=135 (n%)	Total N=222 (n%)
Completed treatment			
Yes	73 (84)	121 (90)	194 (87)
No	14 (16)	14 (11)	28 (13)
Reasons for not completing treatment			
Lack of efficacy	11 (13)	4 (3)	15 (7)
Adverse Event	2 (2)	9 (7)	11 (5)
Withdrawal by subject	1 (1)	1 (0.7)	2 (0.9)

Rescue Treatment	9 (10)	-	9 (4)
Completed Rescue Treatment			
Yes	7 (8)	-	7 (3)
No (due to lack of efficacy)	2 (2)	-	2 (0.9)

Source: adapted from FDA statistical review

Table 11: Disposition for AI447028

	Prior Null or Partial N=205 (n%)	IFN Intolerant/ Ineligible N=235 (n%)	Treatment- Naive N=203* (n%)	Total N=643 (n%)
Completed treatment				
Yes	177 (86)	208 (89)	188 (93)	573 (89)
No	28 (14)	27 (12)	15 (7)	70 (11)
Reasons for not completing treatment				
Lack of efficacy	26 (13)	20 (9)	8 (4)	54 (8)
Adverse Event	2 (1)	2 (1)	6 (3)	10 (2)
Withdrawal by subject	0	5 (2)	0	5 (1)
Lost to follow up	0	0	1	1 (<1)

*2 subjects (AI447028-17-80144 and AI447028-22-80131 in Treatment-naïve cohort) were assigned not randomized to DCV/ASV due to an IVRS programming error

Source: adapted from FDA statistical review

Table 12: Disposition for AI447029

	Genotype 1a N=176 (n%)	Genotype 1b N=178 (n%)	Genotype 4 N=44 (n%)	Total N=398 (n%)
Completed treatment				
Yes	163 (93)	172 (97)	44 (100)	379 (95)
No	13 (7)	6 (3)	0	19 (5)
Reasons for not completing treatment				
Lack of efficacy	10 (6)	1 (1)	0	11 (3)
Adverse Event	2 (1)	5 (3)	0	7 (2)
Lost to follow up	1 (1)	0	0	1 (<1)

Source: adapted from FDA statistical review

Reviewer Comment: Note that the disposition data reports 7 subjects (2%) did not complete due to adverse events in trial 7029. However, the adverse events dataset shows 18 subjects (5%) discontinued study therapy due to adverse events. It is likely that some of the subjects with adverse events were classified by the Applicant with another reason for not completing therapy (i.e. lack of efficacy) in the disposition dataset. (b) (4)

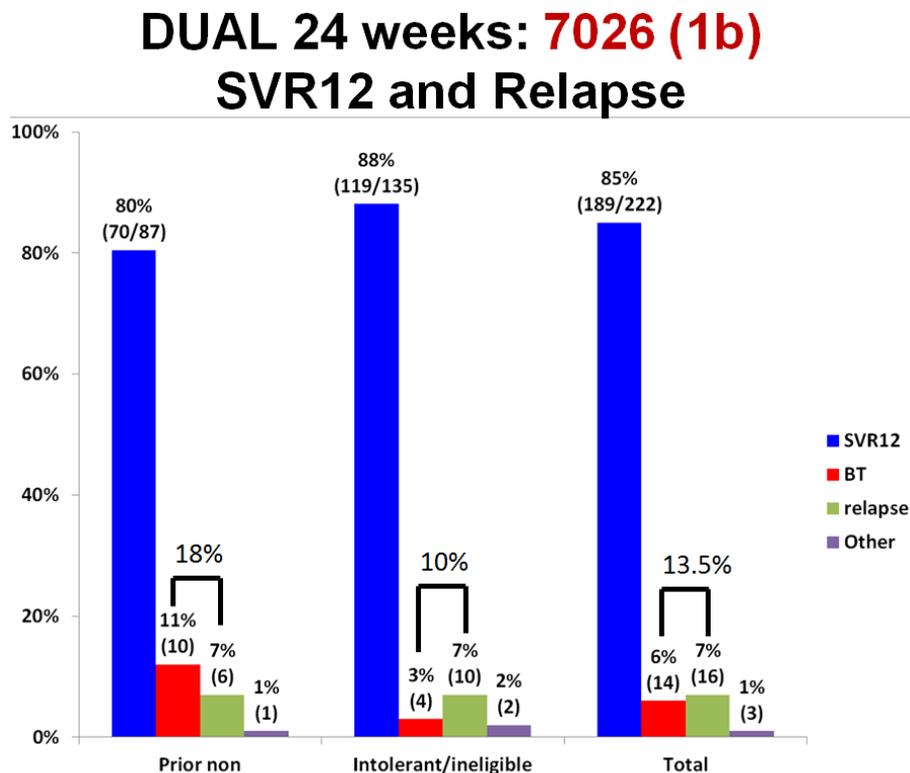
6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint used for FDA analyses was SVR12. The efficacy is discussed by treatment regimen, DUAL from trial 7026 and 7028 and QUAD from trial 7029. The FDA efficacy analyses for the DUAL trials are based on the modified intent-to-treat (mITT) population which included subjects who were randomized and had at least one dose of randomized study drug. In trial 7028, 2 subjects from the treatment naïve cohort were not randomized, due to IVRS error and are therefore excluded from the efficacy analyses (total N=203 compared to safety database of N=205). The FDA primary efficacy analysis for the DUAL trials was conducted using a missing=failure approach. Subjects without an SVR12 result were counted as failures and were not imputed for the following analyses. Imputed analyses were conducted for the QUAD trial, where subjects who were missing an SVR12 result but had an SVR24 result would be imputed using the SVR24 result for the primary endpoint (SVR12). There were only 2 subjects from trial 7029 who were imputed as success for the SVR12 endpoint based on this approach.

Efficacy of DUAL regimen: Trials 7026 and 7028

FDA analyses of efficacy from the 24 week DUAL regimen evaluated in trials 7026 and 7028 show SVR12 rates ranging from 80-90% depending on subpopulation. Figure 2 and Figure 3 summarize the overall efficacy findings by trial and sub-population. The virologic failure rates, shown as breakthrough (BT in red) and relapse (in green) are also highlighted. The 'other' category is non-response due to other reasons such as lost-to-follow-up and discontinuation due to adverse event etc. Additional abbreviations in the figures are defined as follows: Prior non: prior non-response to IFN/RBV and includes null and partial responders; Intolerant/Ineligible: unable to tolerate IFN/RBV or ineligible to take IFN/RBV due to contraindications (b) (4); TN: treatment-naïve.

Figure 2: Primary Efficacy Endpoint (SVR12) for Trial 7026 - DUAL Regimen



Prior non: prior non-responders including Null/partial responders, **BT:** Breakthrough.
 Source: FDA Statistical review

Trial 7026 was non-IND and was not FDA reviewed prior to initiation. Additionally, this trial was initiated prior to FDA recommending use of SVR12 as the primary endpoint, rather than SVR24. As such, the primary endpoint proposed for this trial was SVR24, defined as proportion of subjects below LOQ (<15 IU/mL) HCV RNA, TD or TND at follow-up Week 24.

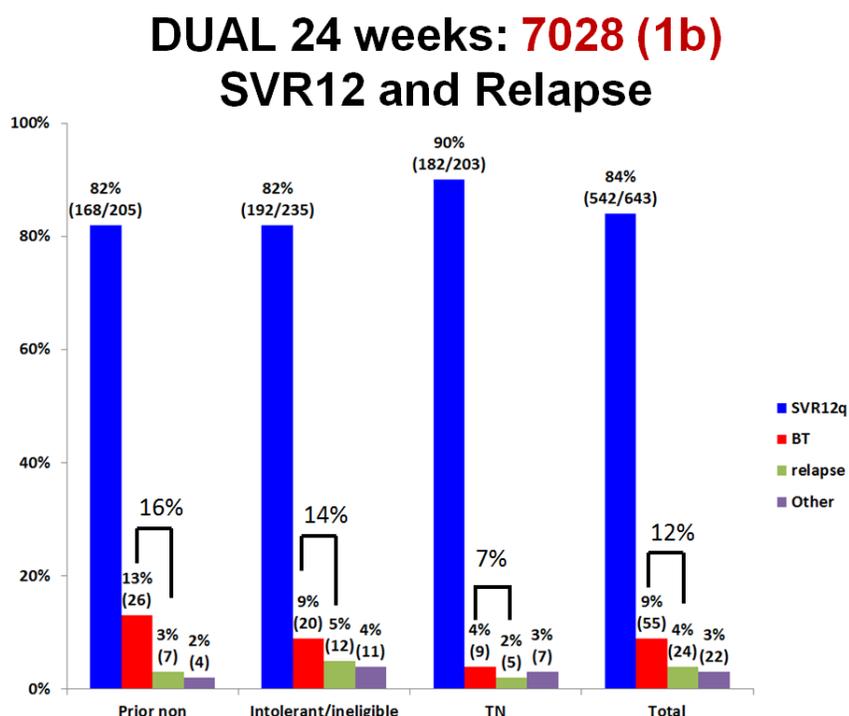
However, for consistency with the other pivotal trials, FDA used a SVR12 analysis to determine the primary efficacy endpoint. The overall SVR12 rate from trial 7026 was 85% (189/222) with 95% confidence interval (CI) of (80%, 90%). The SVR12 rates for prior non-responders and Intolerant/Ineligible cohorts were 80% (70/87) with 95% CI of (71%, 88%) and 88% (119/135) with 95% CI of (81%, 93%), respectively. The SVR24 rates were almost identical to the SVR12 rates in trial 7026 (see 6.1.5 Analysis of Secondary Endpoint(s)).

For subjects not achieving SVR12, 33 subjects (13.5%) were classified as virologic failures. Fourteen subjects (6%) had virologic breakthrough, 16 subjects (7%) had relapse and 3 subjects (1%) were classified as other reasons. The 'other' reasons was detectable HCV RNA (using LOQ) at end-of-treatment (EOT) for all 3 subjects.

See Section 6.1.7 for details regarding SVR rates by baseline characteristics.

Trial 7026 enrolled subjects who were intolerant or ineligible to receive a pegIFN/RBV containing regimen, or those who had previously failed an IFN/RBV regimen (either null or partial response). Therefore, the trial population enrolled into 7026 had limited to no treatment options at the time of enrollment of this trial, and no expectation of SVR. The protocol research hypothesis proposed thresholds or benchmarks for efficacy defined as the lower bound of the estimated 95% CI >45% for the non-responders cohort and >30% for the intolerant/ineligible cohort using SVR24. The protocol was unclear regarding the rationale for these thresholds. We subsequently also applied the higher thresholds defined for trial 7028 (discussion below) to assess the overall efficacy in trial 7026. The lower bound of the estimated 95% CI for both the SVR12 and SVR24 rate far exceeded the 45% and 30% protocol-defined thresholds and exceeded the thresholds used in trial 7028, for the non-responder and intolerant/ineligible cohorts, respectively. Additionally, the DUAL regimen offers a pegIFN/RBV-free oral regimen with improved tolerability.

Figure 3: Primary Efficacy Endpoint (SVR12) for Trial 7028 – DUAL Regimen



Prior non: prior non-responders including Null/partial responders, **BT:** Breakthrough.

Note: 2 subjects from the treatment naïve cohort were not randomized, due to IVRS error and are therefore excluded from the efficacy analyses (total N=203 compared to safety database of N=205)

Source: FDA Statistical review

For Trial 7028 the overall SVR12 was 84% (542/643) with 95% confidence interval (CI) of (81%, 87%). The SVR12 rates for prior non-responders, intolerant/ineligible and treatment-naïve (TN) cohorts were 82% (168/205) with 95% CI of (76%, 87%), 82% (192/235) with 95% CI of (76%, 86%) and 90% (182/203) with 95% CI of (85%, 94%), respectively. See Section 6.1.7 for details regarding SVR rates by baseline characteristics.

For trial 7028 the primary efficacy hypothesis was that the SVR12 rate for the treatment-naïve cohort would exceed the historical control rate (benchmark) of 68%. Per the Applicant, the 68% benchmark was determined using the historical SVR rates of telaprevir (TVR) in combination with pegIFN/RBV in previously untreated, genotype 1b HCV infected subjects. The SVR24 rates for treatment-naïve GT-1b subjects who received TVR in combination with pegIFN/RBV and who received pegIFN/RBV alone, as reported for the ADVANCE trial, were 85% and 51%, respectively (Telaprevir NDA, Statistical Review, April 22, 2011). The treatment difference between TVR/pegIFN/RBV (85%) and the pegIFN/RBV (51%) was 34%. The DUAL regimen would be preserving at least 50% of the historical treatment effect of TVR relative to pegIFN/RBV alone if the SVR rate exceeded 68% ($51 + (34/2) = 68\%$). The Applicant reports an SVR12 rate from the treatment-naïve cohort in 7028, as 89.7% (95% CI: 85.5%, 93.8%), demonstrating the all-oral DUAL regimen exceeded the historical SVR rate observed in TVR/pegIFN/RBV because the lower bound of the 95% CI exceeded 68%.

Reviewer Comment: FDA did not agree with the method of calculation for the 68% benchmark; however, ultimately agreed with the historical rate of 68% based on considering historical data and the clinical factors that the DUAL regimen, an IFN-free, RBV-free, all oral DAA regimen offers by providing improved tolerability compared to the standard of care.

The results from the treatment naïve cohort in trial 7028 far exceed the 68% benchmark (SVR12 90% with 95% CI of (85%, 94%), and the lower bound of the 95% CI is similar to the overall SVR rate observed for TVR (86%) in treatment-naïve genotype 1b subjects. More importantly, use of prescreening for NS5A resistance associated polymorphisms will improve the overall SVR12 rates for treatment-naïve and prior treatment-experienced patients (further discussion below).

In the original submitted protocol for 7028, the benchmarks for prior non-responders and for intolerant/ineligible cohorts were proposed as 59% and 30%, respectively (See the Statistical Review of IND (b) (4) SN 001, SDN 004 for details). However, these benchmarks were deleted from the finalized protocol by the Applicant (see Statistical Review of IND (b) (4) SN 028, SDN 031).

For the intolerant/ineligible cohort, the assumption was the benchmark could be any number above 0% because there is no expectation of spontaneous SVR in these subjects who were unable to take a pegIFN/RBV containing regimen.

The rationale for the 59% benchmark seemed reasonable to FDA for prior non-responders based on the TVR trial results. In the TVR trial 216, the SVR24 rate from the 12 week arm for combined prior non-responders (null and partial responders) was 43% (52/121) with 95% CI of (34%, 52%). Therefore, the 59% benchmark exceeded the upper bound of the 95% CI (52%) of the current standard of care. The lower bound of the 95% CI for the SVR12 rates from 7028 for both the non-responders cohort and the intolerant/ineligible cohorts was 76% and far exceeded the proposed benchmarks.

Of the 203 subjects in the treatment-naive cohort of trial 7028 that were administered the DUAL regimen, 21 (10 %) subjects failed to achieve SVR12. The reasons for failure were as follows:

- Virologic breakthrough: 9 subjects
- Relapse: 5 subjects
- Other – 7 subjects
 - missing post-treatment Week 12 HCV RNA measurements: 4 subjects
 - detectable HCV RNA at end-of-treatment (EOT): 3 subjects

Of the 205 subjects in the null/partial responder cohort of trial 7028, 37 (18.0%) subjects failed to achieve SVR12. The reasons for failure were as follows:

- Virologic breakthrough: 26 subjects
- Relapse: 7 subjects
- Other : 4 subjects
 - missing post-treatment Week 12 HCV RNA measurement: 1 subject
 - detectable HCV RNA at EOT: 3 subjects.

Of the 235 subjects in the intolerant/ineligible cohort of trial 7028, 43 (18%) subjects failed to achieve SVR 12. The reasons for failure were as follows:

- Virologic breakthrough: 20 subjects
- Relapse: 12 subjects
- Other: 11 subjects
 - missing post-treatment Week 12 HCV RNA measurement: 3 subject
 - detectable HCV RNA at EOT: 7 subjects.
 - treatment futility (defined as confirmed HCV RNA \geq LOQ at Week 8): 1 subject

Sensitivity analyses on the primary endpoint were also conducted (observed value approach and imputed analysis) with results consistent with the primary analysis for the DUAL trials. Please see the statistical review for additional details.

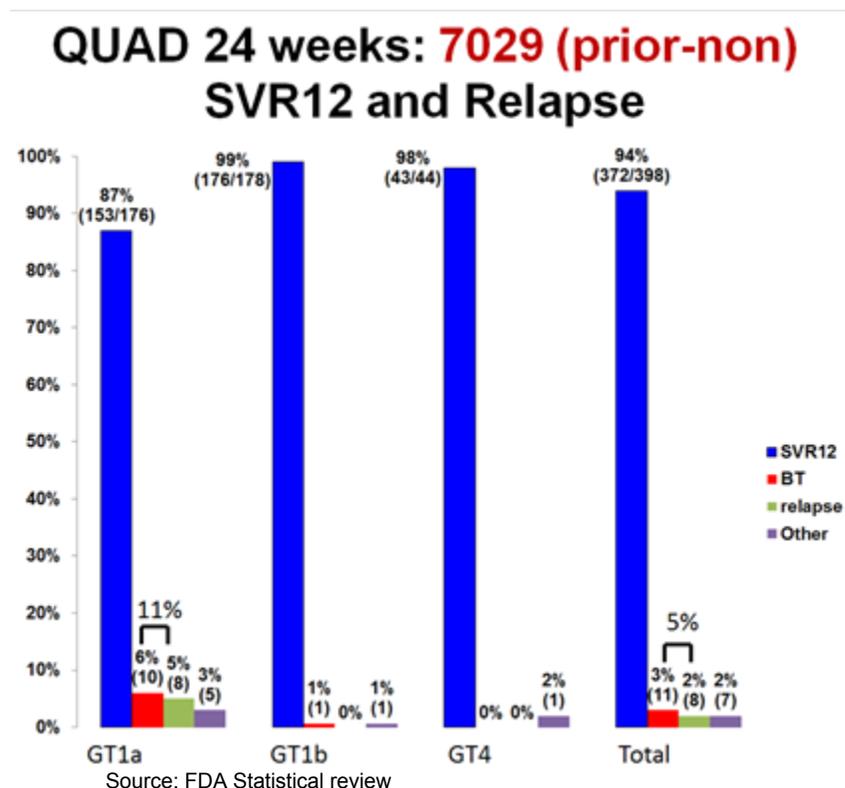
Efficacy of QUAD Regimen

FDA analyses of the efficacy of the QUAD regimen in prior PegIFN/RBV non-responders demonstrated an overall SVR12 rate of 94% (372/398) with 95% CI (91%, 96%). However, the proportion of subjects with genotype 1a who achieved SVR12 was lower at 87% (153/176) with 95% CI (81%, 92%), compared to 99% (176/178) with 95% CI (96%, 100%) of genotype 1b subjects and 98% (43/44) with 95% CI (88%, 100%) of genotype 4 subjects. FDA analyses determined there were no statistically significant baseline factors that affected outcome for the QUAD regimen.

Trial 7029 enrolled subjects who were all prior null or partial responders to a pegIFN/RBV treatment regimen. The protocol did not include formal hypothesis testing because the expected SVR rate was believed to be much higher than that of the current standard of care (i.e. TVR/pegIFN/RBV).

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

Figure 4: Primary Efficacy Endpoint (SVR12) for Trial 7029 - QUAD Regimen



6.1.5 Analysis of Secondary Endpoint(s)

Sustained Virologic Response at Follow-up Week 24 (SVR24) was included as a secondary endpoint for the clinical trials. Subjects who achieved SVR12 in the phase 3 DUAL/QUAD trials generally had durable virologic responses through Follow-up Week 24. Among subjects who achieved SVR12 with available data at Follow-up Weeks 12 and 24, 5/1019 (0.5%) experienced virologic relapse by Follow-up Week 24 (Table 13). Therefore, based on the available data, there was an overall 99.5% concordance of the SVR24 to the SVR12 results for the DUAL and QUAD regimens. Concordance of approximately 98% between SVR24 data and SVR12 data has been demonstrated in over 13,000 subjects receiving a pegIFN alfa-2a or pegIFN alfa-2b or albinterfeon alfa-2b based regimen with or without telaprevir and boceprevir (Chen, et al, 2013). The data from the DUAL regimen represents one of the first demonstrations of high concordance of 99.7% (2/662 or 0.03% of subjects with relapse after Follow-up Week 12) between SVR24 and SVR12 data in an all oral DAA regimen.

Table 13: Subjects from Phase 3 Trials (DUAL/QUAD) who achieved SVR12 but experienced virologic relapse by Follow-up Week 24.

Phase 3 Trial	SVR12 Subjects with Relapse by Follow-up Week 24
AI447028 (DUAL)	1/473 (0.2%)
AI447026 (DUAL-Japanese)	1/189 (0.5%)
AI4447029 (QUAD)	3*/357 (0.8%)
Total	5/1019 (0.5%)

*Excludes 1 subject (AI447029-3-90099) with a transient HCV RNA of 39 IU/mL at Follow-up Week 24, but HCV RNA TND at Follow-up Week 36.

Source: Clinical Virology review

A second analysis of post-SVR12 virologic durability was conducted by Dr. Harrington based on data from a separate, ongoing long-term follow-up study (AI444046) of subjects who received ASV- or DCV-containing regimens in phase 2/3 trials. Considering subjects who received ASV in combination with DCV with or without P/R, long-term follow-up data were available from 254 subjects who achieved SVR12 in the parent treatment protocol (excluding subjects who received P/R add-on rescue therapy), with a median of 266 days of post-SVR12 virology follow-up. Of these subjects, only 1 subject (0.4%, AI447026-2-20188) who received ASV + DCV in phase 3 clinical trial AI447026 experienced confirmed virologic relapse, which occurred at 189 days post-SVR12 (~39 weeks post-treatment). A second subject (AI447011-19-180) had a single transient HCV RNA result of >LLOQ (21,310 IU/mL) at 322 days post-SVR12 that was flanked by results of HCV RNA TND, possibly reflecting a false-positive HCV RNA result.

6.1.6 Other Endpoints

Additional secondary efficacy endpoints included the proportion of subjects with on-treatment failure and the proportion of subjects with viral relapse. These data were presented in Figure 2, Figure 3 and Figure 4 in Section 6.1.4.

Please refer to the Statistical Review and Virology Review for additional details with respect to secondary endpoint analyses.

6.1.7 Subpopulations

As previously mentioned, a number of demographic and baseline characteristics have been shown to predict a lower SVR rate with pegIFN/RBV-based therapy. These include a high HCV RNA at baseline ($\geq 800,000$ IU/mL), advanced disease on histology (bridging fibrosis and cirrhosis), male gender, older age, African American race and absence of the IL28B CC genetic polymorphism. For both the DUAL and QUAD regimen, these demographic and baseline characteristics did not have any statistically significant impacts on the SVR12 data. Table 14 summarizes the SVR12 results by baseline cirrhosis status and demonstrates the consistent SVR12 results across the phase 3 trials, regardless of a baseline diagnosis of cirrhosis. Please see the statistical review by Dr. Wen Zeng for detailed analyses of the subpopulations.

Table 14: Summary of Phase 3 Trial SVR12 rates by Baseline Cirrhosis Category

Trial/Subgroup	SVR12 by Baseline Cirrhosis Category	
	Without Cirrhosis	With Cirrhosis
AI447026	169/200 (85%)	20/22 (91%)
Prior non responders	60/76 (79%)	10/11 (91%)
Intolerant/Ineligible	109/124 (88%)	10/11 (91%)
AI447028	370/427 (85%)	172/206 (84%)
Prior non responders	113/142 (80%)	55/63 (87%)
Intolerant/Ineligible	104/124 (84%)	88/111 (79%)
Treatment-naïve	153/171 (90%)	29/32 (91%)

Trial/Subgroup	SVR12 by Baseline Cirrhosis Category	
	Without Cirrhosis	With Cirrhosis
AI447029	287/305 (94%)	85/93 (91%)
Genotype 1a	115/132 (87%)	38/44 (86%)
Genotype 1b	148/149 (99%)	28/29 (97%)
Genotype 4	24/24 (100%)	19/20 (95%)

Source: Adapted from FDA Statistical Review

However, a significant baseline factor for the direct-acting antivirals is the naturally occurring baseline resistance associated polymorphisms. Accordingly, FDA conducted analyses to identify baseline NS3 and NS5A polymorphisms that were associated with reduced SVR rates in the DUAL phase 3 trials. Baseline ASV (NS3) and DCV (NS5A) resistance analyses for the genotype 1b ASV/DCV (DUAL) regimen were conducted using pooled resistance data from the phase 3 trials 7026 and 7028. Baseline NS3 and NS5A polymorphisms were identified by population nucleotide sequence analysis. A brief summary of these analyses are provided here; however, for full details, please see the Clinical Virology review by Dr. Patrick Harrington.

Asunaprevir (ASV)



Daclatasvir (DCV)

A total of 814 subjects had available efficacy outcome data and baseline NS5A population nucleotide sequence data, with numerous NS5A polymorphisms detected by population nucleotide sequencing.

FDA analyses focused on NS5A positions known to be associated with resistance to DCV or other NS5A inhibitors, including L28, P29, R30, L31, P32, Q54, P58, Q62, A92 and Y93.

Table 15 summarizes the SVR rates for subjects with baseline NS5A polymorphisms (including mixtures) detected at known resistance-associated positions. L31 (including F, I, M, or V), and Y93H polymorphisms were clearly associated with a high rate of virologic failure (approximately 60%) in the phase 3 DUAL genotype 1b trials. Of note, treatment-emergent substitutions at positions L31 and Y93 were also common in subjects with virologic failure.

Approximately 10% of U.S. subjects had the L31F/I/M/V or Y93H polymorphism at baseline, and approximately 15% of U.S. subjects had L28M, R30Q, L31F/I/M/V or Y93H.

Table 15: Prevalence of NS5A polymorphisms L28M, R30Q, L31F/I/M/V and Y93H in genotype 1b subjects and their impact on SVR rates in the Phase 3 ASV/DCV (DUAL) trials. Non-VF-censored analysis.

Polymorphism(s)	NS5A Polymorphism Prevalence (Pooled GT1b Datasets)			SVR in Phase 3 DUAL Trials (Non-VF-Censored, n=806)	
	All Sites (n=1,393)	N. America (n=307)	U.S. (n=236)	with RAP(s)*	without RAP(s)*
L28M	48 (3%)	1 (0.3%)	0 (0%)	20/29 (69%)	676/777 (87%)
R30Q	112 (8%)	15 (5%)	13 (6%)	53/69 (77%)	643/737 (87%)
L31F/I/M/V	73 (5%)	15 (5%)	11 (5%)	14/36 (39%)	682/770 (89%)
Y93H	127 (9%)	20 (7%)	15 (6%)	31/76 (41%)	665/730 (91%)
L28M or R30Q	132 (9%)	16 (5%)	13 (6%)	62/83 (75%)	634/723 (88%)
L28M or R30Q (no L31F/I/M/V or Y93H)	115 (8%)	13 (4%)	11 (5%)	61/72 (85%)	591/625 (95%)
L31F/I/M/V or Y93H	193 (14%)	32 (10%)	24 (10%)	44/109 (40%)	652/697 (94%)
L28M, R30Q, L31F/I/M/V, or Y93H	308 (22%)	45 (15%)	35 (15%)	105/181 (58%)	591/625 (95%)
				Overall SVR rate in dataset: 696/806 (86%)	

*RAP = Resistance-Associated Polymorphisms
Source: Clinical Virology review – Dr. Patrick Harrington

Reviewer Comment: The substantial impact of the L31F/I/M/V or Y93H polymorphism is demonstrated by the 40% SVR12 rate for subjects with either of these polymorphisms compared to 94% for those who do not have them at baseline. While the estimated prevalence in the US is approximately 10% of Genotype 1b subjects, because of the large improvement in SVR rates and the risk of resistance and loss of future treatment options (discussed further in Section 6.1.10), this Reviewer recommends screening for

the L31F/I/M/V or Y93H polymorphism prior to the initiation of DUAL therapy and excluding patients from treatment if either of the polymorphisms are present.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

DCV Dose Selection and Rationale

During the end of phase 2 review, the results from the four phase 2a and 2b studies demonstrate similar antiviral activity among the doses evaluated 10, 20, or 60 mg DCV once daily in combination with pegIFN α -2a/RBV. The applicant also stated DCV 60 mg once daily may be a more appropriate dose for maintaining efficacy while compensating for extrinsic factors (food, poor compliance, strong CYP3A4 inducers) that could impact exposure.

Overall, the combined safety and efficacy analyses suggest 60 mg was an appropriate DCV dose to carry forward into phase 3 development. Furthermore, no exposure-response relationships between safety events and DCV exposure were identified during phase 2, suggesting doses of 60 mg would not lead to an increase in adverse events compared to lower DCV doses.

ASV Dose Selection and Rationale



(b) (4)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

See Section 6.1.5 for discussion of available SVR24 data for the phase 3 trials and from the long term observational trial AI444046.

6.1.10 Additional Efficacy Issues/Analyses

Drug resistance is a potentially important consequence of virologic failure with ASV/DCV-based regimens, as viral populations that are resistant to ASV and DCV are likely to have reduced susceptibility to other NS3/4A protease inhibitors and NS5A inhibitors. In the phase 3 DUAL GT1b trials 7026 and 7028, a total of 128 (128/867; 15%) subjects experienced virologic failure. Among those with available resistance data at failure from the phase 3 DUAL trials, 98% (117/119) and 100% (120/120) had at least 1 resistance substitution in NS3 and NS5A, respectively (note these could be treatment-emergent or present at baseline and maintained at failure). Additionally, 94% of subjects (113/120) had ≥ 2 DCV resistance-associated substitutions detected, most of which included L31 plus Y93 substitutions, and nearly one-third of subjects had ≥ 3 DCV resistance-associated substitutions. Of note, nearly all virologic failure subjects with baseline NS5A resistance-associated polymorphisms had emergent resistance substitutions in NS3 and also additional emergent resistance-associated substitutions in NS5A at failure.

From the pooled DUAL trials 7026 and 7028, 112 subjects had available data to evaluate treatment-emergent DCV-resistance associated substitutions. Overall, 110 subjects (98%) had at least one treatment-emergent resistance associated substitution. The most common treatment-emergent substitutions in NS5A were L31M (30%), L31V (30%) and Y93H (51%), and 32 (29%) subjects had emergent L31+Y93 substitutions.

(b) (4)

Treatment-emergent resistance analysis for the QUAD regimen is based on data available from 20 HCV genotype 1a virologic failure subjects exposed to the QUAD regimen in trial 7029. (b) (4)

Similarly, all 20 subjects (100%) had at least one

treatment-emergent DCV resistance associated substitution in NS5A. Key substitutions included M28T, Q30E/H/K/R, L31M/V, E62V and Y93C/H/N.

Analyses were also conducted to characterize the persistence of ASV and DCV treatment-emergent, resistance-associated substitutions during the drug-free follow-up period after failing treatment with ASV- or DCV-containing regimens (b) (4)



The persistence of DCV resistance-associated substitutions in NS5A was more striking. Through 24 weeks of follow-up, 71/72 (99%) subjects had persistence of treatment-emergent DCV resistance-associated substitutions in NS5A, again based on a population sequencing assay. In the long term follow-up study, nearly all subjects with at least one key DCV resistance-associated substitution continued to have substitutions detected through the end of follow-up, with a median duration of nearly 2 years post-treatment.

Currently, there are no data to support an optimal re-treatment strategy for subjects who fail DUAL therapy. Overall 29 subjects (6%) of 524 subjects who were treated with DUAL therapy and experienced virologic breakthrough or futility, received the addition of pegIFN/RBV (QUAD) as 'rescue' therapy for 24 weeks. This 'rescue' strategy resulted in poor SVR rates (SVR12 of 17%; mITT analysis) and is therefore not considered a reasonable re-treatment option. We anticipate that future data will be available to support various combinations of other classes of DAAs with different resistance profiles to provide a therapeutic option. For example, the NS5B nucleotide analogue sofosbuvir does not share resistance pathways with ASV or DCV and therefore should retain full activity in patients who fail treatment with ASV/DCV-based regimens, although dosing in combination with PegIFN/RBV and/or an additional "active" DAA would be necessary for optimal efficacy.

Please refer to the clinical virology review by Dr. Patrick Harrington for further detailed discussion of the resistance analyses.

7 Review of Safety

Safety Summary

The safety database for both products is comprehensive with over 6000 subjects exposed to DCV and over 3,000 subjects exposed to ASV in phase 1, 2 and 3 trials. In total, safety data from 13 trials are included in these applications providing data from 2,052 subjects in support of DCV and from 1,525 subjects in support of ASV, respectively. The phase 3 data from the DUAL and QUAD regimen includes 1,367 subjects in total. The remaining supportive phase 2 trials, limited to subjects exposed to the proposed dose and duration, contribute data from 745 subjects exposed to DCV, ASV or the combination plus pegIFN/RBV and 174 subjects exposed to placebo plus pegIFN/RBV. Table 8 provides a summary of the number of subjects from each phase 3 and phase 2 trial to support the individual NDAs.

Both the DUAL and QUAD regimens were generally well tolerated by the clinical trials populations. Across the phase 3 program, there were no on-treatment deaths. There was a single on-treatment death in a phase 2 trial of ASV 200 mg plus pegIFN/RBV due to Staphylococcus sepsis at Week 24 of treatment. This death was not considered related to study drug. Serious Adverse Events (SAEs) were reported by 5% of subjects exposed to the DCV/ASV (DUAL) regimen and 5% of subjects exposed to the DCV/ASV/pegIFN/RBV (QUAD) regimen. SAEs considered to be study drug were reported by 1% of DUAL-exposed subjects and 2% of QUAD-exposed subjects, overall. The most frequent reason for related SAEs in subjects exposed to the DUAL regimen was liver-related events (mostly elevation of liver biochemistries, in particular, ALT). For the QUAD regimen, anemia was the most frequently reported drug related SAE (2 subjects), which reflects the known association of ribavirin with hemolytic anemia.

Overall, across the phase 3 trials, the discontinuation rate due to AEs was low at 3% (40/1367 subjects). The proportion of subjects with AEs considered related to study drugs that led to discontinuation was also low at 5% for 7026 (11/222), 1% for 7028 (7/645) and 4% for 7029 (16/398), respectively. Additionally, comparing the first 12 weeks of the placebo controlled treatment-naïve cohort from the DUAL trial 7028, 3 subjects (1.5%) in the DUAL group compared none in the placebo group discontinued due to AE. In the phase 3 DUAL trials (7026 and 7028), the most frequent reason for discontinuation from was due to liver biochemistry laboratory abnormalities or liver-related events. In contrast, only 1 subject exposed to the QUAD regimen in 7029 discontinued due to a liver-related event. However, as expected, for subjects exposed to pegIFN/RBV (P/R) in the QUAD regimen in phase 3 and the supportive phase 2 data (DCV/P/R and ASV/P/R) most AEs leading to discontinuation were consistent with the known safety profiles of pegIFN and RBV, including rash and anemia. Additionally, the rate of discontinuation from the phase 2 trials was similar between the treatment and

placebo groups, indicating the addition of the single DAA, DCV or ASV, respectively, to pegIFN/RBV did not increase rates of discontinuation.

Headache, pyrexia, fatigue, diarrhea and nasopharyngitis were the most common AEs reported by more subjects exposed to DUAL from either trial 7026 or 7028 compared to placebo subjects. Only nausea and dizziness were reported at the same rate or at a lower rate for DUAL subjects than placebo subjects. Overall, generally subjects tolerated the DUAL regimen well over 24 weeks of treatment. The most commonly (>20%) reported AEs from the QUAD trial are all labeled AEs for pegIFN and/or RBV including: fatigue, headache, pruritus, asthenia, insomnia, influenza-like illness and rash. Nasopharyngitis is the only event that was reported more frequently in subjects exposed to DUAL, but this was only observed in trial 7026 and not trial 7028. Unlike telaprevir and simeprevir, 2 other NS3/4A protease inhibitors, ASV does not appear to have a significant safety signal for skin and soft-tissue events. Likewise, trial data for use of DCV with pegIFN/RBV or with sofosbuvir with or without RBV did not reveal a skin-related safety signal for DCV.

Two prominent findings during development of ASV and ASV/DCV prompted a target review of hepatic safety. The first was the phase 2 finding of dose-related increases of liver biochemistry elevations (both frequency and severity) associated with ASV (in combination with pegIFN/RBV). The second was a subject from trial 7026 who presented with pyrexia, peripheral eosinophilia and elevated liver biochemistries who had biopsy confirmed liver damage with eosinophils present. The following safety section provides detailed analyses of the DUAL and QUAD regimen phase 3 data, as well as pertinent findings from the phase 2 data that examine the safety issue of liver toxicity for these NDAs.

In summary, the liver-related findings are complicated and it remains unclear at the present time whether the findings of pyrexia and eosinophilia represents a different mechanism of potential liver toxicity, is a separate syndrome entirely, or is related to the previously identified dose-related liver toxicity associated with ASV. Additionally, the presented data will show that liver-related AEs and laboratory findings were more frequently reported in the DUAL regimen compared to the QUAD regimen, and are more frequently reported in Japanese subjects from trial 7026 than from the global trial 7028 (that included very few Japanese subjects). No significant exposure-response was found for the Japanese subjects compared to non-Japanese subjects. Currently, there is not a full understanding of the potential mechanism(s) that may be responsible for these events and whether race is a significant component of this presentation. While serious liver-related events occurred in few subjects across the development program, the concern remains that broader use of ASV could result in life-threatening morbidity or mortality. These safety issues continue to be investigated at the time of this review and will be the key focus at an upcoming Advisory Committee for these NDAs.

7.1 Methods

DCV has been studied in a comprehensive clinical development program with > 6000 subjects exposed to DCV in phase 1, phase 2, and phase 3 studies, including 5,696 subjects with HCV. In 25 phase 2 and 3 studies, 3,415 subjects with HCV have been exposed to the recommended dose of DCV at 60 mg QD. ASV has also been studied in a comprehensive clinical development program with 3,404 subjects exposed to ASV in phase 1, phase 2, and phase 3 studies, including 2,912 patients with HCV. In 9 completed and ongoing phase 2 and 3 studies, 2,159 subjects with HCV have been exposed to the recommended dose of ASV at 100 mg BID softgel capsule (or 200 mg BID tablet).

Safety data from 13 trials are included in these applications in subjects infected with HCV GT-1, -2, -3, and -4 are presented for five different DCV-combination (DUAL, QUAD, DCV/PegIFN/RBV, DCV/SOF, DCV/SOF/RBV) and three different ASV-combination (DUAL, QUAD and ASV/pegIFN/RBV) regimens providing safety data in 2,052 subjects for DCV and 1,525 subjects for ASV, respectively (see Table 8).

Safety data for these NDAs are submitted by the Applicant as clinical overviews (for DCV and ASV), summaries of clinical safety (for DCV and ASV), final clinical study reports, and electronic datasets. The Integrated Summary of Safety (ISS) includes information on deaths, SAEs, discontinuations due to AEs and other significant AEs (e.g., liver-related events). Narratives are provided for all subjects who died, developed an SAE, discontinued from the trial because of an AE or had other significant medical events (e.g. grade 3 or 4 liver-related events). In the datasets assessment of causality by the investigator as “drug-related” was generalized to all drugs in the treatment regimen and not specific to any one drug; however, narratives allowed for causality assessment for each drug in the regimen by both the Applicant and the Investigator. Case report forms are provided for all treated subjects who experienced death or discontinuations due to adverse events.

Summary results of integrated pivotal phase 3 safety analyses are presented, with pertinent phase 2 and Safety Update Report (SUR) data included where deemed appropriate for both NDAs. Additional discussion of the SUR is included in Section 7.7 Additional Submissions / Safety Issues.

Minor differences between the Applicant’s results and FDA’s results can be attributed to differences in the methods for conducting the analyses and do not significantly alter the final conclusions. Medical Dictionary for Regulatory Activities (MedDRA) terms are used in the analyses of AE tables in this review. The on-treatment period was defined as beginning on the first day of active study therapy and ended 7 days after the last dose of study therapy. The exception to this was for subject who failed the DUAL regimen and received rescue therapy; the on-treatment period for these subjects began on the

first day of active study therapy and ended on Day 1 of rescue therapy or 7 days after the last dose of DCV/ASV therapy, whichever was earlier.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Clinical Trials for Safety Evaluation of DCV/ASV (DUAL) regimen

The Applicant's summary of clinical safety provides safety data to support the use of the DUAL (all oral DCV/ASV regimen) from 2 pivotal trials: 1) AI447028: a phase 3 trial conducted globally in subjects with HCV GT1b, who were treatment-naïve, prior-non responders (null or partial) or intolerant/ineligible to IFN/RBV based therapy and 2) AI447026: a phase 3 trial conducted in Japan that included GT1b subjects who were prior non-responders (null or partial) to IFN-base therapy (pegIFN α or IFN β /RBV) and subjects who were intolerant/ineligible to IFN-based therapy. Both pivotal trials included subjects with compensated cirrhosis. Safety data from 2 additional phase 2 trials (AI447011 (n=18) conducted globally, AI447017 (N=33) conducted in Japan) are considered supportive. Note that AI447011 included separate groups of subjects who were treated with DCV/ASV (DUAL) and the DCV/ASV/pegIFN/RBV (QUAD) regimen.

Clinical Trials for Safety Evaluation of DCV/ASV/pegIFN/RBV (QUAD) regimen

Primary clinical safety data to support the use of the QUAD regimen are provided from the pivotal phase 3 trial AI447029: conducted globally in subjects with HCV GT1 or GT4 who were prior non-responders (null or partial) to pegIFN α /RBV. AI447029 included subjects with compensated cirrhosis at baseline. Safety data from the QUAD group of the phase 2 trial AI447011 are considered supportive for this regimen.

Supportive Trials Providing Safety Data for DCV

Supportive safety data are provided from 6 double-blind, randomized, active-controlled phase 2 trials of DCV in combinations with pegIFN α /RBV: AI444010, AI444011, AI444014, AI444021, AI444022 and AI444031. Collectively, these trials provide safety data for the use of DCV in HCV patients with compensated liver disease, including cirrhosis. These trials provide exposure data to the recommended dose of DCV 60 mg QD in combination with pegIFN α /RBV in 505 subjects with HCV GT1, 2, 3 and 4, including 53 subjects with cirrhosis.

Additionally, safety data are provided from the phase 2 trial AI444040 (n=211) that evaluated DCV in combination with sofosbuvir (SOF, Solvaldi™) with or without RBV in HCV GT1, 2, and 3 patients, including subjects who had failed prior therapy with telaprevir or boceprevir in combination with pegIFN α /RBV.

Supportive Trials Providing Safety Data for ASV

Supportive safety data are provided from one phase 2a/b trial (AI447016) of ASV in combination with pegIFN α /RBV in treatment-naïve subjects. This trial provides supportive safety data for the recommended dose of ASV (b) (4) in combination with pegIFN α /RBV in 189 subjects with HCV GT1 and 4.

Other Available Safety Data

Safety data from the non-interventional, rollover, long-term observational trial AI444046 and the retreatment trial AI444026 provide supportive data. Additional data (SAEs) from ongoing trials across both development programs, including for compassionate use, were provided where appropriate by the Applicant for full safety evaluation (b) (4).

Reviewer Comment: The safety analyses and conclusions in this review are primarily based upon the treated pivotal phase 3 trial population. The trial entry criteria may mitigate potential safety concerns that may be observed with wider usage of DCV or ASV.

7.1.2 Categorization of Adverse Events

The Applicant coded AEs for the integrated analysis using MedDRA version 16.1. Some differences in reporting of AEs between the individual Clinical Study Reports and the Summary of Clinical Safety may occur due to different versions of MedDRA (e.g. 16.0 versus 16.1). However, an assessment of the Applicant's coding of events was performed to assure appropriate mapping of the investigators' verbatim terms to the selected MedDRA Preferred terms. Particular attention was given to serious adverse events, grade 3/4 adverse events, and adverse events that led to study drug discontinuation. Additionally, a random check of adverse events without respect to severity or causality of adverse events was performed. No issues of concern were identified.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant pooled the phase 3 and phase 2 data for their main safety analyses. Because of the small number of subjects from the phase 2 trials (total N=51 for DUAL and N=20 for QUAD) and the review team decision to display only the phase 3 (b) (4) FDA did not pool these data for the presentation of the main safety analyses. All the supportive phase 2 data was evaluated separately and any important safety findings are highlighted in the appropriate places throughout this review.

Generally, the phase 3 trials were not pooled for the safety analyses; however, pooling of the DUAL-exposed subjects from trials 7026 and 7028 was done and is specified in the appropriate places throughout the safety review.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The overall exposure for DCV at 60 mg once daily for 24 weeks is 2,052 subjects for NDA 206843. The overall exposure for ASV at 100 mg twice daily phase 3 (b) (4) formulation or at 200 mg twice daily (b) (4) formulation for 24 weeks is 1,525 subjects for NDA 206844.

Please refer to Section 6.1.2 for a summary of participant demographics in the phase 3 pivotal trials.

Reviewer comment: This reviewer considers the overall exposure to DCV and ASV and the demographics of the clinical trials population in relation to the target treatment population to be adequate. The Applicant is commended on their recruitment of women in the phase 3 clinical trials. Of note, however, African Americans/Blacks remain under-represented in these pivotal trials.

7.2.2 Explorations for Dose Response

Dr. Fang Li (Pharmacometrics) performed analyses assessing the correlation of DCV and ASV exposures (based on C_{max} and AUC₂₄ values) with adverse event frequency, particularly for pyrexia/eosinophilia and liver biochemistry findings for the phase 3 DUAL trials. Please refer to the FDA Pharmacometrics review for additional details.

The exposure-safety analyses evaluated whether there was a potential relationship between predicted asunaprevir or daclatasvir exposure and liver biochemistry abnormalities. During the drug development program, higher asunaprevir exposure was observed in subjects with clinically relevant liver biochemistry laboratory abnormalities. This was not observed for daclatasvir. Only a limited number of grade 3 or higher liver biochemistry laboratory abnormalities were observed with the proposed asunaprevir or daclatasvir dosage regimens.

During the NDA review, an additional safety issue was identified in subjects who presented with self-reported pyrexia and increased eosinophils with or without liver biochemistry abnormalities (see Section 7.3.5 for detailed discussion, including additional exposure response discussion). Overall there was no clear demonstration of increased exposure for DCV or ASV leading to increased adverse events of elevated liver biochemistries or pyrexia and eosinophilia, with and without liver involvement.

7.2.3 Special Animal and/or In Vitro Testing

Appropriate nonclinical evaluation for both DCV and ASV and the combination have been completed. Please see Section 4.3 and Dr. Peyton Myers Pharmacology/Toxicology review for further details.

7.2.4 Routine Clinical Testing

Routine clinical evaluation and laboratory testing was performed at pre-specified regular intervals (Weeks 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 for 24 week duration trials or continued every 4 weeks through Week 48 for 48 week duration trials during the phase 2 and phase 3 trials. The frequency and scope of this testing was deemed adequate. Safety assessments primarily included the following: physical examinations, measurement of vital signs, clinical laboratory testing, and ECG monitoring. Additional testing was performed as indicated or deemed clinically necessary by the investigator during the trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolic, clearance and interaction workup was adequate. Please refer to Section 4.4 and to the Clinical Pharmacology Review for details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The known safety profiles of the currently FDA approved HCV protease inhibitors (refer to Section 2.4 for details) were taken into careful account in the selection of safety analyses. Specifically, the Applicant and this Reviewer performed detailed assessments for serious skin reactions/rash, dysguesia, anemia, neutropenia, thrombocytopenia, hyperbilirubinemia, and anorectal disorders based on the AE profile of this drug class. FDA results were generally consistent with the Applicant's findings for the drug-class analyses. Some select analyses are discussed further in Sections 7.3.4 Significant Adverse Events and 7.4.2 Laboratory Findings.

7.3 Major Safety Results

7.3.1 Deaths

DUAL and QUAD

There were no on-treatment deaths in the phase 3 trials evaluating DCV/ASV as DUAL therapy or as QUAD over 24 weeks duration. However, there was one death in a

subject from 7029 exposed to QUAD which occurred during follow-up and is summarized below.

Subject AI447029-16-90224: This is a 60 yo male with cirrhosis with significant history of esophageal varices, splenomegaly, gout and elevated uric acid who was treated with QUAD therapy. On Study Days 9-19, the subject was diagnosed with fatigue, exertional dyspnea, and grade 1 anemia which led to a dose reduction of ribavirin. On Study Day 27-31 the subject was hospitalized due to grade 3 dehydration, orthostatic hypotension, tachycardia, exertional dyspnea, worsening anemia (grade 3) and acute renal failure. Ribavirin was interrupted due to anemia during the hospitalization. The subject continued on therapy, but had dose modifications to PegIFN and ribavirin between Study Days 42 -68 due to thrombocytopenia and anemia. On Day 82, the subject was re-admitted to the hospital due to bronchospasm reported as due to smoking marijuana, complicated by aspiration pneumonitis which required intubation and care in the ICU. On Day 86, the subject was found to have diastolic dysfunction by echocardiogram and grade 2 cardiac failure was diagnosed on Day 87. All study drugs were permanently discontinued during this hospitalization (exposure totals: 11.7 weeks DCV and ASV, 11.6 weeks RBV and 9 weeks PegIFN). The subject was extubated and the events were reported as resolved. The subject remained off study therapy. On Day 167, the subject achieved SVR12, despite early discontinuation of QUAD at approximately Week12. On study Day 205, 123 days after discontinuation of therapy, the subject died of a newly diagnosed pneumonia (separate incident). Limited details were available. The death from pneumonia was not considered related to study drugs. Additionally, the acute respiratory failure, aspiration pneumonitis, community acquired pneumonia and diastolic congestive heart failure were also assessed as not related to study therapy.

Reviewer Comment: This single death occurring in the post-treatment period does not raise a safety concern. Based upon the reported information, I agree with the investigator's assessment of the events that were considered to be unlikely related to study drugs.

Deaths Reported from Supportive Safety Database

Overall in the phase 2 safety database (Integrated Safety Summary database) and the AI444040 trial, 5 subjects died during treatment or follow-up periods. Four subjects were exposed to either DCV + P/R or ASV + P/R (2 subjects each group) and one subject was exposed to PBO + P/R. No subjects exposed to DCV + SOF in AI444040 died. Brief descriptions of the 4 subjects exposed to DCV or ASV in combination with PR who died are provided below.

AI444011-16-81: 57 yo male with GT1a cirrhotic CHC treated with DCV/P/R who died on Day 38 of follow up due to sepsis, hepatic failure, renal failure and hemorrhagic shock. The events were considered related to study drugs.

AI444011-58-69: 48 yo male with GT1b cirrhotic CHC treated with DCV/P/R who died on Day 197 of follow up period due to hepatocellular carcinoma. The event was considered not related to study drugs

AI447016-46-20145: 55 yo female with GT1b non-cirrhotic CHC treated with ASV 200 mg BID/P/R who developed Staphylococcus bacteremia and septic shock leading to death on treatment Day 177 (Week 24 on-treatment). The events were considered not related to study drugs

AI447016-47-20043: 41 yo male with GT1a non-cirrhotic CHC treated with ASV 200 mg BID/P/R who developed an infection leading to multisystem organ failure as cause of death. The SAE of infection started on Day 66 of the follow-up period, and the subject died 13 days later. The event was considered not related to study drugs.

MO Comment: Based on review of these cases no new clinical safety concerns, clustering or trends emerge. All events were considered by the Investigators and the Applicant as not related to study drugs. This reviewer agrees with these causality assessments and believes it unlikely the deaths were related to use of DCV or ASV, because of both the nature of the events, the comorbidities of the target population (e.g. hepatocellular carcinoma), the timing of the events (mostly during follow up period) and the concomitant use of pegIFN/RBV.

7.3.2 Nonfatal Serious Adverse Events

DUAL Regimen: Trials 7026 and 7028

Of the 747 subjects exposed to the DUAL regimen in 7026 and 7028, 54 subjects (7%) reported nonfatal SAEs of any grade. Of these, 7 subjects (1%) were considered to have drug-related events. ALT increased (2 subjects, 0.2%) was the only drug-related SAEs reported in more than 1 subject in the phase 3 DUAL trials; however another subject also had a related SAE of hepatic enzyme increased. The other 4 subjects with drug-related SAEs reported pyrexia, myasthenia gravis, pyelonephritis and atrial fibrillation.

The SAE of myasthenia gravis (Subject AI447026-7-20104) was determined to be pre-existing by a positive anti-acetylcholine receptor (AChR) antibody test performed on serum collected prior to study, indicating that the subject had subclinical myasthenia gravis before study start.

The SAE of atrial fibrillation (grade 3) in a 63 year old male (Subject AI447028-138-80883) occurred on Day 117 of DUAL therapy and did not lead to interruption or discontinuation of therapy; although the investigator deemed the event as related to

study therapy. The subject received treatment and the SAE resolved within 10 days and the subject achieved SVR12.

In the treatment-naïve cohort during the first 12 weeks of treatment in 7028, SAEs were reported for 7 (3%) subjects and 1 (1%) subject in the DCV/ASV and placebo arms, respectively. There were no reported drug-related SAEs from the treatment-naïve placebo arm in trial 7028.

In the supportive phase 2 trials for the DUAL regimen, AI447011 and AI447017, there were 3 subjects reporting drug-related SAEs; 2 subjects (AI447017-1-1008 and AI447017-3-3005) both from the Japanese trial AI447017, reported SAEs of pyrexia and 1 subject reported grade 2 (aggravation of pre-existing) hypochondriasis (this subject discontinued at Week 8 and was lost-to-follow up). Additional detailed analyses of pyrexia, eosinophilia and liver-related events are provided below in Section 7.3.5.

QUAD Regimen: Trial 7029

Of the 398 subjects exposed to the QUAD regimen in 7029, 22 subjects (6%) reported nonfatal SAEs of any grade. Of these, 9 subjects (2%) reported SAEs considered to be drug-related (to any drug in the regimen) events. Of the reported drug-related SAEs, anemia was the only related SAE reported in 2 subjects; all others were reported in single subjects. Hemolytic anemia is a labeled AE for ribavirin, a component of the QUAD regimen.

Other Supportive Phase 2 Trials for DCV and ASV

Additionally, there were no novel safety signals or trends from the SAE reporting from analyses of the supporting phase 2 data for DCV or ASV. Overall, on-treatment SAEs regardless of causality were reported for 29 subjects (6%) on DCV/pegIFN/RBV and 12 subjects (7%) on placebo/pegIFN/RBV. The proportion of subjects with drug-related SAEs for subjects exposed to DCV/pegIFN/RBV was 3% compared to 2% in the placebo/pegIFN/RBV group. Anemia was the only drug-related SAE reported in more than 1 subject (1 DCV/pegIFN/RBV subject and 3 placebo/pegIFN/RBV subjects).

On-treatment SAEs, regardless of causality, were reported in 16 (9%) of ASV/pegIFN/RBV subjects compared to 3 (4%) of placebo/pegIFN/RBV subjects. SAE reported in 2 subjects were: ALT increased (2 subjects in ASV/pegIFN/RBV) and abdominal pain (1 subject in ASV/pegIFN/RBV and 1 subject placebo/pegIFN/RBV); all other events were reported in single subjects. Drug related SAEs were reported in 6 subjects (3%) exposed to ASV/pegIFN/RBV compared to none from the placebo/pegIFN/RBV arm. Again, the only drug-related SAE reported in more than 1 subject was ALT increase (2 subjects total).

It is important to note that causality to the drug was reported to include the entire drug regimen and was not specific to the individual drugs.

Safety from DCV/SOF with and without RBV - Trial AI444040

On-treatment SAEs were reported for 7% (n=15) of subjects overall. A higher proportion of subjects in the 24-week duration groups reported SAEs compared to the 12-week duration groups (9-12% vs 2%). Of the 15 subjects with SAEs, 1 subject had an SAE leading to discontinuation of study therapy (AI444040-13-145; grade 2 cerebrovascular accident in current tobacco smoker with hypercholesterolemia and a reported family history of CVA, considered not related- the subject met SVR12 and SVR48). Most subjects with SAEs had relevant medical conditions that may have contributed to the SAE (e.g. anxiety in subject with bipolar disorder and depression, psoriasis flare in subject with history of psoriasis, acute renal failure in subject with HTN and cocaine use)

Only the SAEs of overdose (of DCV/SOF) in 4 subjects were considered to be related to study therapy by the investigator. These were events of inadvertent single extra doses of study medications reported as SAEs as per protocol; the events were not symptomatic and did not require treatment.

Reviewer Comment: In reviewing the SAEs observed for DCV and SOF with and without RBV, I agree with the investigators' assessments. In general, the subjects had underlying risk factors for the SAEs and there is no trend for a novel safety signal, albeit, this is a small phase 2 trial and was not powered to identify safety signals. Additionally, the subjects who had dosing mistakes also had risk factors or comorbid conditions that might increase the risk of dosing errors. These subjects all had psychiatric histories, neurologic deficits or history of or potential current use of illicit drugs

7.3.3 Dropouts and/or Discontinuations

Overall, across the phase 3 trials, the on-treatment discontinuation rate due to AEs was low at 3% (39/1367 subjects: 11 subjects from 7026, 10 subject from 7028, and 18 subjects from 7029). The proportion of subjects with drug-related AEs leading to discontinuation were also low at 5% for 7026 (11/222), 1% for 7028 (7/645) and 4% for 7029 (16/398), respectively. Additionally, comparing the first 12 weeks of the placebo controlled treatment-naïve cohort from the DUAL trial 7028, 3 subjects (1.5%) in the DUAL group compared none in the placebo group discontinued due to AE.

Across the phase 3 trials, the most frequent reasons for discontinuation due to AEs were due to increases in liver biochemistries (e.g. ALT, AST, and total bilirubin). However, liver-related discontinuations occurred more frequently on DUAL compared to QUAD therapy; 17 subjects (2%; 17/867) from the combined DUAL trials 7026 and 7028

compared to 1 subject (1/398; 0.2%) from the QUAD trial 7029. In total from trial 7026, 10 of the 11 subjects that discontinued study drug did so because of liver-related events. Similarly, 7 of the 10 subjects that discontinued from 7028 were also because of liver-related events. Additional details of liver related events leading to discontinuation for the DUAL trials are provided below in Section 7.3.5.

Reviewer Comment: It is interesting that the rates of liver-related discontinuations, primarily due to elevations of liver biochemistries, occurred more frequently on the DUAL regimen compared to the pegIFN containing QUAD regimen. Although not routinely associated with chronic HCV, hepatic flare, or acute exacerbation of chronic hepatitis C (ae-CHC) has been well described in the literature (Rumi, 2005 and Sagnelli, 2014). Rumi describes genotype 2c and genotype 1b subjects to be at higher risk of ae-CHC, while Sagnelli states genotype 2, IL28B CC genotype to be at higher risk and that these patients show a less favorable outcome with more rapid progression to liver cirrhosis. Interestingly, patients who had ae-CHC had higher SVR rates of approximately 81% compared to 61% of subjects who did not have ae-CHC. The difference was not statistically significant in this small subgroup from the study, but is of clinical interest.

Hepatic flare, while on therapy with the DUAL regimen may be contributing to the high ALTs observed in some patients. Additionally, one theory to explain the lower incidence of ALT abnormalities and liver-related discontinuations for the QUAD regimen is that the immune-modulating effects of pegIFN might be involved in decreasing the frequency of these events for subjects on the QUAD regimen. Additional input from the internal FDA consultation and the Advisory Committee will be important in working through these outstanding safety issues.

As noted above, 17 subjects of the total of 21 subjects who discontinued study drug from the DUAL trials, discontinued due to liver-related events. The remaining 4 subjects discontinued due to the following events:

- 1 subject discontinued from trial 7026 due to myasthenia gravis (discussed in 7.3.2 Nonfatal Serious Adverse Events)
- 3 subjects discontinued due to AEs from trial 7028:
 - 1 subject from 7028 (Subject # AI447028-51-80180) discontinued due to brain neoplasm (SAE, not related)
 - 1 subject (Subject # AI447028-87-80851) discontinued due to constipation and bronchiectasis (both AEs considered grade 3/severe but not drug-related)
 - 1 subject (Subject # AI447028-111-80406) had QT prolongation on ECG that led to discontinuation at Week 24 and was not considered drug related (case discussed in 7.4.4 Electrocardiograms (ECGs))

AEs leading to discontinuation for the 18 subjects (5%) exposed to the QUAD regimen in trial 7029 were generally related to the labeled AEs for pegIFN/RBV. Rash (including

the preferred terms rash generalized, exfoliative rash, erythema, and dermatitis exfoliative) led to discontinuation for 6 subjects (2%) from trial 7029 (no subjects from trials 7026 or 7028 discontinued due to rash). Vertigo, malaise and neutropenia were AEs reported as leading to discontinuation in 2 subjects each from 7029. All other AEs leading to discontinuation were reported in 1 subject and included: weight decreased, fatigue, depression, pruritus, neurological symptom and lichenoid keratosis.

The AEs leading to discontinuation from the supportive phase 2 trials were consistent with known profile of pegIFN/RBV. For subjects exposed to DCV/pegIFN/RBV in phase 2, AEs leading to discontinuation occurred in 7% (33/505) of subjects compared to 9% (15/174) of placebo/pegIFN/RBV subjects. Anemia and rash were the most frequent AEs leading to discontinuation of study therapy (3 subjects each). A similar pattern was observed in the ASV phase 2 subjects where 5% (10/189) of subjects exposed to ASV/pegIFN/RBV versus 6% (4/72) of placebo/pegIFN/RBV subjects discontinued due to AEs. Each AE leading to discontinuation of study drugs was reported by a single subject in either group, except rash (2 ASV/pegIFN/RBV-treated subjects). However, when evaluated in totality, liver-related events were the most frequently observed reason for discontinuation. Liver biochemistry abnormalities leading to discontinuation of study drugs were reported in 4 subjects (2%) exposed to ASV/pegIFN/RBV compared to 1 subject (1%) exposed to placebo/pegIFN/RBV. These events included: increased ALT, increased AST and increased transaminases each in 1 ASV/pegIFN/RBV subject, hyperbilirubinemia (1 ASV/pegIFN/RBV subject) and hypertransaminasemia (1 placebo/pegIFN/RBV subject).

Lastly, two subjects (<1%) had an AE leading to discontinuation of study therapy in the phase 2 trial of DCV/SOF with and without RBV (AI444040). One subject had a grade 2 cerebrovascular accident (discussed above in Section 7.3.2) and one subject had grade 3 fibromyalgia; neither event was considered related to study therapy.

In summary, the most frequent reason for discontinuation from DUAL therapy was due to liver biochemistry abnormalities or liver-related events. In contrast, only 1 subject exposed to QUAD in 7029 discontinued due to liver-related events; however, as expected, for subjects exposed to pegIFN/RBV (P/R) in the QUAD regimen and the supportive phase 2 data (DCV/P/R and ASV/P/R) most AEs leading to discontinuation were consistent with the known safety profiles of pegIFN and RBV, including rash and anemia. The phase 2 trials generally reflect similar safety findings leading to discontinuation, albeit in smaller numbers, from the DUAL and QUAD trials. Additionally, the rate of discontinuation in the phase 2 trials was similar between the treatment and placebo groups, indicating the addition of DCV or ASV to pegIFN/RBV did not increase discontinuation rates but that most subjects discontinued due to events attributable to pegIFN/RBV (e.g. rash and anemia). However, abnormalities of liver biochemistries were observed numerically more frequently in the ASV-exposed subjects when compared to DCV/PegIFN/RBV or DCV/SOF with and without RBV subjects.

7.3.4 Significant Adverse Events

All cause, grade 2-4 AEs were evaluated for the phase 3 trials to determine which moderate to severe AEs were reported most frequently. Overall, 37%, 41% and 68% of subjects from trials 7026, 7028 and 7029, respectively, experienced at least one AE that was considered at least moderate (grade 2) to severe (grade 4) in intensity. As summarized in Table 16 below, the known AEs associated with use of pegIFN and RBV drive the commonly reported AEs from the QUAD regimen. For example, the proportions of subjects complaining of rash, pruritus, fatigue, asthenia, influenza-like illness, alopecia, depression and irritability are all higher in the QUAD subjects compared to those exposed to the DUAL regimen. One notable exception is the similar reporting rate of pyrexia between the Japanese pegIFN-free DUAL trial 7026 and the QUAD trial 7029 where subjects were exposed to pegIFN which is known to cause pyrexia, particularly upon initiation of therapy. Additionally there is a higher rate of reported increased ALT and AST from the DUAL trial 7026 compared to both 7028 and 7029. More detailed discussion of these safety events are in Section 7.3.5.

The reported events from trials 7026 and 7028 of the DUAL regimen, other than the exceptions mentioned previously, are otherwise generally comparable to the placebo arm.

Table 16: All Cause Grade 2-4 Adverse Events On-Treatment in ≥ 5% From Any Treatment Arm – Phase 3 Trials

	AI447026 DUAL	AI447028 DUAL	AI447029 QUAD	
Preferred Term	DCV 60mg QD + ASV 100 mg BID (24W) N=222	DCV 60mg QD + ASV 100 mg BID (24W) N=645	PLACEBO (12W) N=102	DCV 60mg + ASV 100mg BID+ PegIFN + RBV (24W) N=398
<i>Total subjects with an event</i>	91 (41%)	240 (37%)	18 (18%)	269 (68%)
FATIGUE	2 (1%)	38 (6%)	3 (3%)	64 (16%)
ANAEMIA	8 (4%)	1 (<1%)	1 (1%)	50 (13%)
ALT INCREASED	29 (13%)	14 (2%)	1 (1%)	4 (1%)
AST INCREASED	23 (10%)	5 (1%)	1 (1%)	4 (1%)
PRURITUS	1 (<1%)	12 (2%)	2 (2%)	48 (12%)
NEUTROPENIA	1 (<1%)	2 (<1%)	0	47 (12%)
HEADACHE	6 (3%)	33 (5%)	1 (1%)	43 (11%)
ASTHENIA	0	16 (2%)	1 (1%)	37 (9%)
NAUSEA	3 (1%)	20 (3%)	1 (1%)	34 (9%)
INFLUENZA LIKE ILLNESS	0	6 (1%)	0	34 (9%)
INSOMNIA	5 (2%)	10 (2%)	0	28 (7%)
RASH	4 (2%)	6 (1%)	0	28 (7%)
DIARRHOEA	5 (2%)	24 (4%)	3 (3%)	25 (6%)
PYREXIA	12 (5%)	9 (1%)	0	24 (6%)
ALOPECIA	1 (<1%)	3 (<1%)	1 (1%)	23 (6%)
DRY SKIN	0	2 (<1%)	0	21 (5%)
COUGH	0	19 (3%)	1 (1%)	20 (5%)
DEPRESSION	0	9 (1%)	0	20 (5%)
THROMBOCYTOPENIA	5 (2%)	3 (<1%)	0	20 (5%)
IRRITABILITY	0	1 (<1%)	0	19 (5%)
DECREASED APPETITE	2 (1%)	3 (<1%)	0	18 (5%)

Source: AE and ADSL datasets

To further characterize the more significant adverse events, analyses were completed for treatment-related (not specific to any drug in the regimen) grade 3 or 4 adverse reactions for the phase 3 trials. The following table provides a summary of the data. Only related grade 3 or 4 events that had in total, at least 2 subjects from the phase 3 trials are included in the table. All other related grade 3 or 4 events were reported in single subjects from any phase 3 trial.

Overall, subjects exposed to QUAD therapy in 7029 had the highest proportion (22%) of grade 3 or 4 related AEs. A higher proportion of subjects (14%) from the DUAL trial 7026 had grade 3 or 4 related events compared to the DUAL trial 7028 (3%), which was comparable to the placebo arm (3%). This higher proportion of reporting is related to laboratory-related abnormalities (primarily liver-related). This may reflect patterns of AE reporting as laboratory events are not consistently reported as AEs in clinical trials; a more objective assessment is using the reported laboratory data (see analyses for liver-related laboratory analysis in Section 7.3.5 and other laboratory analyses in Section 7.4.2).

Similar to the all-cause grade 2-4 analyses, the related grade 3 and 4 events are most frequently reported from trial 7029 and reflect the pegIFN/RBV associated, and labeled, adverse events (i.e. neutropenia, anemia, fatigue, thrombocytopenia, weight decreased etc.). Aside from the laboratory related events, the related grade 3 and 4 AEs from the DUAL exposed subjects are comparable to the placebo subjects.

Table 17: Related Grade 3 or 4 AEs in ≥ 2 Subjects From Phase 3 Trials

	AI447026 DUAL	AI447028 DUAL	AI447029 QUAD	
	DCV 60mg QD + ASV 100 mg BID (24W) N=222	DCV 60mg QD + ASV 100 mg BID (24W) N=645	PLACEBO (12W) N=102	
Preferred Term			DCV 60mg + ASV 100mg BID+ PegIFN + RBV (24W) N=398	
<i>Total subjects with an event</i>	32 (14%)	18 (3%)	3 (3%)	88 (22%)
NEUTROPENIA	1 (<1%)	1 (<1%)	0	33 (8%)
ANAEMIA	4 (2%)	0	1 (1%)	14 (4%)
FATIGUE	0	2 (<1%)	0	9 (2%)
THROMBOCYTOPENIA	2 (1%)	1 (<1%)	0	7 (2%)
WEIGHT DECREASED	1 (<1%)	0	0	6 (2%)
RASH *	0	0	0	6 (2%)
ASTHENIA	0	0	0	4 (1%)
HEPATIC ENZYME INCREASED	0	1 (<1%)	0	4 (1%)
ALT INCREASED	17 (8%)	5 (1%)	1 (1%)	2 (1%)
AST INCREASED	12 (5%)	2 (<1%)	1 (1%)	2 (1%)
HYPERBILIRUBINAEMIA	0	1 (<1%)	0	2 (1%)
LYMPHOPENIA	3 (1%)	0	0	2 (1%)
NEUTROPHIL COUNT DECREASED	1 (<1%)	0	0	2 (1%)
VERTIGO	0	0	0	2 (1%)
BLOOD BILIRUBIN INCREASED	2 (1%)	0	0	1 (<1%)
HAEMOGLOBIN DECREASED	1 (<1%)	0	0	1 (<1%)
HEADACHE	0	1 (<1%)	0	1 (<1%)
HYPERTENSION	0	1 (<1%)	1 (1%)	1 (<1%)

*Rash pooled terms: rash, rash generalized, toxic skin eruption, erythema, exfoliative rash and dermatitis exfoliative.

Source: AE and ADSL datasets

AEs of Interest for DCV

Hepatotoxicity was observed in nonclinical toxicity studies with DCV; however, in clinical trials with DAA combinations without ASV (DCV/SOF) or with DCV + PegIFN/RBV a dose dependent, or duration dependent hepatotoxicity for DCV is not seen. These findings are discussed in detail in Section 7.3.5.

Other NS5A inhibitors in development had eye-related toxicities observed in nonclinical studies. Based on these observations, safety data related to the eye were further evaluated. Overall in the phase 3 safety database, 106 (8%) of subjects reported an AE under the MedDRA SOC Eye Disorders; this includes 4 placebo subjects from trial 7028. Moderate or severe AEs that were considered related to study drugs were reported by 19 subjects (1.4%) across the phase 3 trials. Fifteen of these subjects were exposed to pegIFN/RBV in the QUAD regimen in trial 7029, which are associated with eye-related AEs. Specifically, 6 subjects (2%) reported dry eye, 3 subjects (2%) visual impairment, 2 (1%) subjects reported blurred vision and 2 subjects (1%) reported reduced visual acuity. From the DUAL trials, 3 subjects from 7028 reported moderate to severe-related events (1 each: reduced visual acuity, erythema of eyelid, macular degeneration) and 1 subject from 7026 reported asthenopia (eye strain). The most frequent treatment-emergent, all cause AEs were allergic conjunctivitis (2%), blurred vision (1%) and visual impairment (1%). The supportive phase 2 data had a similar pattern of reporting with no reported SAEs, and overall the most frequent reports of all cause AEs being dry eye and blurred vision (4% overall for each).

Considering the totality of the eye-related safety data, there was no significant trend observed for eye events related to DCV, including the fact that there was no specific nonclinical toxicity signal related to eye findings. The events that were observed are consistent for the population that was evaluated in the clinical trials (approximately 20% of subjects in the phase 3 trials are 65 years or older) or are associated with use of pegIFN/RBV.

Gastrointestinal disorders were also a common AE reported in DCV-containing treatment regimens. Analysis of gastrointestinal events from the phase 3 safety database is included below.

AEs of Interest for ASV

Detailed discussion of hepatotoxicity, rash, and pyrexia associated with eosinophilia with and without liver-related events are presented in Section 7.3.5 and comprise the main safety findings of this review. Other safety issues related to the HCV protease inhibitor drug class events were evaluated and are briefly described below.

Telaprevir, another protease inhibitor, has been associated with ano-rectal events, mostly related to proctalgia. In the controlled clinical trials, 29% of subjects treated with telaprevir combination treatment experienced ano-rectal adverse events, compared to 7% of those treated with peginterferon alfa and ribavirin alone. The majority of these events (e.g., hemorrhoids, ano-rectal discomfort, anal pruritus, and rectal burning) were mild to moderate in severity; less than 1% led to treatment discontinuation and all resolved during or after completion of telaprevir dosing. Analysis by the following preferred terms was completed for the phase 3 safety database: proctalgia, rectal haemorrhage, anal fissure, anal pruritus, proctitis, hemorrhoids, ano-rectal discomfort,

and anal pruritus. Anal pruritus was the most frequently reported ano-rectal event in 8 subjects (2%) in 7029, and in 4 subjects (1%) in 7028 and none in placebo. Two subjects from trial 7028 reported rectal hemorrhage, but all other events were reported in single subjects. Anal pruritus (2%) and hemorrhoids (2%) from trial 7029 were the only drug-related ano-rectal events reported in more than a single subject across all phase 3 trials. There was 1 drug-related event of hemorrhoids from trial 7028 and there were no drug-related events in trial 7026. No subjects reported any ano-rectal events leading to discontinuation. Overall, there was not a safety signal for ano-rectal events with use of ASV in combination with DCV in the DUAL or QUAD regimens.

GI intolerance has been associated with both telaprevir (nausea, vomiting and diarrhea) and simeprevir (nausea). The Applicant included analysis of Gastrointestinal Disorders defined by the following MedDRA PTs: nausea, vomiting, and anorexia. In general, the Applicant reports that grade 1 or 2 events occurred in approximately 12% (n=112) of DUAL-exposed subjects (including the phase 2 trials AI447017 and AI447017). No subjects had grade 3 or 4 events, and no events were considered serious or led to discontinuation of therapy. No subjects from the phase 3 trials had an AE report of anorexia.

Because no subjects reported anorexia across the phase 3 trials and because diarrhea is a frequently reported GI event, and given the association of telaprevir with diarrhea, FDA analysis for gastrointestinal (GI) disorders included the MedDRA PTs: nausea, vomiting and diarrhea and evaluated the phase 3 database (trials 7026, 7028 and 7029). Overall, GI disorders were reported by 17% of DUAL-exposed subjects (n=38) from 7026, 25% of DUAL exposed subjects (n=159) from 7028, 20% of placebo subjects (n=20) from 7028 and 31% (n=122) of QUAD-exposed subjects from 7029. There were no reported grade 3 or 4 AEs for nausea or vomiting, and only 3 subjects (1 from 7029 and 2 from 7028) reported grade 3 diarrhea.

Related GI disorder AEs were reported by 11% of subject from 7026 (n=24), 17% of subjects from 7028, 17% of subjects from placebo and 26% of subjects (n=104) from 7029. All GI disorder related AEs were considered grade 1 or 2, except for a grade 3 AE of diarrhea in 1 subject (0.3%) from 7029. No events were considered serious and no events led to discontinuation of treatment.

In summary, GI disorders in DUAL exposed subjects were reported in proportions similar or less than those who were exposed to placebo. Events were reported at higher proportions for QUAD exposed subjects in comparison to DUAL or placebo-exposed subjects; however, overall events were mild to moderate and did not lead to study drug discontinuation across the phase 3 trials.

7.3.5 Submission Specific Primary Safety Concerns

Two prominent findings during development of ASV and ASV/DCV prompted a target review of all hepatic safety. The first finding was transaminase elevations observed with higher doses of ASV in phase 2. The second finding was a case of biopsy confirmed liver damage with eosinophils in the Japanese phase 3 trial AI447026. This case was reported to FDA during the ongoing phase 3 trials. These findings are briefly described below.

Transaminase elevations in Phase 2

Results from a dose finding trial (AI447016) of ASV in combination with PegIFN/RBV in treatment-naïve subjects with genotypes 1 and 4 HCV infection demonstrated a trend in the frequency and magnitude of ALT and AST elevations, and occasionally bilirubin elevations in the ASV treated groups, most frequently at doses > 200 mg BID using the phase 2 tablet formulation. Overall, 2 subjects from AI447016 (Subjects AI447016-16-10043 and AI447016-23-10017) who were non-cirrhotic and received ASV 600 mg QD + PegIFN/RBV, also met Hy's Law laboratory criteria. Additionally, 1 subject (AI447016-40-10061) who received ASV 600 mg BID + PegIFN/RBV discontinued due to transaminase elevations (peak ALT 179, AST 181 on Day 48) without bilirubin elevations. Please refer to ASV Dose Selection and Rationale Section IV.B for details. Consequently, all trials assessing doses higher than 200 mg BID were dose reduced to 200 mg BID (using the phase 2 tablet formulation). Therefore, assessing transaminase elevations with and without increases in bilirubin was identified as a safety signal to further assess in phase 3.

In the phase 2 development of DCV in combination with PegIFN/RBV compared to placebo and DCV in combination with sofosbuvir (SOF) a specific hepatotoxicity signal was not apparent. No trends for increases in liver biochemistries were observed for DCV exposed subjects compared to placebo subjects.

Initial Case of Pyrexia and Eosinophilia in Phase 3: Subject AI447026-2-10122

During the DUAL trial AI447026, **Subject 2-10122**, a 57 year old Japanese male without cirrhosis presented with fever (38.4°C), grade 4 ALT and AST elevations (Baseline was approximately 2x ULN), grade 3 bilirubin elevation, grade 2 elevated CRP and eosinophilia after 4 weeks of DUAL therapy. (Note: at Week 2 bilirubin elevation began but ALT and AST were in normal range, see lab listing and graphic profile below). Study medication was discontinued and the subject was admitted to the hospital for 3 days for detailed observation and liver biopsy and further laboratory evaluation. The liver biopsy was reported as the following:

Moderate infiltration of eosinophils, lymphocytes and plasma cells are observed in the liver lobules and portal areas with focal bleeding and blood stasis in the sinusoids. The portal areas show fibrous expansion and interface hepatitis (piecemeal necrosis) is extensively observed. There are eosinophils and pigmented phagocytes sporadically observed in the lobules and are accompanied by necrosis of hepatocytes. Fibrosis extends from the portal area to the surrounding area and bridging fibrosis is observed partially.

Given the patient's medical history and other backgrounds, drug induced hepatic injury is suspected, even though the above findings are non-specific observations. No malignancy observed.

Reviewer Comment: There are some prospective data available from the Drug Induced Liver Injury Network (DILIN) registry (Kleiner, 2014) and from a large meta-analysis of case reports (Bjornsson, 2007) of DILI that demonstrates that necrosis was associated with poor outcome, whereas eosinophils on liver biopsy were associated with a milder injury. Bjornsson also points out that for the majority of drugs evaluated in their report, the absence of eosinophilia in peripheral blood seems to be a better predictor of poor outcome than the absence of eosinophils on liver biopsy. In reported biopsies, an inflammatory reaction was generally more common among patients who recovered without therapeutic intervention. Kleiner states eosinophils are also associated with immunoallergic response which may carry a better prognosis than other kinds of DILI. The liver biopsy in the index case has both poor prognostic signs of necrosis of hepatocytes, extensive piecemeal necrosis, partial bridging fibrosis and focal bleeding; however, this subject also has both peripheral eosinophilia and eosinophils on liver biopsy which may indicate an immunoallergic component to this case of DILI. Additionally, this subject improved rapidly on prednisone therapy.

Additional laboratory tests showed elevated cytomegalovirus (CMV) IgG at 13.9 (ref range: 0.00 - 1.99), elevated Epstein Barr virus (EBNA)/IgG/enzyme immunoassay at 1.9 (ref range: 0.00 - 0.49). The subject was treated with steroids (prednisolone).

Approximately 20 days after discontinuing treatment, AST, bilirubin, CRP, and eosinophils returned to within normal limits.

Examination of available drug exposure data from this subject revealed high DCV/ASV levels (50-100 fold increased trough exposure for DCV and ASV). Incorrect dosing was identified at Week 2 by the subject's report (DCV 120 mg instead of 60 mg); however, the full etiology of the high drug exposures in this subject remains uncertain. The Applicant did verify that the subject's ASV dosing was correct and that the subject did not take over-the-counter or herbal medications. Additionally, ASV PK has been shown to be highly sensitive to liver dysfunction as demonstrated in the ASV hepatic

impairment study; all measures of worsening hepatic function correlated with marked changes in ASV plasma exposure.

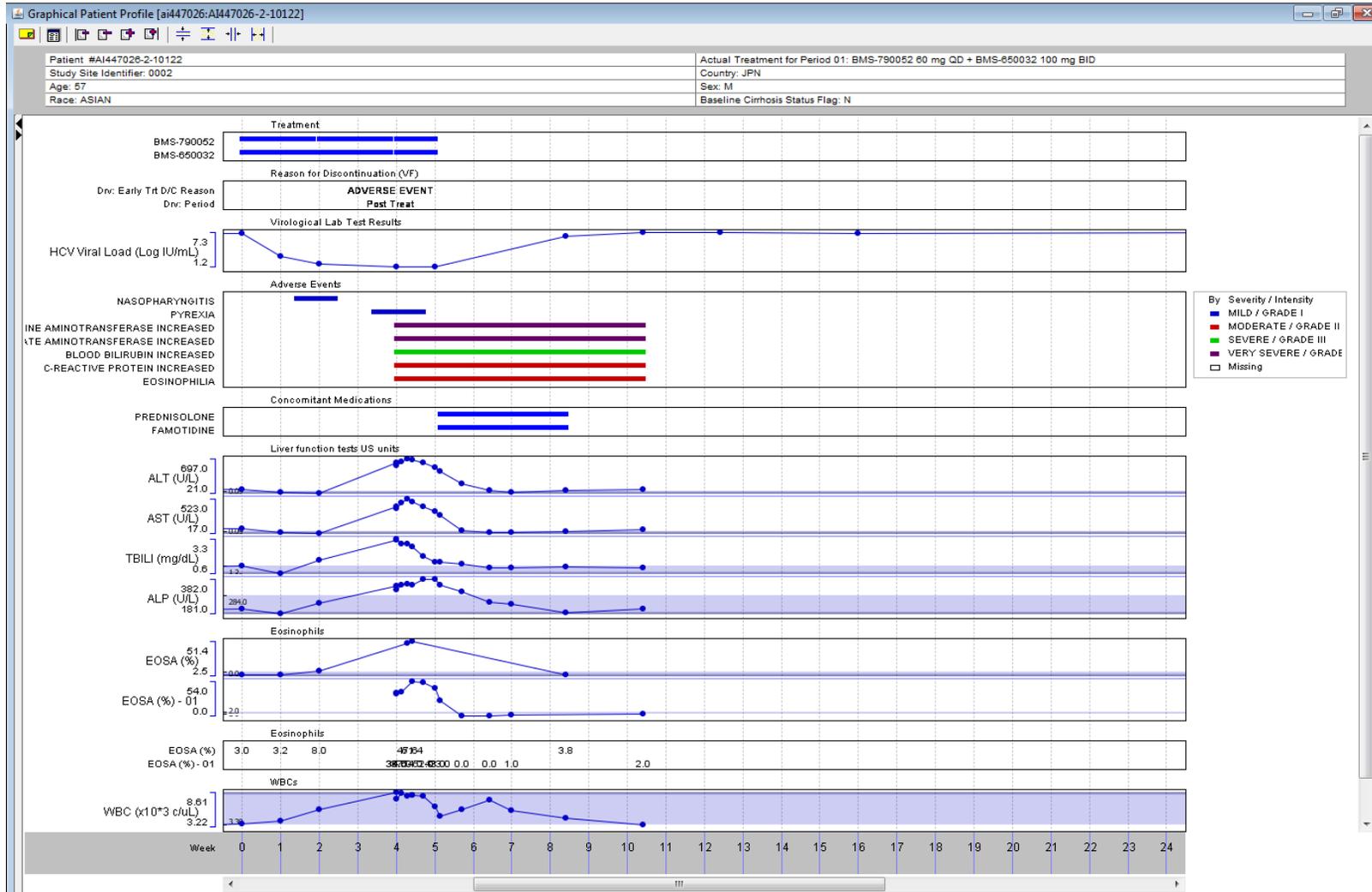
This subject relapsed post-treatment and was a virologic failure.

Summary of liver biochemistry data are provided:

LFT				
	AST	TBILI	ALT	ALP
Units	U/L	umol/L	U/L	U/L
Range	- 37	- 20.5	- 40	- 284
Day-18	83	17.1	101	197
Day1	74	20.5	94	208
Day8	25	10.3	39	181
Day15	17	27.4	21	237
Day29	379, 408	56.4, 54.7	558, 609	341, 320
Day30	456	49.6	623	344
Day31	523	49.6	697	350
Day32	480	46.2	674	346
Day34	409	32.5	607	379
Day36	339	25.7	514	382
Day37	280	25.7	439	346
Day41	51	22.2	198	304
Day46	20	17.1	65	248
Day50	20	17.1	38	234
Day60	44	18.8	69	184
Day74	67	17.1	92	207

Below Figure 5 provides a graphic view of the subject's HCV viral load, AEs, concomitant medications, eosinophil laboratory results and liver biochemistry results over time (represented in weeks).

Figure 5: Graphic Patient Profile of Initial Case of Pyrexia, Eosinophilia with Liver Involvement



Based on this event, a recommendation of increased monitoring of subjects with unexpected pyrexia was added to the protocol and investigators were notified. In addition, hypersensitivity “criteria” (definition) were developed by the Applicant and ongoing study protocols were amended to add: 1) a discontinuation rule for subjects who develop pyrexia concurrent with eosinophilia and increased ALT and AST; and 2) AE monitoring guidance of other signs and symptoms for subjects who develop pyrexia while on study. Hypersensitivity was defined as pyrexia $\geq 38.7^{\circ}\text{C}$ with concurrent (i.e., occurring within 28 days after the onset date of pyrexia) eosinophilia defined as absolute eosinophilia count of $> 1.5 \times 10^9$ cells/L and ALT and AST $\geq 5 \times \text{ULN}$ (laboratory data meeting criteria had to be from the same day), and no evidence of acute viral (excluding HCV), bacterial, or parasitic infection. Of note, additional discussion is provided in the Hy’s Law analysis section.

Based on these findings a detailed evaluation of liver biochemistry analyses and pyrexia and eosinophilia with and without liver involvement was conducted. At this time, we are uncertain if the findings of hepatotoxicity/elevation of transaminases and pyrexia and eosinophilia with and without liver involvement represent one clinical presentation or distinct events. The sections below first describe liver biochemistry analyses and cases of potential drug induced liver injury followed by details from the analyses of pyrexia and eosinophilia. Our preliminary assessment noted several differences with respect to findings in the analyses below between trial 7026 conducted in Japan and the global trials 7028 and 7029. These differences suggest that there may be racial differences for the presentation of pyrexia and eosinophilia.

Overview of Liver Biochemistry Analyses

First, an overview of liver biochemistries by toxicity grade is described for the phase 3 trials and the phase 2 DCV (non-ASV containing) trials. Secondly, shift analyses (baseline versus maximum increase in ALT, AST, alkaline phosphatase and total bilirubin) are presented.

Liver Biochemistry Analyses by Toxicity Grade: Phase 3 DUAL and QUAD Regimens

Generally, as expected with treatment of HCV, most subjects’ ALT and AST values improved or normalized with treatment with DUAL or QUAD during the phase 3 trials. Overall, baseline median ALT was 59 U/L (range: 13, 377) for trial 7026; 60 UL (range: 7, 475) for trial 7028, and 66 U/L (range: 12, 364) for trial 7029. Median ALT nadirs for the phase 3 trials were 14 U/L, 17 U/L and 23 U/L for 7026, 7028 and 7029, respectively. However, based on the potential for hepatotoxicity, analyses to evaluate the potential for changes in liver biochemistries and to further characterize the potential for drug induced liver toxicity were completed for the phase 3 trials.

Analyses of laboratory data for treatment-emergent graded liver biochemistry abnormalities are summarized in below. Note in this analysis, subjects who failed on-treatment and started 'rescue' therapy with pegIFN/RBV in the DUAL trials 7026 and 7028, were excluded only after the start of pegIFN/RBV. These analyses represent any change after baseline and a subject could have more than one event for a given laboratory parameter and could have more than one treatment emergent laboratory abnormality (e.g. ALT, AST and total bilirubin). The denominator used is the total number of subjects per trial or arm as indicated and not by the number of subjects with available data which was the method used by the Applicant.

Overall, the proportions of treatment emergent grade 3 or 4 laboratory elevations of ALT and AST were similar between the DUAL treatment in 7028, the placebo arm in 7028 and the QUAD treatment in 7029. In contrast, the proportions of subjects with treatment emergent grade 1-4 elevations of ALT and for AST were higher in the Japanese DUAL trial 7026, compared to the global DUAL trial 7028, the placebo arm in 7028 (except for grade 1 ALT) and even the QUAD treatment regimen in 7029. A similar pattern is observed for alkaline phosphatase where 8% of 7026 subjects had grade 1 events compared to 2% of subjects in both trials 7028 and 7029, respectively, and no events in placebo. Grade 1 total bilirubin elevation was observed in 22% of 7029 QUAD subjects (ribavirin is part of the QUAD regimen and is associated with bilirubin elevations due to hemolytic anemia), 16% of 7026 subjects and 6% of 7028 DUAL subjects and 7% of placebo subjects. Overall, few subjects had treatment-emergent grade 2 total bilirubin elevations, the highest proportion was observed in 33 subjects (8%) in trial 7029, compared to 2% of subjects both DUAL trial and the placebo arm. Grade 3 total bilirubin events were observed in 1% or less of each treatment arm and placebo. Note that direct bilirubin measurements were only available for about 33% of the phase 3 subjects, so analyses were completed using total bilirubin.

Table 18: Treatment-Emergent Liver Biochemistry Laboratories by Toxicity Grade for the Phase 3 Trials

Lab Test and Emergent Toxicity Grade	AI447026	AI447028	AI447029		
	DCV 60mg QD + ASV 100 mg BID (24W) N=222	DCV 60mg QD + ASV 100 mg BID (24W) N=645	PLACEBO (12W) N=102		
ALT	GRADE 1 (1.25-2.5 x ULN)	18 (8%)	51 (8%)	17 (17%)	28 (7%)
	GRADE 2 (2.6-5.0 x ULN)	23 (10%)	33 (5%)	9 (9%)	24 (6%)
	GRADE 3 (5.1-10.0 x ULN)	12 (5%)	9 (1%)	2 (2%)	12 (3%)
	GRADE 4 (> 10 x ULN)	6 (3%)	8 (1%)	0	0
AST	GRADE 1 (1.25- 2.5 x ULN)	21 (9%)	39 (6%)	13 (13%)	34 (9%)
	GRADE 2 (2.6-5.0 x ULN)	11 (5%)	21 (3%)	6 (6%)	24 (6%)
	GRADE 3 (5.1-10.0 x ULN)	8 (4%)	8 (1%)	1 (1%)	13 (3%)
	GRADE 4 (> 10 x ULN)	3 (1%)	4 (1%)	0	0
Alk Phos*	GRADE 1 (1.25 - 2.5 x ULN)	17 (8%)	13 (2%)	0	8 (2%)
	GRADE 2 (2.6 --5 x ULN)	1 (<1%)	0	0	0
TBili	GRADE 1 (1.1-1.5 x ULN)	35 (16%)	38 (6%)	7 (7%)	89 (22%)
	GRADE 2 (1.6-2.5 x ULN)	8 (2%)	16 (2%)	2 (2%)	33 (8%)
	GRADE 3 (2.6 – 5.0 x ULN)	1 (<1%)	2 (<1%)	1 (1%)	4 (1%)

*No treatment emergent elevations beyond Grade 1 were reported
Source: Laboratory and Subject Level Analysis Datasets

Phase 2 DCV – Non-ASV Containing Regimen.

Safety data for DCV not in combination with ASV is available from the phase 2 program and from trial AI444040 which evaluated DCV in combination with sofosbuvir (SOF) for 12 to 24 weeks duration.

Based on the pooled phase 2 data supporting DCV alone (6 trials with subjects treated with DCV 60 mg QD + PegIFN/RBV n=505; placebo/PegIFN/RBV n=174), most observed transaminase and bilirubin abnormalities were grade 1 and 2. Rates of grade 3 or 4 abnormalities were similar between the DCV/PegIFN/RBV and placebo/PegIFN/RBV treatment groups. Grade 3/4 ALT increases were reported for 11 (2%) DCV/PegIFN/RBV and 4 (2%) placebo/PegIFN/RBV subjects. Grade 3/4 AST was reported by 3% of DCV subjects (n=13) and 3% of placebo subjects (n=6). Similar rates between DCV treated and placebo subjects were also reported for grade 3/4 Total Bilirubin: 1% DCV subjects (n=5) versus 2% of placebo subjects (n=4), respectively. The median change in ALT from nadir to highest value on-treatment was 12 U/L (range:-165-385 U/L) for DCV-treated subjects and 7 U/L (range: -247 to 322) among

placebo treated subjects. No subjects discontinued therapy due to ALT or AST abnormalities and only 1 subject (AI444031-25-159; 1/505; 0.2%) had an increased total bilirubin (grade 4) leading to discontinuation. One placebo subject (1/174; 0.6%) also discontinued study therapy due to hepatic failure. There were no cases of protocol-defined potential Drug-Induced Liver Injury (pDILI) identified in subjects treated with DCV/PegIFN/RBV in these placebo-controlled trials; however 5/505 (1%) of subjects met the laboratory criteria of Hy's Law (for further discussion see reviewer comment in Hy's Law section below).

In trial AI444040 (DCV/sofosbuvir with and without RBV), no grade 3/4 ALT, AST or total bilirubin elevations were reported and no cases of pDILI were identified. In general, most subjects in AI444040 had normal liver biochemistry values on treatment.

Reviewer comment: Based on the totality of data, ASV appears to have a higher risk of drug-associated liver injury compared to DCV. It is clear that there is the potential for transaminase abnormalities related to use of DCV in combination with pegIFN/RBV and 1 subject (AI444031-25-159) in phase 2 on DCV/pegIFN/RBV regimen had liver injury with some liver dysfunction; however, the subject also had relapse of HCV which likely contributed to the liver decompensation. More reassuring are data from AI444040 where there were no cases of significant liver biochemistry abnormalities or liver-related AEs.

Baseline Versus Maximum Increase Analyses (Shift Analyses)

To account for baseline elevations in liver biochemistries commonly associated with hepatitis C infection, analyses of baseline versus maximum increase in ALT, AST, alkaline phosphatase, and total bilirubin (Shift Analyses) were completed for the phase 3 trials. Table 19 displays the Shift Analyses for AI447026, AI447028 and AI447029 for ALT and total bilirubin. The following general observations are made from these analyses:

- Subjects with cirrhosis did not have more frequent or more severe changes from baseline for ALT, AST, Alk Phos or Total Bilirubin compared to subjects without cirrhosis (data not shown)
- A small proportion of subjects from each trial had significant shifts in ALT and AST (further description of individual subjects who met Hy's Law criteria or significant elevations in ALT are discussed in section VIII below)
- The shifts from baseline in ALT and AST are not usually accompanied by significant shifts in Alk Phos or Total Bilirubin

- Overall, 12 of 867 subjects (1.3%) exposed to the DUAL regimen developed a shift in Total Bilirubin from Baseline $<2xULN$ to Maximum of $\geq 2x ULN$ and $<5 x ULN$. In the QUAD regimen, 12 of 398 subjects (3%) developed a shift in Total Bilirubin from Baseline $<2xULN$ to Maximum of $\geq 2x ULN$ and $<5 x ULN$

Table 19: Summary of Shift Analyses: Maximum Post-Baseline versus Baseline Liver Biochemistries (ALT and TBili) for Phase 3 Trials

		AI447026 - DUAL								AI447028 - DUAL								AI447029 - QUAD							
		DCV 60mg QD + ASV 100mg BID (24W) N = 222								DCV 60mg QD + ASV 100 mg BID N = 645								DCV 60mg + ASV 100mg BID + PegIFN + RBV (24W) N = 398							
ALT Baseline	ALT Maximum	ALT < 2x ULN		2x ≤ ALT < 5x ULN		5x ≤ ALT < 10x ULN		ALT ≥ 10x ULN		ALT < 2x ULN		2x ≤ ALT < 5x ULN		5x ≤ ALT < 10x ULN		ALT ≥ 10x ULN		ALT < 2x ULN		2x ≤ ALT < 5x ULN		5x ≤ ALT < 10x ULN		ALT ≥ 10x ULN	
		Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
ALT < 2x ULN		99	44.59	63	28.38	1	0.45	0	0.00	426	66.05	118	18.29	1	0.16	0	0.00	266	66.83	59	14.82	1	0.25	0	0.00
2x ≤ ALT < 5x ULN		22	9.91	15	6.76	4	1.80	1	0.45	47	7.29	26	4.03	7	1.09	1	0.16	26	6.53	30	7.54	3	0.75	0	0.00
5x ≤ ALT < 10x ULN		6	2.70	3	1.35	1	0.45	0	0.00	6	0.93	3	0.47	0	0.00	0	0.00	5	1.26	5	1.26	0	0.00	0	0.00
10x ≤ ALT < 20x ULN		4	1.80	3	1.35	0	0.00	0	0.00	4	0.62	0	0.00	0	0.00	0	0.00	2	0.50	1	0.25	0	0.00	0	0.00
ALT ≥ 20x ULN		1	0.45	0	0.00	0	0.00	0	0.00	4	0.62	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

		DCV 60mg QD + ASV 100mg BID (24W) N = 222								DCV 60mg QD + ASV 100 mg BID N = 645								DCV 60mg + ASV 100mg BID + PegIFN + RBV (24W) N = 398							
TB Baseline	TB Maximum	TB < 2x ULN		2x ≤ TB < 5x ULN		5x ≤ TB < 10x ULN		TB ≥ 10x ULN		TB < 2x ULN		2x ≤ TB < 5x ULN		5x ≤ TB < 10x ULN		TB ≥ 10x ULN		TB < 2x ULN		2x ≤ TB < 5x ULN		5x ≤ TB < 10x ULN		TB ≥ 10x ULN	
		Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
TB < 2x ULN		218	98.20	0	0.00	0	0.00	0	0.00	633	98.14	0	0.00	0	0.00	0	0.00	381	95.73	1	0.25	0	0.00	0	0.00
2x ≤ TB < 5x ULN		4	1.80	0	0.00	0	0.00	0	0.00	9	1.40	1	0.16	0	0.00	0	0.00	12	3.02	4	1.01	0	0.00	0	0.00
5x ≤ TB < 10x ULN		0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
10x ≤ TB < 20x ULN		0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
TB ≥ 20x ULN		0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Note: Subjects who have only baseline visit information or who were missing a baseline visit but had post baseline visits were not included in the Subject Counts, therefore, the percents may not add up to 100

Overview of Potential Drug-Induced Liver Injury and Hy's Law Cases

Because of the observed elevations of ALT during drug development, the Applicant implemented monitoring rules in their clinical protocols to assess potential drug-induced liver injury (pDILI) which took into consideration the chronic HCV population, including those with cirrhosis. Cases of pDILI were to be reported as serious adverse events (SAEs). In the protocols, pDILI was defined as concurrent ALT \geq 5x Baseline or nadir value, whichever is lower, **and** \geq 10 x ULN **and** TBILI \geq 2 x ULN on study (on treatment or during follow-up) for treated subjects. Concurrent was defined as the bilirubin elevation occurring within 30 days subsequent to the ALT elevation. In total, 4 subjects from the phase 3 clinical trials met these criteria [Subjects AI447026-2-10122, AI447026-1-20265, AI477028-44-80975 and AI447029-95-90110]. These subjects also met the more stringent laboratory criteria for Hy's Law which FDA used to more broadly screen for subjects who may have drug related liver toxicity. The narratives for the subjects meeting Hy's Law laboratory criteria are included in the section below.

Hy's Law Analyses

Hy's Law refers to the observation made by Dr. Hy Zimmerman that drug induced hepatocellular injury (i.e. aminotransferase elevation) accompanied by jaundice had a mortality of 10-50%. Hepatocellular injury sufficient to impair bilirubin excretion has been used by the FDA to identify drugs likely to cause severe liver injury. The definition used by the FDA as an indicator of clinical concern for drug-induced liver injury includes: ALT or AST $>$ 3x upper limit of normal (ULN), total bilirubin $>$ 2x ULN without an initial increase in alkaline phosphatase, and no other explanations for the increases in liver enzymes (e.g. viral hepatitis, pre-existing or acute liver disease, another drug capable of causing the observed injury).

Due to a number of confounding factors, the appropriate application and interpretation of Hy's Law in the setting of treatment trials for chronic hepatitis C in general, is unknown. All of the subjects in the pivotal phase 3 trials for DCV/ASV were chronically infected with HCV and 25% (338/1367) of subjects across the phase 3 trials were classified as having cirrhosis. All subjects in the QUAD trial 7029 were co-administered PegIFN/RBV, and the administration of interferon is known to increase the risk of hepatitis exacerbations and hepatic failure, particularly in patients with underlying cirrhosis. The criteria for pDILI were agreed upon with FDA and were deemed appropriate for the study population to monitor for significant cases while also preventing premature discontinuation from clinical trials. However, to fully evaluate the clinical safety database, the more conservative Hy's Law laboratory criteria were used for capturing all potential cases. Therefore, expert hepatology evaluation and input on these identified cases as to whether these cases do or do not represent drug-induced liver injury attributable to DCV, to ASV or the combination will be extremely important to our overall assessment of these safety issues. These cases are part of the ongoing

consultation process and will be discussed as part of the planned Advisory Committee meeting.

Overall from the phase 3 trials, there were 9 DCV/ASV exposed subjects (0.7%; 9/1265) who met the laboratory criteria for Hy's Law (using ALT values), as discussed above, and 1 subject (1%; 1/102) who was randomized to placebo in trial 7028. Narratives for these subjects by trial are summarized below. The following summarizes the findings of these 9 DCV/ASV exposed subjects who met Hy's Law criteria by screening laboratory data using ALT values:

- 3 subjects discontinued early (including 1 subject who discontinued during Week 24), the remaining 6 subjects completed 24 weeks
- 3 subjects had cirrhosis at Baseline and 6 subjects did not have cirrhosis at Baseline
- In all 9 DCV/ASV exposed subjects, ALT improved to near or below Baseline levels during follow-up (3 subjects) or while remaining on study drug (6 subjects). However, the subject with the initial case of pyrexia/eosinophilia required medical intervention (steroids).
- 8 of 9 subjects achieved SVR12
- 3 cases were confounded by concomitant events or comorbidities of non-TB mycobacterial infection, Gilbert's disease and hepatocellular carcinoma

Analyses showing ALT and total bilirubin (TBILI) over time for the 9 subjects who met Hy's Criteria (placebo subject excluded) are provided in the figures 6 and 7 below. There is no distinct pattern to the TBILI changes observed in these subjects. For ALT, while there is no clear pattern to the elevations, generally, subjects have increases between Weeks 6 and 12.

Note that the Applicant also identified a single subject from trial 7029 (subject AI447029-25-901102) who met the laboratory criteria for Hy's Law when using AST values (not ALT values). However, this subject's peak AST value was grade 2 and had improved compared to the baseline AST level. The subject completed study therapy and achieved SVR12. This subject is not considered to represent a drug-induced liver injury case as there was a net decrease in both ALT and AST levels during treatment.

Reviewer comment: As part of further investigation of hepatotoxicity and pyrexia/eosinophilia associated with use of DCV/ASV during the review process, the Applicant convened an external panel of experts to review the totality of the hepatic safety data. On August 26, 2014 the Applicant submitted a document entitled "Liver/Pyrexia/Eosinophilia Safety Review Prepared in Collaboration with External Expert Panel." The expert panel included Dr. (b) (4)

(b) (4)

The report included a summary and expert opinion on each subject who fulfilled Hy’s Law Biochemical Criteria from the phase 2 and phase 3 trials. The Applicant identified a total of 23 cases meeting the biochemical-criteria of Hy’s law including 6/918 (0.7%) subjects treated with DCV/ASV, 4/418 (1%) subjects treated with DCV/ASV/pegIFN/RBV, 5/505 (1%) subjects treated with DCV/pegIFN/RBV, 7/213 (3%) subjects treated with ASV/pegIFN/RBV and 1/246 (0.4%) subject treated with placebo/pegIFN/RBV in phase 2 and 3 clinical trials. Causality considered whether the biochemical abnormalities could be attributed to DCV and/or ASV, and not whether any should be classified as a “Hy’s law case”, as classically defined. This is because the risk of liver failure based on the incidence of “Hy’s Law Cases” observed in clinical trials has not been based on data from patients with pre-existing liver disease, which is similar to the rationale FDA supported for use of the modified criteria for potential DILI in the clinical trials. The experts felt use of the term “Hy’s Law Case” was not appropriate for this patient population. There were four causality assessment assignments: Probably related, possibly related, unlikely related, and indeterminate (insufficient data). The following table provides a summary of the panel assessment of the identified cases by regimen:

Table 20: Summary of Applicant’s Consultant Panel Causality Assessment of Cases Meeting Hy’s Law by Laboratory Data

Treatment Regimen	Probable	Possible	Unlikely	Indeterminate (Insufficient data)	Total by regimen
DCV/ASV	5	1			6
DCV/ASV/pegIFN/RBV	2		2		4
DCV/pegIFN/RBV	1	2	2		5
ASV/pegIFN/RBV	2	2			4
ASV 600mg QD or BID/pegIFN/RBV	3				3
Placebo			1		1
Total by Causality	13	5	5	none	23

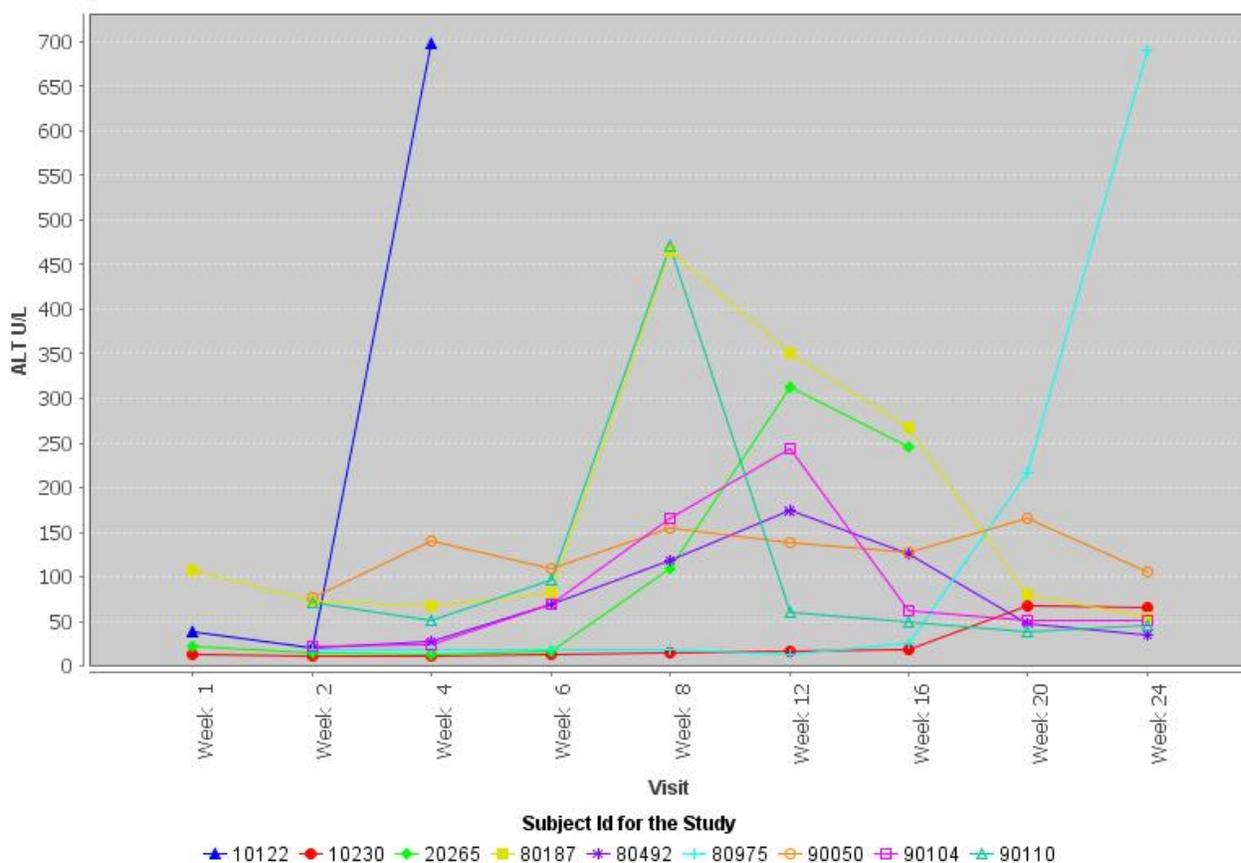
In summary, among the 22 subjects identified who were treated with DCV and/or ASV containing regimens and who met laboratory criteria for Hy’s Law, the panel assessed the treatment regimen as the probable cause for the liver biochemical abnormalities in 13 subjects. Among these 13 subjects, 4 demonstrated evidence of increased liver dysfunction associated with the biochemical abnormalities. Two out of the 4 subjects experiencing liver dysfunction were able to complete their courses of treatment without

progression of liver injury and two had treatment discontinued. All 4 subjects recovered and were never clinically ill. The overall opinion of the expert panel was that DCV/ASV containing regimens are capable of rarely causing hepatocellular injury and that this liver injury can cause liver dysfunction. While liver failure was not observed in the clinical trials, the risk for liver failure remains possible. Additionally, the panel had consensus that the issue of hepatotoxicity appeared related to ASV and not DCV.

Internal FDA consultation regarding the hepatic safety is ongoing.

Figure 6 : ALT by Study Visit for Hy's Law Subjects

- Subset of patients

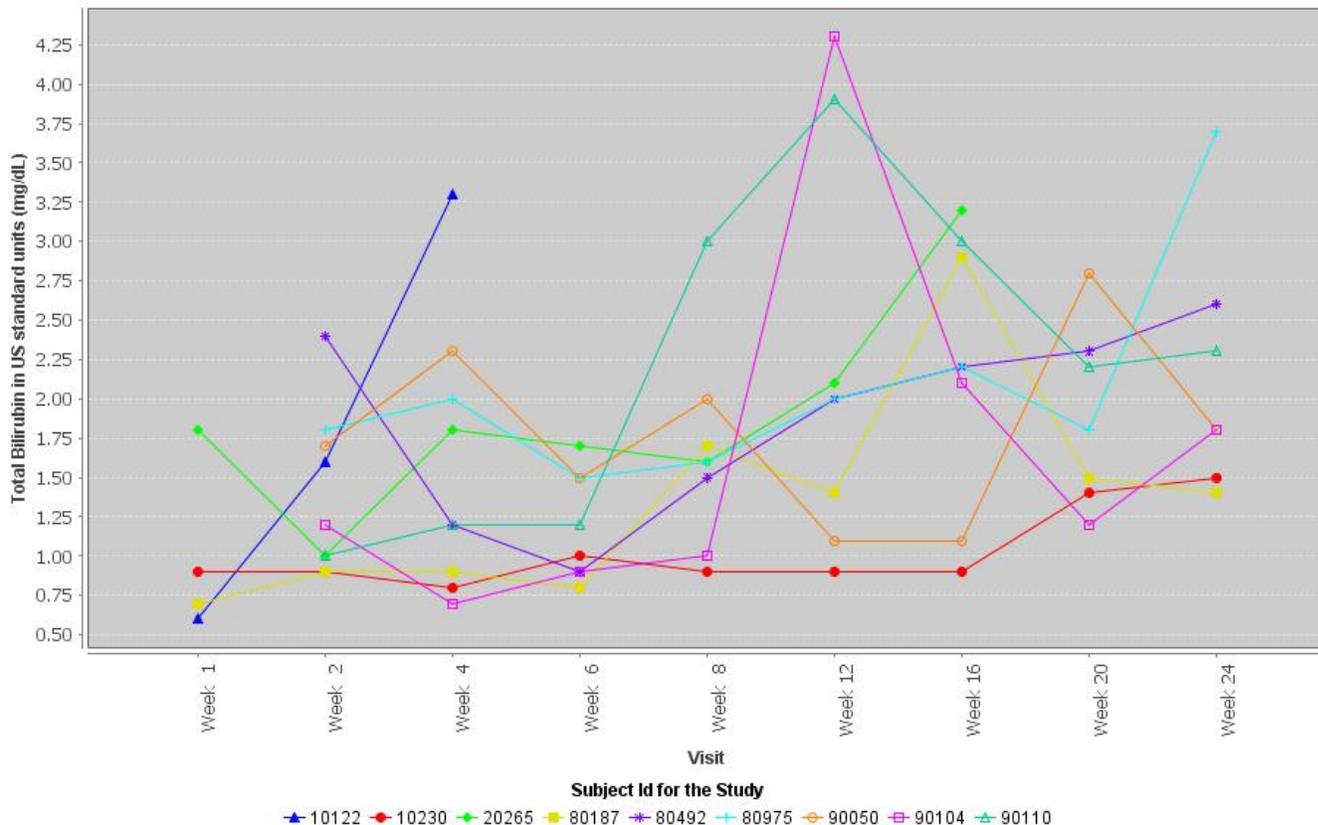


ALT by Study Visit for 9 subjects who met Hy's Law lab criteria

Patient Selection Criteria: <html> Demographics.Unique Subject Identifier =A1447026-1-20265,A1447026-19-10230,A1447026-2-10122 \$ OR D...
 Output Filter: Laboratory Results with US Units.Drv: Lab Test or Examination Code =Alanine Aminotransferase (ALT) AND Laboratory Results ...

Figure 7 : Total Bilirubin by Study Visit for Hy's Law Subjects

- Subset of patients



Total Bilirubin (mg/dL) by Study Visit for 9 subjects who met Hy's Law lab criteria

Patient Selection Criteria: <html> Demographics.Unique Subject Identifier=AI447026-1-20265,AI447026-19-10230,AI447026-2-10122 \$ OR Demographics.Unique Su...

Output Filter: Laboratory Results with US Units.Drv: Period=On Treat AND Laboratory Results with US Units.Drv: Visit Number=DAY 1,WEEK 1,WEEK 12,WEEK 16,WE...

Three Cases Meeting Hy's Law Laboratory Criteria in Trial 7026

Case 1 AI447026-19-10230: This is a 69 year old male without cirrhosis who was a prior partial responder. HCV RNA on Day 1 was 7.1 log IU/mL. This patient also had a relevant medical history of non-TB mycobacteriosis. On Day 111 lab tests showed ALT of 67 U/L (grade1), AST 67 U/L (grade1), ALP of 238 U/L (normal range) and TBili of 23.9 µmol /L (grade1). The subject remained on study drugs and lab values were stable on Day 139. No pyrexia, eosinophilia or rash/dermatologic involvement was observed. On Day 153, the ALT worsened to grade 2 at 172 U/L and AST worsened to grade 3 at 173 U/L, and grade 1 TBili of 25.7 µmol/L. On Day 160, the subject's hepatic enzymes peaked, with ALT of 203 U/L, AST of 219 U/L, TBIL of 51.3 µmol/L, however ALP was within normal, (294 U/L). At CT scan (region not specified) on Day 160 showed worsening of non-TB mycobacterial infection. Subject was discontinued from study

drugs on Day 160 (Day 168 would have completed full 24 weeks) and treatment with carbocysteine and pentoxyverine was started for 20 days (Days 160-180). On Day 181, the liver lab tests were within normal ranges and the event was considered resolved. The subject achieved SVR24. The investigator considered the events of increased ALT, increased AST, increased blood bilirubin and mycobacterial infection to be related to study therapy.

LFT				
	AST	TBILI	ALT	ALP
Units	U/L	umol/L	U/L	U/L
Range	- 31	- 20.5	- 44	- 361
Day-14	34	12	22	283
Day1	32	13.7	21	306
Day7	22	15.4	13	293
Day15	27	15.4	12	273
Day27	26	13.7	12	245
Day40	29	17.1	14	234
Day55	30	15.4	15	227
Day69	27	15.4	16	241
Day83	30	15.4	18	237
Day111	67	23.9	67	238
Day125	57	23.9	51	263
Day139	65	20.5	65	276
Day153	173	25.7	173	274
Day160	219	51.3	203	294
Day167	36	29.1	51	286
Day181	28	18.8	16	246
Day188	27	20.5	13	227

Case 2 AI447026-2-10122: This was the index case mentioned in the introduction of this section. More complete details are provided here.

Subject AI447026-2-10122 is a 57-year old male with chronic genotype 1b HCV infection, **without cirrhosis**, baseline AST/ALT elevations approximately 2 times ULN, and relevant medical history of an unspecified amount of alcohol use who was previously a partial responder to pegylated interferon alfa (pegIFN α)-2b/ribavirin (RBV) therapy.

The subject began treatment with DCV 60 mg QD and ASV 100 mg BID on Day 1 ((b) (6)). Relevant baseline laboratory results included: HCV RNA of 7.1 log IU/mL; aspartate aminotransferase (AST) 74 U/L (reference range: 10-37 U/L); ALT 94 U/L (reference range: 5-40 U/L); lactate dehydrogenase (LDH) 213 U/L (reference range: 107-220 U/L); ALP 208 U/L (reference range: 96-284 U/L); gamma-glutamyl

transpeptidase (GGT) 88 U/L (reference range: 0.00-73.00 U/L); total bilirubin 20.5 µmol/L (reference range: NA-20.5 µmol/L); direct bilirubin 6.8 µmol/L (reference range: 0.00-6.8 µmol/L); C-reactive protein (CRP) 1 mg/L (reference range: 0.00-2.5 mg/L); white blood cell count (WBC) 3.620 x 10⁹/µL (ref.range 3.39-9.55 x 10⁹/µL); and eosinophils 0.03 fraction (ref. range. 0.00-0.078 fraction). The AST/ALT levels decreased to < ULN by Day 8 (16 Mar 2012).

On Day 25 ((b) (6)), the subject developed fever (grade 1 pyrexia) that persisted until Day 29 ((b) (6)) with a maximum body temperature of 38.4 degrees Celsius. On Day 29 ((b) (6)), the subject's laboratory results showed increased liver function tests with an AST of 379 U/L, ALT of 558 U/L, total bilirubin of 56.4 µmol/L and direct bilirubin of 35.9 µmol/L (see laboratory data in Table 6.1-3). The CRP was also elevated to 41.4 mg/L and eosinophil count increased to 0.34 on the same day. An ultrasound of the abdomen (06 Apr 2012) suggested mild liver injury but no ascites. The subject did not have any dermatological reaction and no lymphadenopathy was present upon examination. The subject had no prior history of drug hypersensitivity reactions. The investigator reported serious adverse events of grade 4 increased AST and grade 4 increased ALT, grade 3 blood bilirubin increased, grade 2 increased C-reactive protein and a non-serious adverse event of grade 2 eosinophilia. **The study therapy was discontinued** with the last dose given the day before the Day 29 visit. HCV viral load was undetectable at the time of the event.

The event of pyrexia resolved on Day 34 ((b) (6)).

With regard to viral testing and serologies, cytomegalovirus (CMV) IgG was 13.9 (reference range: 0.00–1.99), Epstein Barr virus (EBNA) IgG was 1.9 (ref range 0.00–0.49) and Epstein Barr virus VCA/IgG-FA was at 40 (reference range: 0.00-9.99) on Day 32 ((b) (6)). On Day 36 ((b) (6)), the subject was hospitalized for detailed examination and laboratory tests. The liver biopsy showed liver damage with eosinophil infiltration, which according to the investigator would be typical histology of a drug allergy-induced liver injury. In the absence of dermatological reaction and lymphadenopathy, it was the investigator's opinion that this was an "atypical case". Treatment was initiated with a daily oral dose of 30 mg prednisolone on Day 37 ((b) (6)). On Day 37 the viral test results included, Human herpes virus (HHV) 6, 7 and 8: positive and EB virus: positive; HSV-CF was at 16 (reference range: 0-3.99), the hepatitis A, B and E virus were negative, Parvo virus B19: negative, Varicella-Zoster virus: negative, Herpes simplex virus: negative, and CMV: negative. On Day 39 ((b) (6)), the patient was discharged.

After approximately one week of treatment with prednisolone, the liver tests and eosinophils showed a recovery trend with an AST of 51 U/L, ALT of 198 U/L and eosinophils of 0. Prednisolone was tapered over time, to 20 mg on Day 41 ((b) (6)), to 10 mg on Day 46 ((b) (6)) and to 5 mg on Day 50 ((b) (6)) and was continued until Day 60 ((b) (6)). The events of increased ALT, increased

AST, increased blood bilirubin, increased C-reactive protein and eosinophilia, all resolved by Day 74 ((b) (6)).

The investigator considered the events of increased ALT, increased AST, increased blood bilirubin, increased C-reactive protein and eosinophilia to be related to the study therapy. Examination of drug exposure data revealed significantly elevated trough levels of both ASV and DCV at the week 4 visit. ASV concentration was 2,950 ng/mL (mean trough ASV levels typically 30-50 ng/mL) and DCV concentration was 2,090 ng/mL (mean trough DCV levels typically 150-250 ng/mL). Incorrect dosing was subsequently identified at week 2 by the patient's report (DCV 120 mg instead of 60 mg); no dosing errors with ASV were found. The subject did not take any over the counter or herbal medications.

The cause of the high drug exposures in this patient is uncertain. Although there was no dermatologic involvement or lymphadenopathy, a drug-induced hypersensitivity syndrome could not be excluded.

With regard to viral response, HCV RNA was undetectable by week 4 when the event occurred. Study drug was stopped at week 4 and the **subject experienced a relapse** approximately 30 days after discontinuation of treatment at post-treatment week 4.

Table 6.1-3: LFT Values for Subject AI447026-2-10122

	AST	TBILI	ALT
Units	U/L	µmol/L	U/L
Range	- 37	- 20.5	- 40
Day-18	83	17.1	101
Day1	74	20.5	94
Day8	25	10.3	39
Day15	17	27.4	21
Day29	379, 408	56.4, 54.7	558, 609
Day30	456	49.6	623
Day31	523	49.6	697
Day32	480	46.2	674
Day34	409	32.5	607
Day36	339	25.7	514
Day37	280	25.7	439
Day41	51	22.2	198
Day46	20	17.1	65
Day50	20	17.1	38
Day60	44	18.8	69
Day74	67	17.1	92

TBILI = total bilirubin

Case 3 AI447026-1-20265: This subject is a 71 year old male **without cirrhosis** and with a 50 year history of alcohol use (350 ml beer/month).

On Day 55 the subject's laboratory test values showed alanine aminotransferase (ALT) of 109 U/L (baseline: 48 U/L; reference range: NA-30 U/L), aspartate aminotransferase (AST) of 58 U/L (baseline: 36 U/L; reference range: NA-30 U/L), alkaline phosphatase (ALP) of 225 U/L (baseline: 212 U/L; reference range: NA-338 U/L), and total bilirubin (TBIL) of 27.4 µmol/L (baseline: 27.4 µmol/L; reference range: NA-20.5 µmol/L).

On Day 69, the laboratory test values showed further increase in the hepatic enzymes with ALT of 312 U/L, AST of 181 U/L and TBIL of 35.9 µmol/L. ALP was normal on Day 71, the elevated hepatic enzymes improved slightly with ALT of 294 U/L (grade 3), AST of 152 U/L, ALP was normal at 275 U/L, and TBIL at 27.4 µmol/L. His INR was 1.16 on Day 71 and increased to 1.27 on Day 85.

Study drugs were discontinued due to the elevated ALT, AST and TBIL with last doses received on Day 89. After study drugs were stopped, the ALT and AST rapidly resolved, while mild elevation of the TBili remained; however, it was improved compared to the subject's baseline (see table below). The investigator did not report these events as an SAE because they did not meet protocol criteria for potential DILI (pDILI) [Note; this subject did meet criteria for pDILI and is included in that analysis by the Sponsor; it remains unclear why the investigator did not believe the subject met the pDILI criteria]. The subject **achieved an SVR24**.

LFT				
	AST	TBILI	ALT	ALP
Units	U/L	umol/L	U/L	U/L
Range	- 38	- 20.5	- 44	- 338
Day-33	31	29.1	35	239
Day1	36	27.4	48	212
Day7	19	30.8	23	208
Day13	16	17.1	15	210
Day27	18	30.8	14	215
Day41	13	29.1	16	215
Day55	58	27.4	109	225
Day69	181	35.9	312	271
Day71	152	27.4	294	275
Day85	136	37.6	246	292
Day90	141	54.7	235	308
Day97	28	42.8	59	279
Day108	19	23.9	19	282
Day118	19	29.1	16	275

Four Cases meeting Hy's Law Laboratory Criteria in 7028 [Including Placebo Subject]

Case 1 AI447028-45-80287 (placebo)-

This is a 59-year old White male **without cirrhosis** who was treatment-naive for chronic hepatitis C infection, genotype 1b. His baseline HCV RNA on Day 1 ((b) (6)) was 9064465 IU/mL. Relevant medical history included left knee arthritis.

On Day 55 the subject underwent elective total knee arthroplasty. On Day 57 the subject experienced extreme fatigue, grade 2 syncope, grade 1 hypotension and Grade 3 anemia (Hb 60 g/L; Baseline 151 g/L; Ref range: 132-170 g/L). The same day, an EKG showed a right bundle branch block and left axis deviation. Chest x-ray was negative for acute cardiopulmonary disease [verbatim as reported]. A nonserious grade 2 hematoma of left knee and SAE of grade 3 post-procedural hemorrhage was reported. The subject continued placebo study therapy. The subject was started on treatment with acetaminophen/hydrocodone, enoxaparin, hydralazine, and warfarin on Day 57. The acetaminophen/hydrocodone and warfarin was stopped on Day 58. The subject received blood transfusions on Day 58 and Day 59 and event of anemia was considered resolved on Day 59. The subject stopped hydralazine and enoxaparin on Day 70. [Note: there is no discussion of the liver biochemistry abnormalities in the patient narrative]

As per protocol, the subject **completed the study (placebo)** and received the last doses of placebo (DCV and ASV) on Day 84. The subject's last available HCV RNA was 8597814 IU/mL on Day 85. On Day 85, the event of hematoma resolved.

LFT

	ALP	AST	TBILI	ALT
Units	U/L	U/L	mg/dL	U/L
Range	- 135	- 37	- 1.1	- 47
Day-36	72	107	.7	178
Day1	72	156	.5	214
Day8	63	123	.7	163
Day16	65	83	.4	112
Day28	70	72	.6	94
Day43	63	96	.5	120
Day64	150	103	3.5	128
Day85	85	39	.5	40

Case 2 AI447028-44-80975

This is a 26 year old male **without cirrhosis** and with a significant history of Gilbert's syndrome. His baseline HCV RNA was 1,354,934 IU/mL.

The subject remained on-study with DCV/ASV and **completed therapy** on Day 167. Consistent with a medical history of Gilbert's syndrome, the subject's on-treatment bilirubin levels fluctuated between 26 µmol/L and 38 µmol/L while his direct bilirubin levels remained stable, ranging between 5 µmol/L to 9 µmol/L.

On Day 168, 1 day after completing study therapy, the subject's laboratory test results showed alanine aminotransferase (ALT) of 690 U/L (grade 4, baseline: 46 U/L, reference range: NA-47 U/L), aspartate aminotransferase (AST) of 253 U/L (baseline: 29 U/L, reference range: NA-37 U/L), total bilirubin level of 64 µmol/L (baseline: 25.7 µmol/L, reference range: NA-19 µmol/L) and direct bilirubin level of 7.01 µmol/L (baseline: 7 µmol/L, reference range: NA-3 µmol/L). The subject was asymptomatic with no clinical hepatic decompensation. The subject did not receive treatment for this event.

On Day 176, the ALT, AST, total bilirubin and direct bilirubin levels were 160 U/L (grade 2), 41 U/L (grade 0) 32 µmol/L (grade 2) and 8.0 µmol/L, respectively. On Day 197 the event of increased hepatic enzyme resolved with ALT and AST levels of 25 U/L and 22 U/L, respectively. On the same day, Day 197, total bilirubin values remained increased at 34 µmol/L (grade 2) and, consistent with the subject's baseline total bilirubin values. The direct bilirubin on the same day was 8 µmol/L.

The subject **achieved SVR12**. Investigator causality was considered related for the event of increased hepatic enzymes. The Applicant's causality assessment was that elevated liver enzymes were not related to DCV and were possibly related to ASV.

LFT

Units	ALP U/L	AST U/L	TBILI / umol/L	ALT U/L
Range	- 135	- 37	- 19	- 47
Day-34	66	30	34.2	50
Day-20	70	38	42.8	58
Day1	59	29	25.7	46
Day15	61	17	30.8	18
Day29	56	17	34.2	19
Day42	59	19	25.7	19
Day57	61	19	27.4	19
Day83	62	17	34.2	14
Day113	65	21	37.6	26
Day141	71	75	31	217
Day168	79	253	64	690
Day176	68	41	32	160
Day197	65	22	34	25

Case 3 AI447028-8-80187

This is a 56 year old prior null responder **with cirrhosis** and BL HCV RNA of 1,071,012 IU/mL. Subject was treated with DCV/ASV and on Day 57 his ALT and AST were grade 3 (402 U/L and 318 U/L, respectively); both increased from grade 2 at baseline. Total bilirubin remained in normal range. Based on these labs, the investigator reported a non-serious adverse event of grade 3 increased ALT on the same day (Day 57). No treatment was provided for the events. On Day 63 ((b) (6)), his LFTs showed further increase with ALT 465 U/L (grade 3), AST 327 U/L (grade 3), and TBIL 29 µmol/L (grade 1). Due to the ALT elevations, study therapy was interrupted from Day 72 to Day 77. Study therapy was resumed on Day 78 with ASV 100 mg BID and DCV 60 mg QD. The investigator assessed the nonserious adverse event of grade 3 increased ALT to be related to study therapy.

On Day 85 ((b) (6)), the subject's LFTs decreased and were ALT 351 U/L (grade 3), AST 300 U/L (grade 3), and TBIL 24 µmol/L. On Day 91 ((b) (6)), a computed tomography (CT) scan of the liver and magnetic resonance imaging (MRI) scan showed hepatocellular carcinoma, and the investigator reported a serious adverse event of grade 4 hepatocellular carcinoma. His liver enzymes continued to decrease and on Day 116 the subject underwent laparoscopic segmental liver resection and hernia repair via laparoscopic procedure. The subject was discharged on Day 119. The subject's liver tests continued to improve while on study medication and on Day 141, ALT was 81 U/L, AST 86 U/L and Tbili 26µmol/L. **The subject completed therapy** and received last doses of study drug on Day 169.

Approximately one month after completed therapy on Day 196, the subject's LFTs were considered normal and the events resolved. On Day 231 a repeat CT scan of chest, abdomen and pelvis and triphasic liver showed a 6.1 cm lesion in the liver consistent with recurrent hepatoma. On Day 239 the subject was re-hospitalized and underwent transarterial chemoembolization (TACE) of liver lesion segment VII.

On Day 311 ((b) (6)), a repeat TACE procedure was arranged but the clinician was not able to identify any lesions to TACE. On Day 312, the subject underwent CT scan of the chest and abdomen and pelvis which did not show recurrent hepatoma. The events of hepatocellular carcinoma and procedural pain were ongoing at the time of database lock. The treatment with temazepam and zopiclone were ongoing at the time of database lock.

The subject **achieved SVR12**.

LFT

	ALP	AST	TBILI	ALT
Units	U/L	U/L	umol/L	U/L
Range	- 135	- 37	- 23	- 52
Day-30	74	167	22	162
Day1	83	137	13	167
Day8	101	100	12	108
Day14	87	60	16	73
Day29	75	51	15	67
Day43	79	66	13	83
Day57	78	318	22	402
Day63	70	327	29	465
Day85	96	300	24	351
Day112	120	243	35, 31	267, 249
Day123	78	171	49	139
Day141	79	86	26	81
Day168	72	66	24	54
Day196	89	42	15	29

Case 4 AI447028-84-80492

67-year old male who was a null responder to prior peginterferon alfa/ribavirin (pegIFN α /RBV) therapy for chronic hepatitis C infection, genotype 1b, **with compensated cirrhosis**. His baseline HCV RNA on Day 1 was 11,351,895 IU/mL. The subject had a relevant medical history of splenomegaly, liver nodule, liver cysts, alcohol and tobacco use, and hypertension.

Pretreatment AST levels were mildly elevated at screening (45 U/L) and within normal range on baseline Day 1 (35 U/L). Pretreatment ALT levels at screening (53 U/L) and baseline Day 1 (48 U/L) were mildly elevated (grade 1). TBILI was elevated (grade 1) at screening (Day -21, 1.5 mg/dL) and baseline Day 1 (1.9 mg/dL).

Peak ALT level (174 U/L [$>3x$ ULN]) occurred on Day 85 and began decreasing when tested at the next visit on Day 113 (125 U/L). The subject's ALT level was within normal range by Day 141 (47 U/L), remaining normal thereafter through the last assessment on Day 197 (16 U/L). TBILI $> 2x$ ULN was observed on Day 113 (2.2 mg/dL) and Day 141 (2.3 mg/dL), and remained elevated on Day 169 (2.6 mg/dL). At the last assessment on Day 197, TBILI was still elevated but decreased to baseline levels (1.3 mg/dL on (b) (6)).

Elevations of ALT and/or TBILI were observed between Day 57 and Day 169 with ALT > 3 x ULN at Day 85 and TBILI > 2x ULN between Days 113-169. Alkaline phosphatase was within normal ranges throughout the study. Study therapy remained ongoing despite these transient elevations.

Grade 1 alpha fetoprotein increase was reported on Day 85 with AFP levels of 44 ng/mL (baseline 11.4 ng/mL); the investigator considered the event related to study drug. No treatment was given and no action was taken regarding study drug. The event resolved on Day 197 with AFP level of 11.5 ng/mL. Ultrasound of the abdomen on Days 67, 95, and Day 266 and a CT scan of the abdomen was performed on Day 169 to follow previously diagnosed (prior to treatment) splenomegaly and hyperechoic nodule. No obvious tumor was found; findings included suspicion of a tiny nodule in the gallbladder, cysts in both lobes of the liver, and a left inguinal hernia.

The subject **completed study therapy** and achieved **SVR12**.

LFT				
	ALP	AST	TBILI	ALT
Units	U/L	U/L	mg/dL	U/L
Range	- 135	- 37	- 1.1	- 47
Day-21	65	45	1.5	53
Day1	65	35	1.9	48
Day15	64	22	2.4	20
Day29	66	24	1.2	27
Day43	66	47	.9	69
Day57	67	78	1.5	118
Day85	67	104	2	174
Day113	75	79	2.2	125
Day141	72	45	2.3	47
Day169	65	32	2.6	35
Day197	63	23	1.3	16

Three Cases meeting Hy's Law Laboratory Criteria in 7029

Case 1 AI447029-25-90104

This is a 60 year old female, prior null responder **without cirrhosis** with baseline HCV RNA on Day 1 of 10,479,854 IU/mL. Relevant medical history included cholecystectomy.

On Day 56 the subject's laboratory test results showed ALT of 165 U/L (baseline: 41 U/L, reference range: NA-47 U/L), AST of 118 U/L (baseline: 38 U/L, reference range: NA-37 U/L), TBILI of 17.1 µmol/L (baseline: 13.7 µmol/L, reference range: NA-18.8

µmol/L) and ALP of 67 U/L (baseline: 64 U/L, reference range: NA-135 U/L). The investigator reported a non-serious event of grade 2 increased hepatic enzyme.

On Day 86, the subject's laboratory test results showed ALT of 243 U/L (grade 3), AST of 253 U/L, TBILI of 51.3 µmol/L and ALP of 70 U/L. On Day 94, her laboratory test results showed ALT of 193 U/L, AST of 210 U/L, TBILI of 73.5 µmol/L and ALP of 71 U/L. The **study therapy with ASV was interrupted** due to the event of increased hepatic enzyme from Day 101 to Day 113. She continued to receive the regular dose of DCV, RBV and pegIFNα-2a. She did not receive treatment for the event of increased hepatic enzymes. On Day 113, her laboratory test results showed ALT of 27 U/L, AST of 28 U/L, total bilirubin of 29.1 µmol/L and ALP of 64 U/L. She **resumed treatment with ASV on Day 114**. On Day 142, her laboratory test results showed ALT of 51 U/L, AST of 34 U/L, TBILI of 20.5 µmol/L and ALP of 61 U/L. On the same day (Day 142), the event of increased hepatic enzyme was considered resolved.

The patient **completed study and achieved SVR12 and SVR24**.

LFT

	ALP	AST	TBILI	ALT
Units	U/L	U/L	umol/L	U/L
Range	- 135	- 37	- 18.8	- 47
Day-39	57	32	12	38
Day1	64	38	13.7	41
Day16	56	22	20.5	22
Day31	52	26	12	24
Day46	57	64	15.4	70
Day56	67	118	17.1	165
Day86	70	253	51.3	243
Day94	71	210	73.5	193
Day107	64	41	35.9	62
Day113	64	28	29.1	27
Day142	61	34	20.5	51
Day170	66	52	30.8	51
Day197	57	28	13.7	27

Case 2 AI447029-25-90110

A 61-year old male **without cirrhosis** who was a prior partial responder, genotype 4e and baseline HCV RNA on Day 1 of 8,724,982 IU/mL was enrolled and received QUAD therapy.

On Day 56 his laboratory test results showed ALT of 432 U/L (baseline: 34 U/L, reference range: NA-47 U/L) (grade 3), AST of 268 U/L (baseline: 31 U/L, reference range: NA-37 U/L) (grade 3), ALP of 114 U/L (baseline: 69 U/L, reference range: NA-

135 U/L), and TBILI of 27.4 µmol/L (baseline: 12 µmol/L, reference range: NA-18.8 µmol/L) (grade 1). This was reported on the same day (Day 56) as a grade 3 serious adverse event of increased hepatic enzyme. On Day 61 his laboratory test results showed further increases in the levels of ALT (470 U/L) (grade 3), AST (317 U/L), ALP (119 U/L), and TBILI (46.2 µmol/L). Thus, the subject met the protocol defined potential drug induced liver injury (pDILI) criteria on Day 61, based on the concomitant increase in both ALT and TBILI. Physical examination was unremarkable with no signs of decompensation, jaundice or fever. He received a single dose of ASV 100 mg on Day 64 and on Day 65 through **Day 73 all ASV dosing was interrupted**. He continued to receive the regular dose of RBV, DCV, and pegIFNα-2a. On Day 68 ((b) (6)), the subject's ALT, AST, ALP levels decreased to 216 U/L (grade 2), 105 U/L (grade 2), 124 U/L respectively but his TBILI increased to 51.3 µmol/L (grade 3). On the same day (Day 68), his hemoglobin (Hb) level was 100 g/L (baseline: 146 g/L, reference range: 132-170 g/L) and grade 1 anemia was reported with no modifications made to the ongoing study medications. On **Day 74, the study therapy with ASV was resumed**. On Day 82 his ALT, AST, ALP levels again increased to 242 U/L (grade 3), 155 U/L, 123 U/L, respectively and his TBILI level further increased to 66.7 µmol/L (grade 3). On the same day (Day 82), the RBV dose was reduced to 600 mg total daily dose due to the event of anemia. However, he continued to receive the regular dose of ASV, DCV, and pegIFNα-2a. On Day 89, the subject's laboratory test results showed decreased levels of ALT (100 U/L) (grade 2), AST (76 U/L), ALP (119 U/L), and TBILI (63.3 µmol/L) (grade 3). On Day 98, he was also noted with grade 2 pruritus (without mention of rash). He was started on treatment with hydroxyzine from Day 112. On Day 127, the event of pruritus worsened to grade 3. He was also started on treatment with cholestyramine from Day 141. The event of increased hepatic enzyme was considered resolved with ALT (39 U/L), AST (45 U/L), ALP (106 U/L), and TBILI (37.6 µmol/L) on Day 141.

The **subject completed the study therapy** with the last doses of pegIFNα-2a received on Day 162, ASV, DCV, and RBV received on Day 168. He continued treatment with hydroxyzine till an unknown date in (b) (6). On Day 197, the event of anemia was considered resolved with Hb level of 130 g/L. The events of fatigue and pruritus were considered resolved on an unknown date in (b) (6). The subject continued treatment with cholestyramine until an unknown date in (b) (6).

The subject **achieved SVR12 and SVR24**.

Investigator causality assessment: Elevated liver enzymes were related to daclatasvir and asunaprevir, but not related to peg-alfa-2a and ribavirin. The Applicant's causality assessment was that elevated liver enzymes were not related to daclatasvir but were related to asunaprevir, peg-alfa-2a and ribavirin.

LFT

	ALP	AST	TBILI	ALT
Units	U/L	U/L	umol/L	U/L
Range	- 135	- 37	- 18.8	- 47
Day-24	70	40	12	44
Day1	69	31	12	34
Day15	84	46	17.1	72
Day29	86	41	20.5	52
Day43	79	65	20.5	97
Day56	114	268	27.4	432
Day61	124	317	46.2	470
Day68	119	105	51.3	216
Day82	123	155	66.7	242
Day89	119	76	63.3	100
Day98	112	51	54.7	61
Day112	109	52	51.3	50
Day141	106	45	37.6	39
Day169	99	57	39.3	45
Day197	96	26	12	22

Case 3 AI447029-34-90050

This is a 46 year old male who was a null responder to prior peginterferon alfa/ribavirin (pegIFN α /RBV) therapy for chronic hepatitis C infection, genotype 4A/C/D, **with compensated cirrhosis**. His baseline HCV RNA on Day 1 was 254,982 IU/mL. The subject had a relevant medical history for non-bleeding esophageal varices, alcohol and tobacco use, and hypertension.

Pretreatment ALT levels were elevated (grade 1) at screening (112 U/L on Day -42) and baseline Day 1 (86 U/L). Pretreatment AST levels were elevated (grade 2) at screening (138 U/L on Day -42) and baseline Day 1 (105 U/L). TBILI was within normal range at screening (0.9 mg/dL on Day -42), and elevated (grade 3) at baseline Day 1 (3.5 mg/dL).

Peak measurements of ALT > 3x ULN occurred on Day 57 (155 U/L; grade 2) and Day 140 (165 U/L; grade 2). Peak measurements of TBILI \geq 2x ULN occurred on Day 1 (3.5 mg/dL; grade 3), Day 29 (2.3 mg/dL; grade 2), and Day 140 (2.8 mg/dL; grade 2). Peak measurements of AST occurred on Day 29 (151 U/L grade 2) and on Day 140 (271 U/L; grade 3). Concurrent elevations of ALT > 3x ULN and TBILI \geq 2x ULN were observed on Day 140. All alkaline phosphatase values were within normal range throughout the study, with the exception of the Day 140 value of 145 U/L, which was < 2x ULN. Eosinophil counts were within normal range at all assessments throughout the study. Study therapy remained ongoing despite these transient elevations.

A non-serious AE of rash (verbatim term cutaneous eruptions) was reported twice for this subject, on Day 85 through Day 111 and then again at Day 270 and was considered ongoing at the last assessment. In each case, the rash was considered to be mild / grade 1 in intensity. The first event of rash occurred while the subject was on study drug and was considered related to study drug; no action was taken regarding study drug. The second event of rash occurred approximately 14 weeks after the last dose of study drug and was considered not related to study drug. The subject did not receive treatment for either event.

The subject **completed study therapy and achieved SVR12 and SVR24.**

LFT				
	ALP	AST	TBILI	ALT
Units	U/L	U/L	mg/dL	U/L
Range	- 135	- 37	- 1.1	- 47
Day-42	91	138	.9	112
Day1	92	105	3.5	86
Day15	91	96	1.7	76
Day29	100	151	2.3	141
Day43	89	95	1.5	110
Day57	101	151	2	155
Day85	112	140	1.1	138
Day111	104	123	1.1	127
Day140	145	271	2.8	165
Day169	105	135	1.8	105
Day197	99	117	.9	104

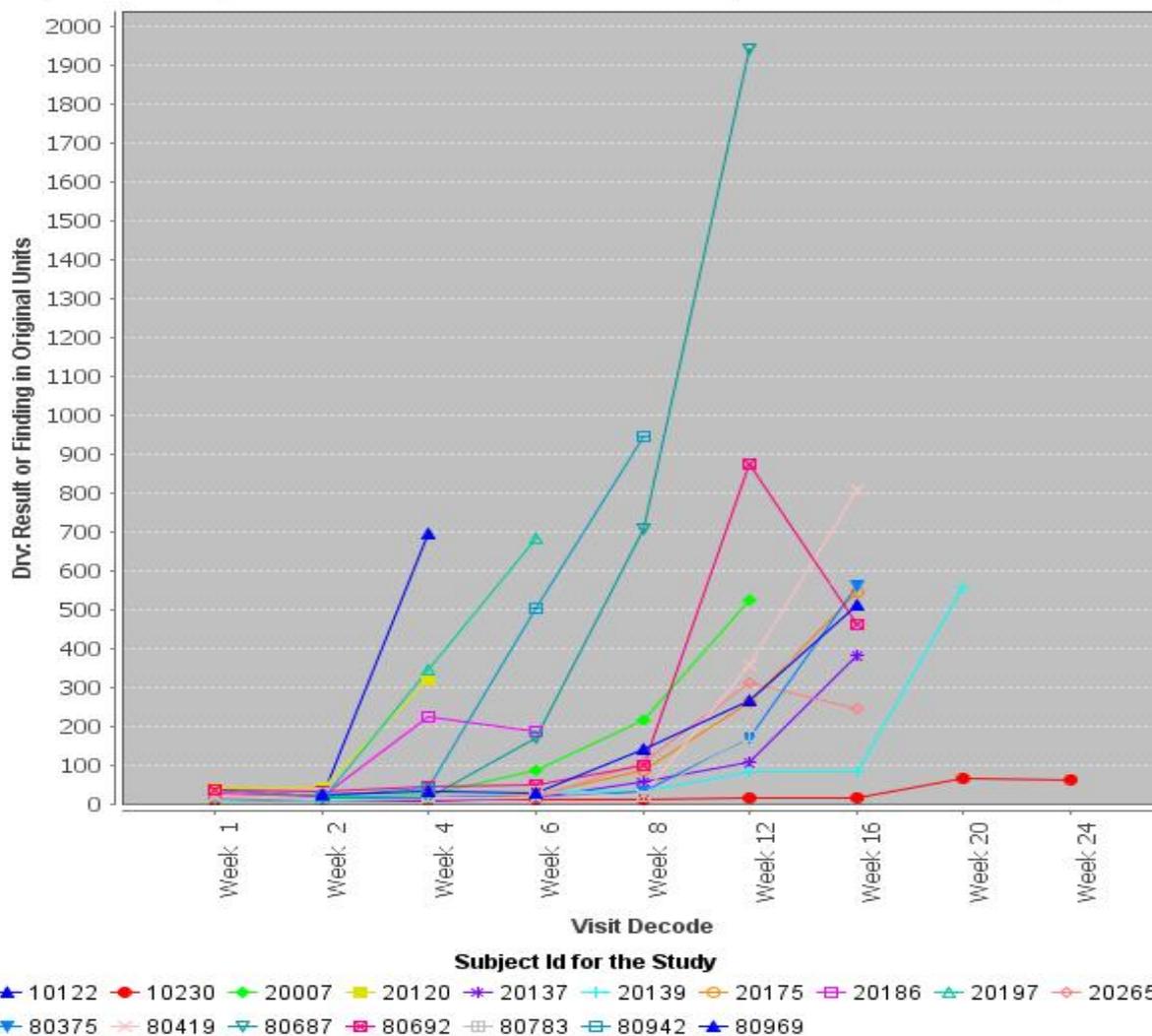
Liver-related Events Leading to Discontinuation

Analyses were completed to evaluate the proportions of subjects who had interruption or discontinuation of study drug therapy based on reported hepatic related adverse events. Overall, 18 subjects (18/1265; 1.4%) from the phase 3 trials discontinued due to reported hepatic-related adverse events. However, the majority (94%) of the discontinuations were from the DUAL trials and proportionally more subjects from the Japanese DUAL trial 7026 (5%) withdrew due to a hepatic related event compared to those in global DUAL trial 7028 (1%) and the QUAD trial 7029 (<1%).

The following figure provides the ALT elevations over time of the 17 subjects from the DUAL trials (the one subject from 7029 is excluded who withdrew due to liver related AEs). Of the 17 subjects, 3 subjects (18%) did not achieve SVR12, while the remaining 14 subjects (82%) did achieve SVR despite early discontinuation. Similar to what was observed in subjects meeting Hy's Law laboratory criteria, ALT elevations leading to discontinuation generally occurred between Weeks 4 and 16.

Figure 8: ALT over Time for Subjects Who Discontinued Due to Liver-Related AEs

ALT by visit for 17 Subjects who Discontinued for Liver Biochemistry Abnormalities - Subset of patients



Patient Selection Criteria: <html> Subject-Level Analysis Dataset.Safety Population Flag =Y \$ AND Adverse E...
Output Filter: Laboratory Results with US Units.Drv: Lab Test or Examination Code =Alanine Aminotransfera...
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As shown in the figure above, 6 subjects had ALT elevations of approximately 700 U/L or higher; 2 subjects from trial 7026 and 4 subjects from trial 7028. The 2 subjects from trial 7026 both had elevated eosinophils at the same time as the ALT and AST elevations; none of the 4 subjects from 7028 had elevated eosinophils related to their transaminase elevations. The 4 subjects from 7028, however, all had drug rechallenge (with DCV and ASV) resulting in significantly higher ALT and AST elevations, without accompanying elevations of total bilirubin, which led to study drug discontinuation. Brief discussion of these subjects' individual trends is provided below.

Trial 7026:

Subject 10122 – This is the initial case of pyrexia/eosinophilia that is discussed in detail above.

Subject 20197 – This 60 yo Japanese female subject was reported with grade 3 increased ALT (ALT 348 U/L; baseline 47) and AST on Day 32, and treatment was interrupted (apparently for 1 day) but not stopped until Day 36. On Day 36, ALT peaked to 683 U/L (grade 4), ALP was 535 U/L and TBIL was 15.4 µmol/L. On the same day, the subject's absolute eosinophil count was reported as 19%. The events of ALT, AST increases were considered resolved by Day 60. The eosinophil count also decreased to 8% with resolution of ALT and AST reported at Day 60. The subject achieved SVR12.

Trial 7028:

Subject 80942 – This 66 yo Chinese female developed grade 4 elevation of ALT (503 U/L) and AST (485 U/L) on Day 42. The subject did not receive treatment for these events and remained on study drug. The DCV dose was interrupted on Day 43, and only 1 dose of ASV was taken on Days 43 and 44, No doses of ASV were taken on Day 45. On Day 50, ALT had further improved with ALT of 169 U/L (grade 2) and AST 61 U/L (grade 1). ASV and DCV dosing were resumed on Day 50. On Day 56 the ALT worsened to 947 U/L and AST to 782 U/L, with a peak TBILI of 15 µmol/L. Study drugs were discontinued on Day 57. The ALT and AST trended down off therapy, and by Day 84 were resolved with an ALT of 36 U/L and AST of 37 U/L. There were no elevations of eosinophils above a normal range. The subject achieved SVR12.

Subject 80687 – This 62 yo White female developed grade 2 fatigue and lethargy on Day 53. On Day 58 ALT was grade 4 at 707 U/L and AST was grade 3 at 336 U/L. DCV and ASV were interrupted on Day 59. On Day 65 the ALT improved to 251 U/L (grade 3), and study drugs were resumed the same day. On Day 71 the ALT worsened to grade 4, with ALT 1943 U/L and AST 885 U/L and study drugs were permanently discontinued. Throughout the duration of the events the TBILI remained within normal limits, never exceeding 11 µmol/L. Additionally, there was no eosinophilia. The subject achieved SVR12.

Subject 80692 – This 50 yo White male developed grade 4 ALT elevation of 864 U/L and grade 3 AST elevation of 325 U/L on Day 84. That same day, the subject took only 1 dose of ASV. Following this event both ASV and DCV were interrupted on Day 88. On 92, ALT improved to 388 U/L and AST to 99 U/L. On Day 95, DCV and ASV were both resumed, with ALT and AST worsening to ALT of 385 U/L and AST 130 U/L, respectively. Study drugs were discontinued with last doses on Day 102, and lab abnormalities resolved to normal values by Day 132. The subject did not have elevated TBili during these events (peak 22.2 µmol/L; 1.2 mg/dL) and no eosinophilia was present. The subject achieved SVR12.

Subject 80419 – This 53 yo White female reported grade 2 fatigue on Day 8. On Day 22, the subject reported grade 1 abdominal pain (ALT and AST values were normal during these events). On Day 83 the subject had grade 3 ALT and AST elevations (298 and 200 U/L, respectively). ASV and DCV dosing was interrupted on Day 102. ALT and AST levels improved to 195 and 104 U/L, respectively by Day 107 and ASV and DCV dosing were restarted. On Day 112, The ALT was 808 U/L and AST was 699 U/L with TBILI remaining within normal limits (peak TBILI of 13.7 $\mu\text{mol/L}$). This subject also had an AE report of rash, and eosinophils remained within normal limits throughout treatment. The subject achieved SVR12.

Analyses for Further Characterization of Pyrexia and Eosinophilia

Because of the known dose-related hepatotoxicity observed within the phase 2 development program, and the concerning initial case of pyrexia and eosinophilia with liver injury, further analyses were done to examine a potential clinical syndrome of pyrexia and eosinophilia with and without liver involvement. Of note, our analyses differ from the Applicant's analyses in that they attributed the constellation of clinical symptoms of pyrexia, eosinophilia and liver test abnormalities as a possible hypersensitivity reaction as noted in the Japanese index case (subject AI447026-2-10122). Therefore, the Applicant's analyses focused on hypersensitivity reaction as defined as pyrexia \geq grade 2 followed within 28 days by the following laboratory abnormalities: eosinophil count of $\geq 1.5 \times 10^9$ cells/L, ALT $\geq 5 \times$ ULN and AST $\geq 5 \times$ ULN, all on the same day; and no evidence of acute viral, bacterial, or parasitic infection, which is defined as no instance of any adverse event preferred term under the System Organ Class "Infections and Infestations." The Applicant concluded that no additional subjects, other than the index case, met the hypersensitivity criteria. We are uncertain if pyrexia and eosinophilia constitute a distinct event resembling a form of drug hypersensitivity/drug fever syndrome or if pyrexia and eosinophilia is part of a clinical presentation of hepatotoxicity and whether this pattern of hepatotoxicity is specific to the Japanese population, acknowledging patterns of hepatotoxicity without eosinophilia observed in the broader population exposed to DCV/ASV.

Therefore, FDA conducted a broad evaluation to identify subjects who may meet clinical characteristics of a drug hypersensitivity reaction by evaluating any subject with an AE report of pyrexia (note: temperature was not routinely collected as a vital sign during the trials), and had at least one laboratory eosinophil count above reported upper limit normal. Based on these broad criteria, 37 subjects were identified from the phase 3 trials (7026, 7028 and 7029). Subsequently, each subject's data was examined to determine other pertinent clinical findings that may support or confound a case of possible pyrexia with eosinophilia. Cases were evaluated to determine if, after the AE report of pyrexia with an accompanying eosinophilia, rash was a part of the clinical syndrome or whether subjects had any ALT increase over normal levels or any elevations of bilirubin or AE reports consistent with significant liver injury.

The following tables provide a summary of these analyses. Table 21 summarizes the clinical findings of those subjects who met the criteria of an AE report of pyrexia and had an elevated eosinophil count by laboratory data **within 2 weeks**. Table 22 summarizes the clinical findings of those subjects who had an AE report of pyrexia with an elevated eosinophil count that was **not within 2 weeks**. It is important to note that although all 3 trials were evaluated with the same criteria, only subjects from the Japanese trial 7026 met the criteria for inclusion in Table 21 (events within 2 weeks). To explore these findings further, the same analysis of AE report of pyrexia and an elevated eosinophil count within 2 weeks was completed using the supportive phase 2 data for DCV and ASV (there are 10 phase 2 trials with various combinations of DCV + pegIFN/RBV, ASV + pegIFN/RBV, DCV/ASV, DCV/ASV + pegIFN/RBV and DCV/sofosbuvir with and without RBV in this phase 2 safety database). Evaluation of the 956 subjects exposed to DCV or ASV or the combination from this database, identified 19 subjects (2%) who met the broad criteria of pyrexia and elevated eosinophil count. Of these 19 subjects, 7 met the criteria of an AE report of pyrexia and had an eosinophil count elevated above normal by laboratory data **within 2 weeks**; and 6 of the 7 subjects are Japanese. The single subject who is not Japanese had a baseline elevated eosinophil count which is higher than those observed while on therapy, and therefore, has a different clinical presentation than the other cases. These phase 2 subjects are summarized in bottom of Table 21.

Any elevation in eosinophil count above upper limit of normal while on-treatment was observed in 113 subjects (51%), 45 subjects (7%) and 15 subjects (4%) of subjects from trials 7026, 7028 and 7029, respectively. The placebo arm from trial 7028 had only 2 subjects (2%) with any elevation in eosinophil count above upper limit of normal. A standardized grading scale was not available for eosinophilia for the clinical trials. Various unit formats were used in reporting eosinophils from the phase 3 and phase 2 trials. Trial 7026 did not use a central laboratory and all the analysis datasets reported absolute eosinophils as a percentage. Trials 7028 and 7029 used $\times 10^3$ c/ μ L or $\times 10^9$ c/L for reporting. Almost uniformly, subjects did not have wbc counts above normal levels at the time of eosinophil elevations. For the few exceptions, wbc elevations were generally at maximum 10-12 $\times 10^9$ cells/L. Because trial 7026 did not use a central laboratory, the reported upper limit of normal varied from approximately 5-7% in this trial. Therefore, a general reference scale used for the eosinophil counts for this analysis for trial 7026 and is provided here:

- 0 to 6% [0.00-0.06] (normal)
- 7 to 10% [0.07-0.10] (slightly elevated) **GREEN in tables**
- 11-20% [0.11-0.20] (elevated) **BLUE in tables**
- Over 20% [0.20] (high) **RED in tables**

A summary of the findings from these analyses are provided below. In addition, graphical profiles of each of the 16 subjects from phase 3 displayed in Table 21 are provided in Appendix B: 16 Subjects with Pyrexia and Eosinophilia Within 2 Weeks –

Phase 3. The graphical profiles provide a visual guide to the observed pattern in these subjects.

Summary of Subjects From Phase 3 Meeting Criteria for Pyrexia and Eosinophilia Within 2 weeks – Table 21

Across the phase 3 trials, 16 subjects met the broad criteria for an AE report of pyrexia with an elevated eosinophil (above upper limit normal) count within 2 weeks (Table 21). All 16 of these subjects (7%; 16/222) were from the Japanese DUAL trial 7026. The typical pattern is that a subject has an AE of pyrexia followed within 2 weeks with a transient increase in eosinophils, all of which occurs within the first 6 weeks on study drug (see Figure 9 and Figure 10, following the tables, to observe trends for eosinophil elevation).

Due to the concern for eosinophilic hepatitis, these subjects were evaluated for any ALT value that was above normal. Of the 16 subjects with pyrexia and eosinophilia within 2 weeks, 6 subjects did not have any increases in ALT and 10 subjects had a least one ALT value above upper limit of normal (see Figure 11 to observe ALT trends). Of these 10 subjects the following observations were made:

- 3 of 10 subjects had an ALT of grade 3 or 4 which met protocol stopping criteria
- 2 subjects had a grade 2 ALT elevation
- 4 subjects had a grade 1 ALT elevation
- 1 subject had a grade 0 elevation (above ULN but < 1.25 x ULN)

In addition, only 1 subject reported mild rash (grade 1) and no other subjects had AE reports of rash. Two subjects from the same clinical site had AE reports of lymphadenopathy, malaise, prolonged PT and thrombocytopenia but by laboratory data all results were normal or grade 0 and 1.

Summary of Subjects from Phase 2 Meeting Criteria for Pyrexia and Eosinophilia Within 2 weeks – Table 21

The same analyses for pyrexia and eosinophilia within 2 weeks was completed using available datasets from the phase 2 trials (n=956). Seven subjects met the criteria for AE report of pyrexia and elevated eosinophil count within 2 weeks from the phase 2 trials (Table 21). One subject was from Argentina and had baseline elevated eosinophils and developed rash which persisted while on treatment. In addition, this subject had a grade 1 ALT elevation that was not above the baseline ALT value. This

subject did not discontinue study drugs and completed therapy. The remaining 6 subjects were Japanese. Four subjects had ALT elevations: 3 subjects with grade 1, one subject with grade 2. One subject had rash but was also administered pegIFN/RBV which confounds this assessment. None of the phase 2 subjects discontinued study therapy.

With the addition of the phase 2 data analysis, there appears to be supporting evidence of a racial component to the findings of pyrexia and elevated eosinophils. Overall, the proportion of Japanese subjects meeting the criteria of pyrexia with eosinophilia **within 2 weeks** in the DUAL trials was 7% (16/222) for trial AI447026 and 12% (4/33) for trial AI447017.

Summary of Subjects from Phase 3 with Pyrexia and Eosinophilia, Not Within 2 Weeks – Table 22

Further analysis identified 21 subjects from the phase 3 trials who met the criteria of having an AE report of pyrexia and an elevated eosinophil count above upper limit normal, but not having both within 2 weeks. In general, unlike the 16 subjects with pyrexia and elevated eosinophils within 2 weeks (discussed from Table 21 above), there is no distinct pattern of eosinophil elevation for the 21 subjects with pyrexia and eosinophilia but not within 2 weeks. There are some subjects with early elevations (between Week 2-6) and several subjects with later elevations after Week 6. (see Figure 10)

Liver involvement in these subjects was infrequent and generally mild when it did occur. Of these 21 subjects, 4 subjects had an ALT above upper limit normal (Table 21; also see Figure 12 following the tables, to observe ALT trends). One subject had a grade 2 ALT elevation (this subject received QUAD), 2 subjects had grade 1 ALT elevations and 1 subject had a grade 0 ALT elevation (above ULN but < 1.25 x ULN). This subject had also started rescue therapy with pegIFN/RBV added to DCV/ASV which confounds the presentation.

Overall, in this group, 3 subjects had rash. All 3 subjects were also exposed to pegIFN/rbv which are both associated with rash. Only 1 subject discontinued due to lack of efficacy; none of the subjects in this group discontinued due to the pyrexia, eosinophilia or liver-related events.

Reviewer comment: Based on FDA findings associated with pyrexia and eosinophilia, the Applicant conducted similar analyses of pyrexia and eosinophilia within 2 weeks. FDA's analysis was purposefully broad to capture all potential cases; therefore, pyrexia could also follow elevation of eosinophils and did not have to precede the lab change, the 2 events only had to be within 2 weeks of each other. Pyrexia was only recorded as a reported adverse event because temperature data was not captured for the trials and therefore, it may have had significant variability in reporting. The Applicant's analysis of phase 3 subjects with pyrexia and eosinophilia within 2 weeks did not include the following 4 subjects which are included in the FDA analysis:

- **Subject AI447026-1-20265:** *This subject reported pyrexia at Day 6 and had an elevation of eosinophils to 13% at Week 2; it is unclear why the Applicant did not include this case. This case was included in a pre-teleconference meeting table submitted by Applicant.*
- **Subject AI447026-7-10193:** *This subject had an eosinophil count of 9.1% at Week 4 with pyrexia following at Week 6. This may not have been included because the pyrexia followed the eosinophil elevation*
- **Subject AI447026-1-10059:** *This subject had an elevation of eosinophil to 10% at Week 4 and a few days later AE report of pyrexia. Again, I believe this case was not included because the eosinophilia preceded the AE of pyrexia.*
- **Subject AI447026-23-20272:** *This subject had an elevation of eosinophils to 9.4% at Week 6 with AE reporting of pyrexia at Week 4 ending at Week 10. It is unclear why this case was not included in the Applicant analysis.*

Additionally, FDA analyses identified 6 subjects from phase 2 who met the criteria for pyrexia and elevated eosinophils within 2 weeks, compared to 5 subjects identified by the Applicant. Two FDA identified cases were different from 2 of the Applicant identified cases. These differences again are likely related to the 2 week window used for the analysis or the fact that an AE report of pyrexia followed an elevation of eosinophil count. Regardless, the overall safety assessment of pyrexia and eosinophilia is not changed by the minor differences in accounting for the identified subjects between FDA and the Applicant.

Table 21: Subjects with AE Report of Pyrexia and Increased Eosinophils (above normal) within 2 weeks

Subj ID	Pyrexia and Eosinophilia (within 2W)	Race	Confounding Factors	ALT increase (over nl)	Max Grade ALT	Time to Max Grade ALT	Inc Bili or symptomatic?	Rash?	D/C?	SVR 12?
Phase 3										
AI447026 (16 subjects of 222 total=7%)										
2-10122	Yes (Eos 54% W4) (liver bx, eosinophilic DILI)	Japanese	High Levels of ASV and DCV, taking 2x DCV dosing	Yes	GD 4 (peak 697)	W4, resolved by W7 on prednisone	GD 2 (2.9)	No	Yes	No
1-20265	Yes (Eos 13% W2)	Japanese	-	Yes	GD 3 (312)	W9	GD 3	No	Yes	Yes
8-20120*	Yes (pyrexia moderate, Eos 34% W3)	Japanese	Cefotiam, Teprenone (hepatic warning)	Yes	GD 3 (323)	W5, resolved by W7	-	No	Yes (W5; achieves SVR12)	Yes
7-20200**	Yes (Eos 22.5% W4)	Japanese	-	Yes	GD 2 (114)	W4, resolved W6 on Tx	-	Yes	No	Yes
11-10115	Yes (Eos 15.8% W4)	Japanese	-	Yes	GD 2 (155)	W22	GD 2 (1 blip then returns to nl)	No	No	No
14-10161	Yes (Eos 26% W4)	Japanese	-	Yes	GD 1 (112)	W24	-	No	No	Yes
7-10193	Yes (Eos 9.1% W4)	Japanese	PR rescue	Yes	GD 1 (50)	W8	-	No	Yes-lack of efficacy	No

Clinical Review
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NDA 206-843 and NDA 206-844
Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Subj ID	Pyrexia and Eosinophilia (within 2W)	Race	Confounding Factors	ALT increase (over nl)	Max Grade ALT	Time to Max Grade ALT	Inc Bili or symptomatic?	Rash?	D/C?	SVR 12?
9-10087	Yes (Eos 37.6% W3)	Japanese	Also PT of lymphadenopathy, Prolonged PT and Thrombocytopenia but by labs data all nl or G0	Yes	GD 1 (43)	W2, resolved W3	-	No	No	Yes
9-20248	Yes (Eos 10.9% W3)	Japanese	Malaise, PT prolonged, Thrombocytopenia (plt 127- GD0)-	Yes	GD 1 (99)	W16, resolved W20	G2 blip at W2, ALT trend down, INR GD1 (1.4) W2	No	No	Yes
15-20271	Yes (Eos 12% W4)	Japanese	-	Yes	GD 0 (41)	W4	GD 1 (1 time) W2	No	No	Yes
18-20093	Yes (Eos 25.9% W4)	Japanese	-	No	-	-	-	No	No	Yes
19-20273	Yes (Eos 15.4% W10) Pyrexia late at W6, then W10-16	Japanese	Conjunctivitis Allergic (W6-24)	No	-	-	-	No	No	No
1-10059	Yes (Eos 10% W3)	Japanese	Second degree burns/wound complication	No	-	-	-	No	No	Yes
23-20272	Yes (Eos 9.4% W6)	Japanese	-	No	-	-	-	No	No	Yes
10-10062	Yes (Eos 16% W4)	Japanese	-	No	-	-	-	No	No	Yes

Clinical Review
 Wendy Carter, D.O.
 NDA 206-843 and NDA 206-844
 Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Subj ID	Pyrexia and Eosinophilia (within 2W)	Race	Confounding Factors	ALT increase (over nl)	Max Grade ALT	Time to Max Grade ALT	Inc Bili or symptomatic?	Rash?	D/C?	SVR 12?
8-20032	Yes (Eos 22% W2, moderate pyrexia)	Japanese	-	No	-	-	-	No	No	Yes
Phase 2										
AI444011 (Phase 2 DCV 60 mg + PR)										
78-392*	Yes (Eos 0.77A; peak 1.02 at W51, BUT 1.07 at Baseline)	White/Argentina	PR, rash that is GD2 & persists W10-W51, No eos above BL level	Yes	GD 1 (75 and not above BL)	W28	-	Yes	No	Yes
AI444021 (Phase 2 DCV 60 mg + PR)										
4-21102	Yes (Eos 10.5%, .354 A) at W1	Japanese	PR, rash	No	-	-	-	Yes	No	Yes
4-21108	Yes (Eos 9%, .215A) at W11	Japanese	PR	No	-	-	-	No	No	Yes
AI447017 (Phase 2 DUAL DCV/ASV) (4 subjects of total 33 in this arm=12%)										
1-1008	Yes (Eos 27.8%) W4	Japanese	-	Yes	GD1 (68)	W2	GD1	No	No	Yes
3-3005	Yes (Eos 35.4%) W3	Japanese	-	Yes	GD2 (143)	W2/nl W4	GD2 (W2)/nl W4	No	No	No

Clinical Review
 Wendy Carter, D.O.
 NDA 206-843 and NDA 206-844
 Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Subj ID	Pyrexia and Eosinophilia (within 2W)	Race	Confounding Factors	ALT increase (over nl)	Max Grade ALT	Time to Max Grade ALT	Inc Bili or symptomatic?	Rash?	D/C?	SVR 12?
3-3015	Yes (Eos 24%) W3	Japanese	-	Yes	GD1 (56)	W3	No	No	No	Yes
3-3017	Yes (Eos 8.5%)	Japanese	-	Yes	GD1 (61)	W25/ GD0 at W3 (39)	No	No	No	Yes

*This case has elevated EOS, ALT and AST at same week

**This case has elevated EOS, ALT and AST with Pyrexia all at Week 4, and develops Arthralgia at W12-W24 (D92-169); all considered related

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NDA 206-843 and NDA 206-844
Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Table 22: Subjects With Events of Pyrexia and Eosinophilia But Not Within 2 Weeks of Reported Pyrexia – Phase 3 Data

Subj ID	Pyrexia and Eosinophilia (within 2W)	Race	Confounding Factors	ALT increase	Max Grade ALT	Time to Max Grade ALT	Inc Bili or symptomatic	Rash	D/C	SVR?
Phase 3										
AI447026 (N=12)										
11-10095	No	Japanese	-	No	-	-	-	No	No	Yes
11-10207	No	Japanese	-	No	-	-	-	No	No	Yes
12-10023	No	Japanese	PR rescue	No	-	-	-	No	No	No
17-20256	No	Japanese	-	No	-	-	-	No	No	Yes
18-10044	No	Japanese	PR rescue	Yes	Gd1	W30	-	No	No	Yes
18-10060	No	Japanese	PR rescue	No	-	-	-	No	Yes...Lack of efficacy	No
18-10257	No	Japanese	-		-	-	-	No	No	Yes
19-20145	No	Japanese	-	No	-	-	-	No	No	Yes
3-10130	No	Japanese	PR rescue	Yes	Gd0	W36 on rescue	-	Yes	No	Yes
4-10090	No	Japanese	PR rescue	No	-	-	-	No	No	No
8-10037	No	Japanese	-	No	-	-	-	No	No	Yes
8-20160	No	Japanese	-	No	-	-	-	No	No	Yes
AI447028- Global Dual (N=3)										
111-80376	No	White	-	No	-	-	-	No	No	Yes
14-80974	No	White	-	No	-	-	-	No	No	Yes
54-80098	No	White	Cough, dysphonia, rhinorrhea	No	-	-	-	No	No	Yes
AI447029 – QUAD (N=6)										
11-90289	No	White	Peg/RBV	No	-	-	-	No	No	Yes
22-90452	No	White	Peg/RBV	No	-	-	-	No	No	Yes
30-90093	No	White	Peg/RBV	No	-	-	-	Yes	No	Yes
41-90194	No	White	Peg/RBV	No	-	-	-	Yes	No	Yes
7-90306	No	White	Peg/RBV	Yes	GD1	W20	GD2 W16	No	No	Yes
96-90490	No	White	Peg/RBV	Yes	GD2	W20	GD2 W2	No	No	Yes

Figure 9: Absolute Eosinophils for 16 Subjects with Pyrexia and Eosinophilia Within 2 Weeks – Phase 3 (Subjects all from AI447026)

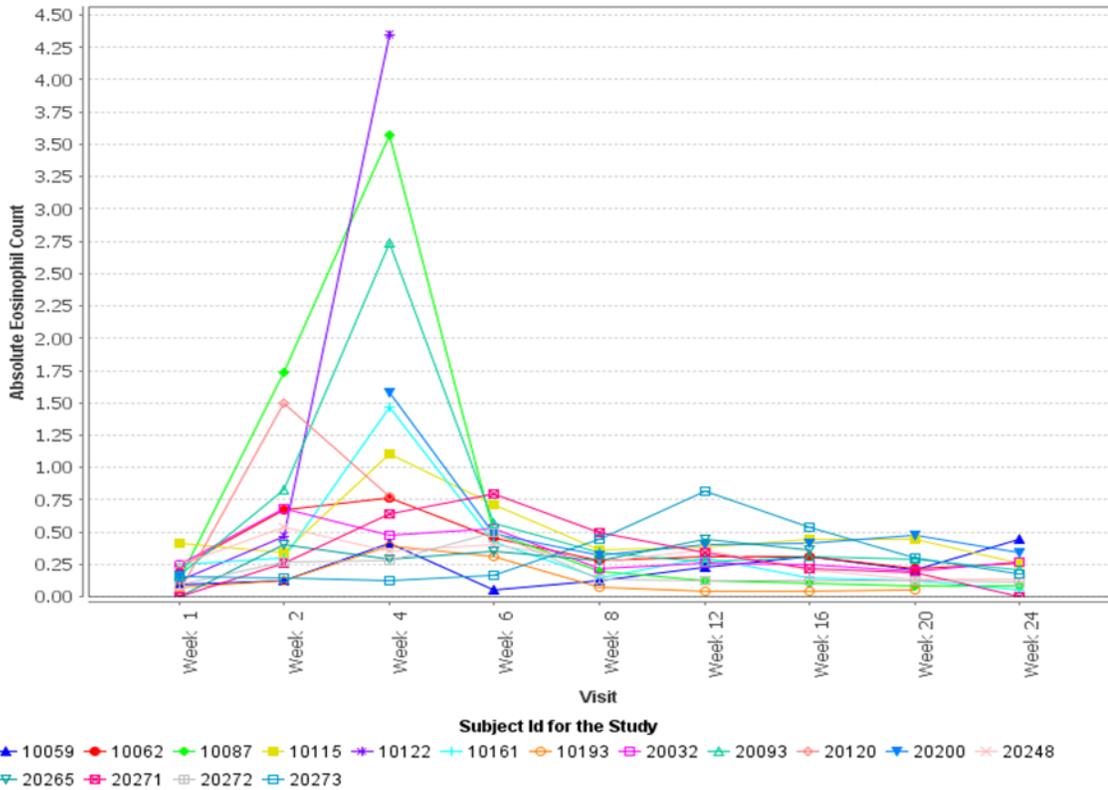


Figure 10: Absolute Eosinophils for 21 Subjects With Pyrexia and Eosinophilia Not Within 2 Weeks – Phase 3 trials

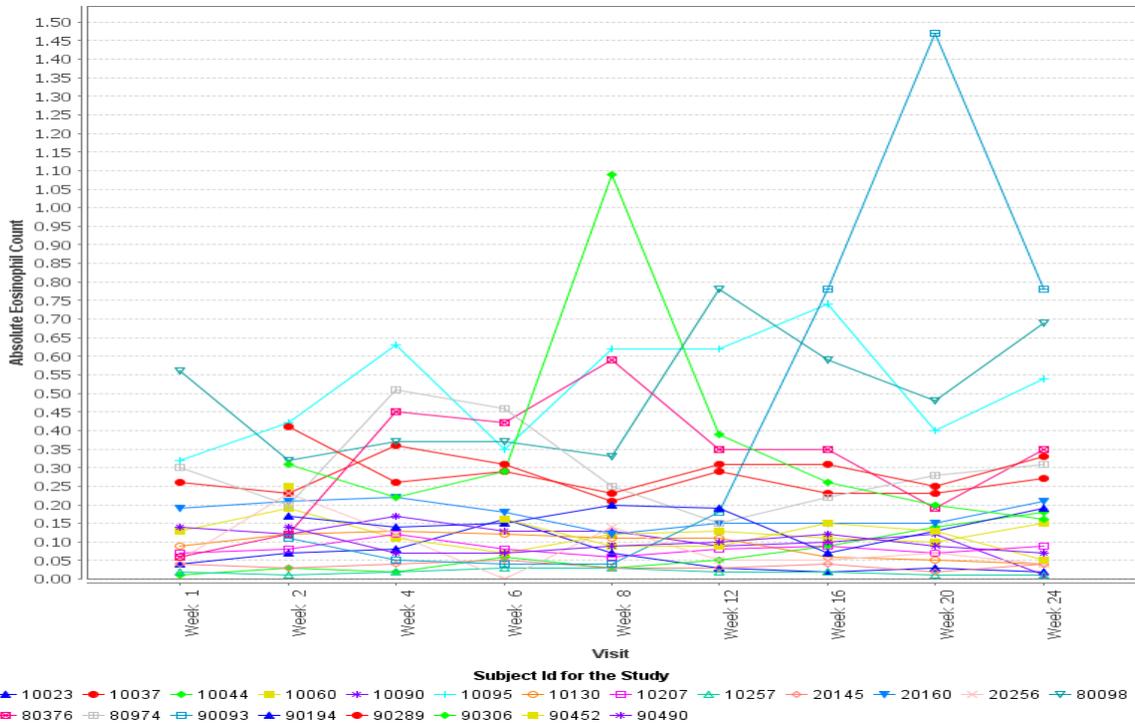


Figure 11: ALT by Visit for 16 Subjects with Pyrexia and Eosinophilia Within 2 Weeks – Phase 3 (Subjects all from AI447026)

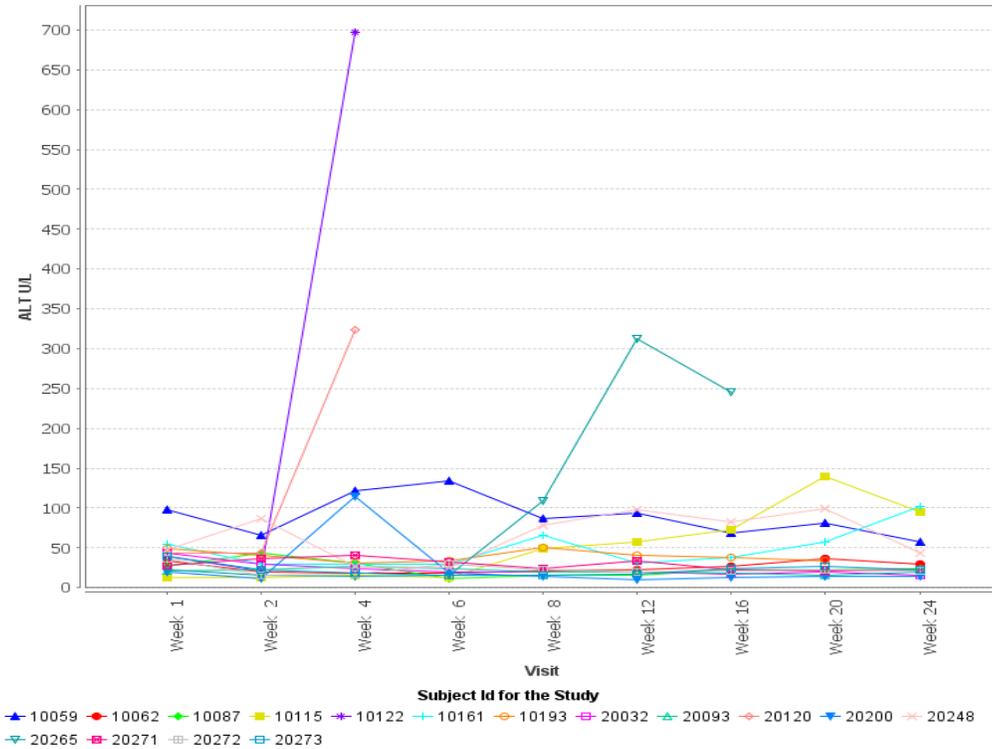
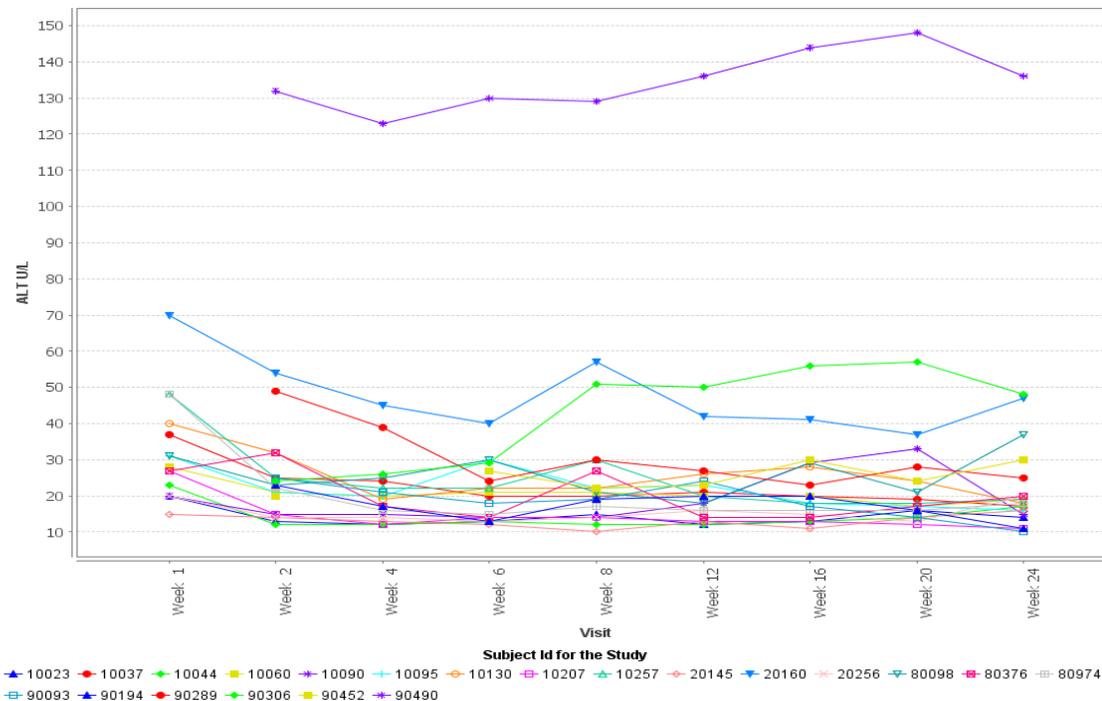


Figure 12: ALT by Visit for 21 Subjects With Pyrexia and Eosinophilia Not Within 2 Weeks – Phase 3



Assessment of Race and Pyrexia and Eosinophilia

Based on assessment of the phase 3 data and the phase 2 data, more Japanese subjects developed pyrexia and eosinophilia compared to non-Japanese subjects. In order to further assess whether these safety issues were also found in other racial groups, the phase 3 trials demographics were more closely evaluated to include subpopulations of Asian subjects. Table 20 provides the summary of the self-reported race of enrolled subjects. As shown below, although 25% of subjects in the DUAL trial 7028 were identified as Asian, only 2 subjects were Japanese; similarly for the QUAD trial 7029, 12% of subjects identified as Asian but only 1 subject was Japanese. Therefore, Asian subjects composed 24% (N=153) of the DCV/ASV exposed population in 7028, yet none of these subjects met the criteria for pyrexia and eosinophilia within 2 weeks. This is in contrast to the 16 subject (7%) of subjects from trial 7026 who did meet the criteria for pyrexia and eosinophilia within 2 weeks.

Table 23: Race and Asian Subpopulation Demographics Table

	AI447026	AI447028		AI447029
Race	DCV/ASV N=222	DCV/ASV N=645	PBO N=102	DCV/ASV + PegIFN/RBV N=398
White	0	452 (70%)	59 (58%)	304 (76%)
Black/African American	0	34 (5%)	8 (8%)	37 (9%)
Other	0	6 (1%)	2 (2%)	9 (2%)
Asian Subpopulations				
Japanese	222 (100%)	2 (<1%)	0	1 (<1%)
Korean	0	65 (10%)	13 (13%)	27 (7%)
Chinese	0	73 (11%)	16 (16%)	13 (3%)
Asian Other	0	13 (2%)	4 (4%)	7 (2%)
Asian Total	222 (100%)	153 (24%)	33 (32%)	48 (12%)

Source: Demographic and Subject level Data Analysis datasets

Analyses of the mean and standard deviation of absolute eosinophils were completed to evaluate the overall trend of eosinophils in the Japanese DUAL trial 7026 compared to the global DUAL trial 7028. As shown in the figures below (Figure 13 and Figure 14), there is an increase in mean absolute eosinophil count between Weeks 2-6 for the Japanese subjects in 7026; however this same pattern is not found in the global DUAL trial 7028 (note the scale differences due to the larger increases in absolute eosinophils in trial 7026). This same pattern was also not observed for Chinese, Korean and Other Asian subgroups or in Black/African Americans or Whites (Figure 15).

Figure 13: Absolute Eosinophils Mean and SD - Trial 7026

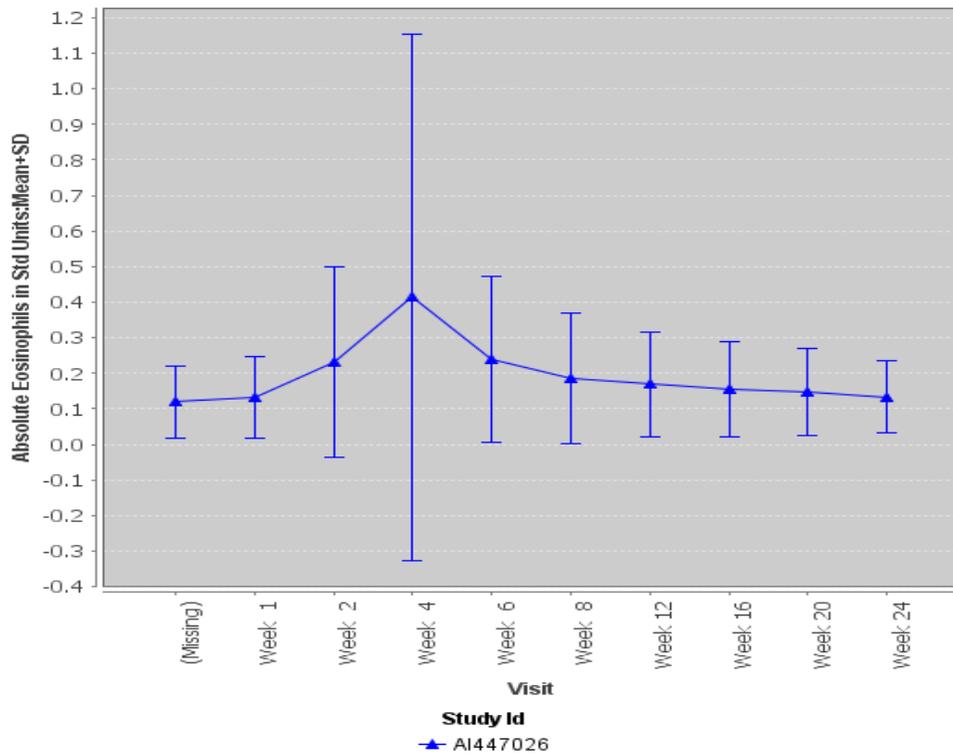


Figure 14: Absolute Eosinophils Mean and SD -- Trial 7028

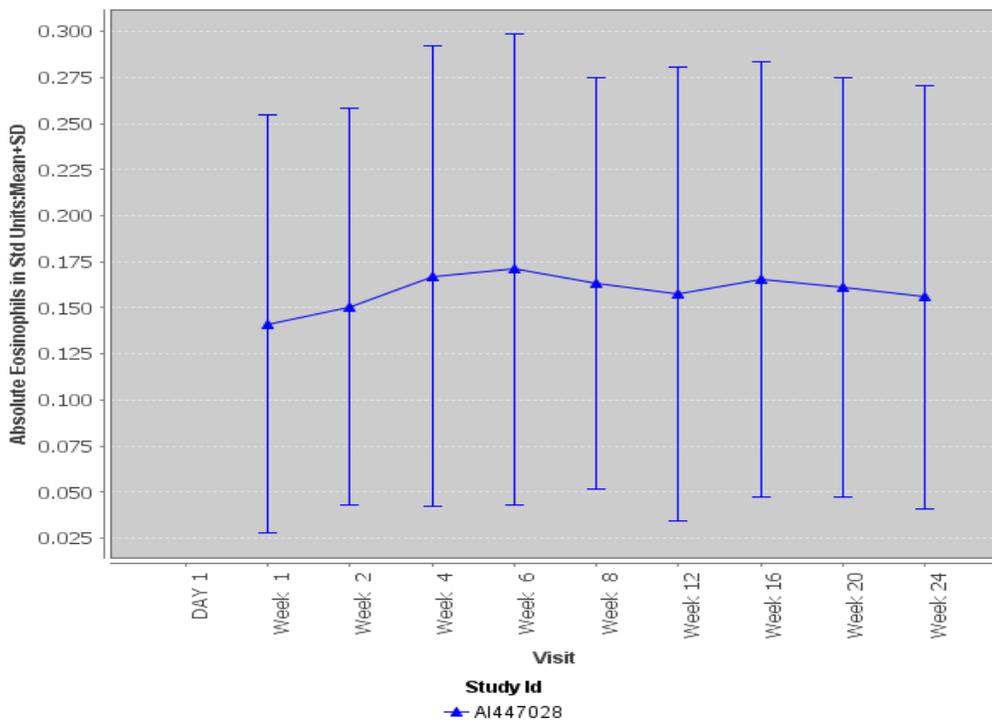
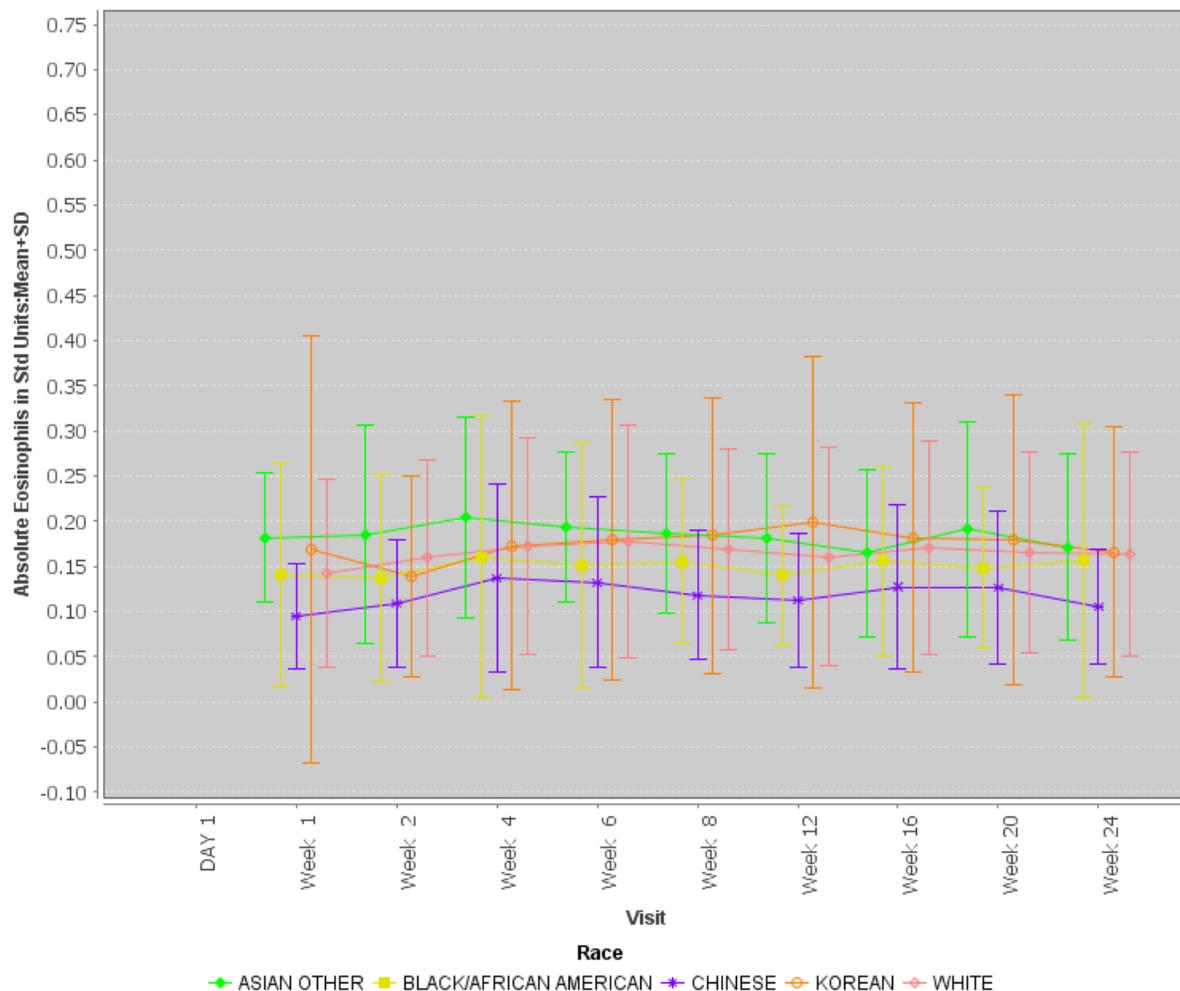


Figure 15: Absolute Eosinophils Mean and SD By Race - Trial 7028



Adverse Event (AE) Reporting of Pyrexia

As part of the overall evaluation of these safety issues, one important caveat has been the AE reporting of pyrexia which is patient-reported and assessed by the investigator as mild, moderate or severe. There was no temperature monitoring in these trials so there are no vital signs data with temperature measurements. Therefore, generally, all the reports of pyrexia are subjective patient reports.

Trends in AE reporting are often observed in one subpopulation of a clinical trials database. For example, fatigue is more frequently reported (even among placebo controls) in North America compared to rest-of-world. Similarly, as observed in the DUAL phase 3 program, pyrexia was more frequently reported in 7026 subjects (13%) compared to the global 7028 subjects (4%). Because of this observed trend, other protease inhibitor drugs with trials completed in Japan and globally were evaluated for observed pyrexia AE reporting trends. In other programs that were evaluated, Japanese subjects had a 50-70% higher reporting rate for pyrexia compared to subjects from North

America or Western Europe. These included subjects randomized to placebo arms in both geographic locations, and therefore suggests independence from drug effect.

While the overall rate of pyrexia reports is higher for the Japanese subjects exposed to DCV/ASV and may not be causally related in all cases, the pattern of associated increases in eosinophilia (within several weeks and at the beginning of drug therapy) with some of these pyrexia reports remains concerning; particularly in light of the index case presentation.

However, in order to further characterize whether a similar pattern of eosinophilia with and without liver involvement was observed in subjects without pyrexia, additional analyses of the DUAL trials 7026 and 7028 were completed. The QUAD trial 7029 was included in the broad screening analyses but was excluded from these further analyses due to the concomitant use of PegIFN and its known association with pyrexia (flu-like illness). Any subject with an elevated absolute eosinophil count (>9%) while on treatment for subjects in trial 7026 and $> 0.7 \times 10^9$ c/L (reported as original units for 7028, and standard units are $\times 10^3$ c/uL) for subjects in trial 7028 were included in the analyses. Note the differences in the eosinophil units are a function of the reported data; trial 7026 reported absolute eosinophils as a percentage unit and 7028 used 10^9 c/L or 10^3 c/uL. Additionally, subjects who had reported an AE of pyrexia were excluded.

In trial 7026, 19 subjects (9%) were identified and in trial 7028 18 subjects (2.4%) were identified as having an elevated absolute eosinophil count on treatment. The absolute eosinophil counts and ALT by study visit were analyzed for both trials and are summarized in the following series of figures. Trial 7026 shows a similar trend of mild to moderate (and occasionally high) transient increase in eosinophils concentrated within the first 2-6 weeks after initiation of DUAL therapy (Figure 16 and Figure 17). Additionally, a few subjects also have a later trend in elevated absolute eosinophils between Weeks 16-24. This same trend is not observed in the 7028 subjects (Figure 19 and Figure 20). With the exception of subjects 21-20197 and 17-20007 who discontinued due to elevated ALT/AST (and are discussed above in the section on discontinuation due to liver-related AEs), no other subjects from trial 7026 had elevations of ALT that led to discontinuation (Figure 18). Similarly, the majority of the 18 subjects (14/18; 78%) from 7028 had ALT within normal limits or grade 0 elevations and no subjects had ALT elevations leading to discontinuation (Figure 21). Of those who did have ALT elevations (n=4), all ALT values were grade 1 (maximum ALT was 114 U/L).

In summary, this analysis suggests in Japanese subjects, regardless of the presence of pyrexia, eosinophilia is transient and in general occurs early in treatment (between Weeks 2-6) and most frequently without liver involvement. In trial 7028 in non-Japanese subjects, mild to moderate elevations in eosinophils were seen, but the pattern appears different from that observed in Japanese subjects. Additionally, the mild to moderate elevations in eosinophils observed in trial 7028 were not generally associated with significant changes in ALT.

Figure 16: Absolute Eosinophil Count by Visit for Subjects with Elevated Absolute Eosinophils without Pyrexia—Trial 7026

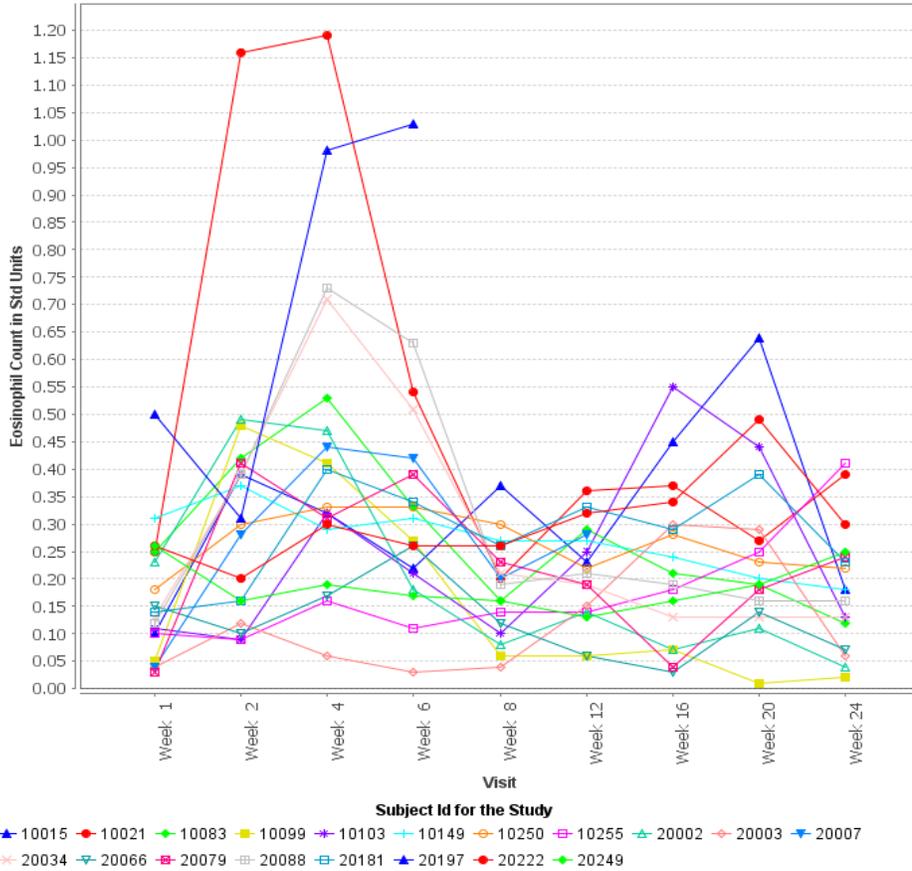


Figure 17: Mean and SD of Absolute Eosinophil Count by Visit for Subjects with Elevated Absolute Eosinophils without Pyrexia—Trial 7026

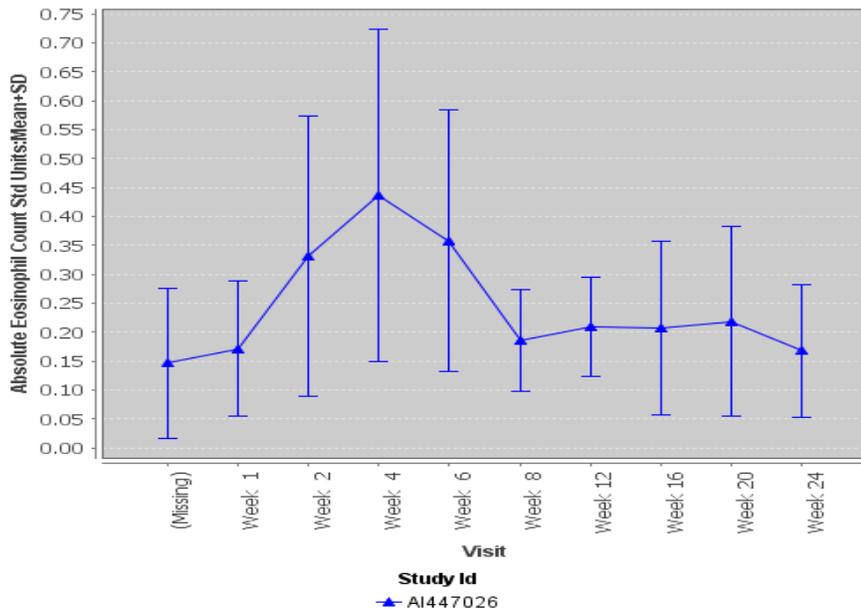


Figure 18: ALT by Visit for Subjects with Elevated Absolute Eosinophils without Pyrexia—Trial 7026

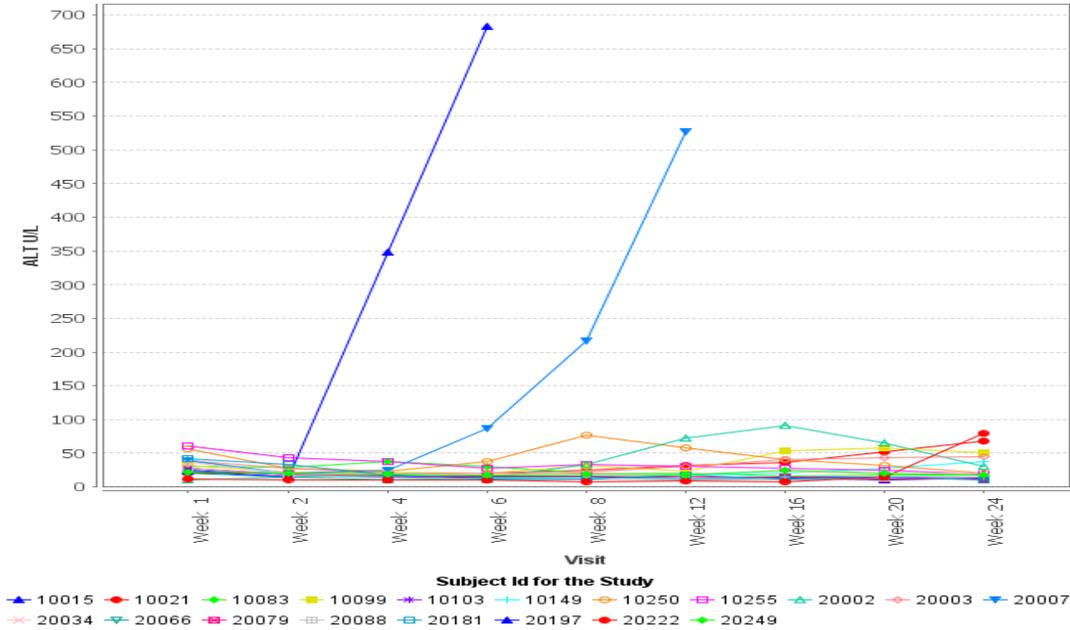


Figure 19: Absolute Eosinophil Count by Visit for Subjects with Elevated Absolute Eosinophils without Pyrexia—Trial 7028

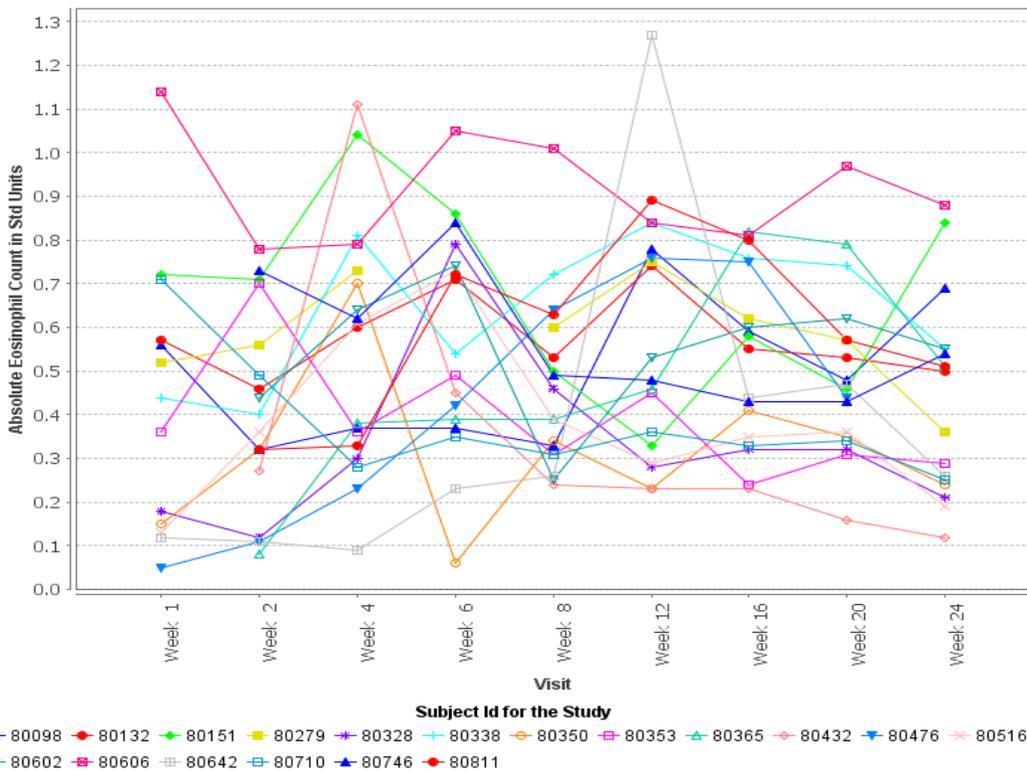


Figure 20: Mean and SD of Absolute Eosinophil Count by Visit for Subjects with Elevated Absolute Eosinophils without Pyrexia—Trial 7028

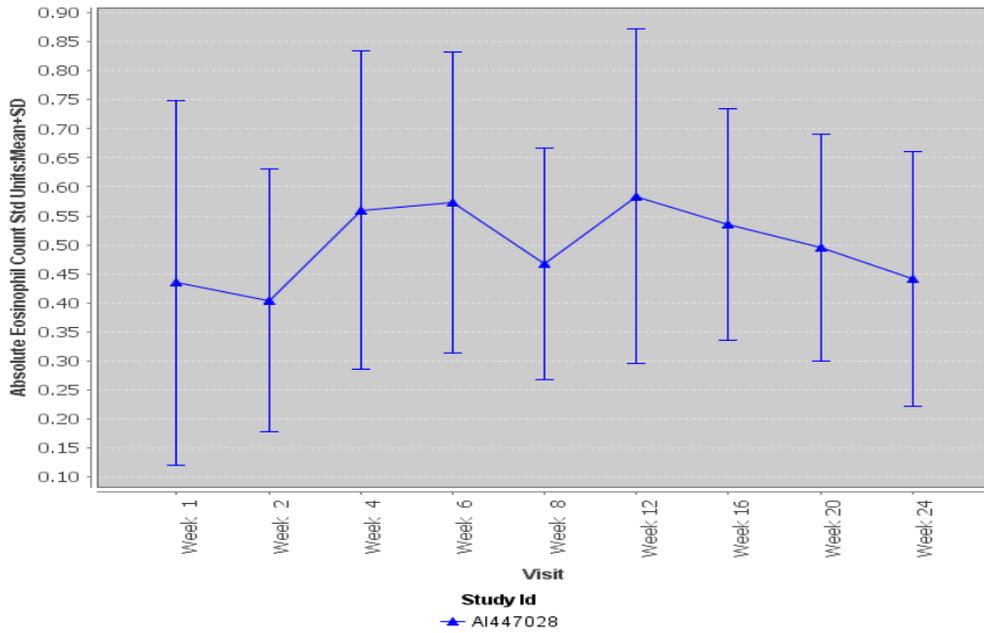
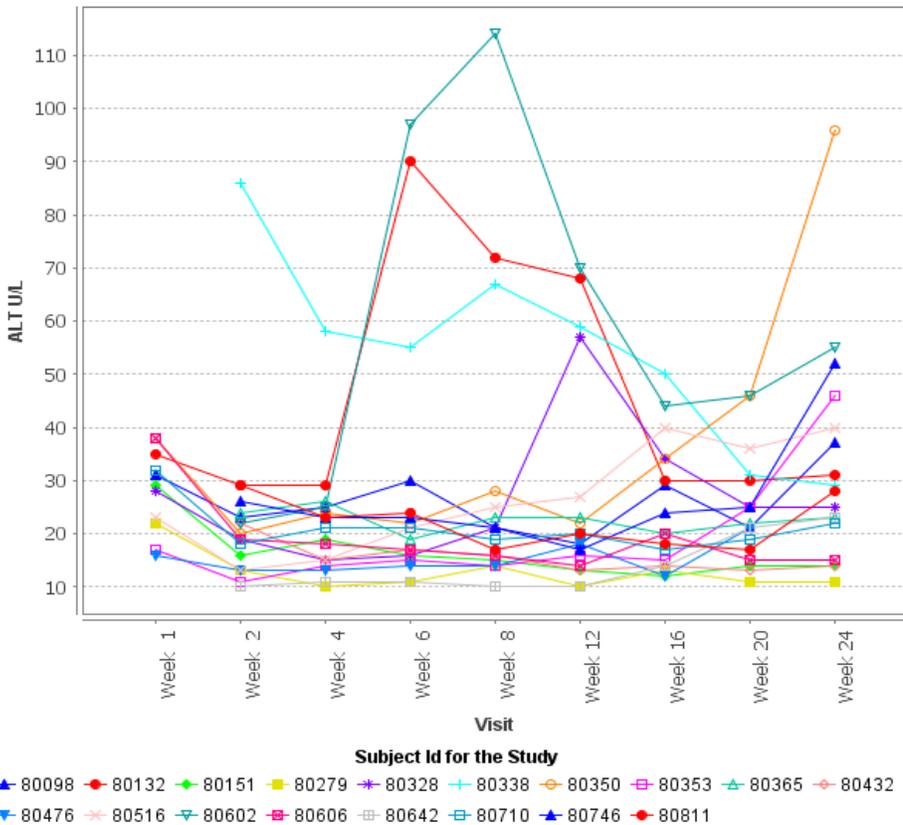


Figure 21: ALT by study Visit for Subjects with Elevated Absolute Eosinophils without Pyrexia—Trial 7028



Analysis of Rash Events as a Component of Hypersensitivity Reaction

Analyses of rash events were conducted to further evaluate if a skin component was emerging in this safety issue and whether the presence of rash may indicate drug hypersensitivity. In the overall phase 3 safety database, rash events (all grades all cause) were not frequently reported with the DUAL regimen (6% in 7026 and 5% in 7028). As expected in 7029, due to the pegIFN/RBV component of the QUAD regimen, rash was more frequently reported (25% of subjects). No subjects from the DUAL program had grade 3 or 4 rash events, while 4 QUAD subjects (1%) had grade 3/4 events. Overall, 5% (12/222) of 7026 subjects, 3% (18/645) of 7028 subjects and 3% (3/102) of placebo subjects had rash considered related to study drugs. No rash event was serious or led to discontinuation of therapy.

As discussed above, only one subject of the 16 subjects from 7026 with pyrexia and eosinophilia within 2 weeks had a mild rash. The subject did not have treatment for the rash and the rash did not lead to study medication discontinuation or interruption. In total, across both the phase 3 and ISS safety dataset analyses for pyrexia and eosinophilia discussed above, 5 additional subjects reported rash, but all were also exposed to pegIFN/rbv. In summary, overall rash was infrequently observed in the DUAL trials and was infrequently observed in the subjects who reported pyrexia with associated eosinophilia and does not appear to be a significant component of this clinical syndrome.

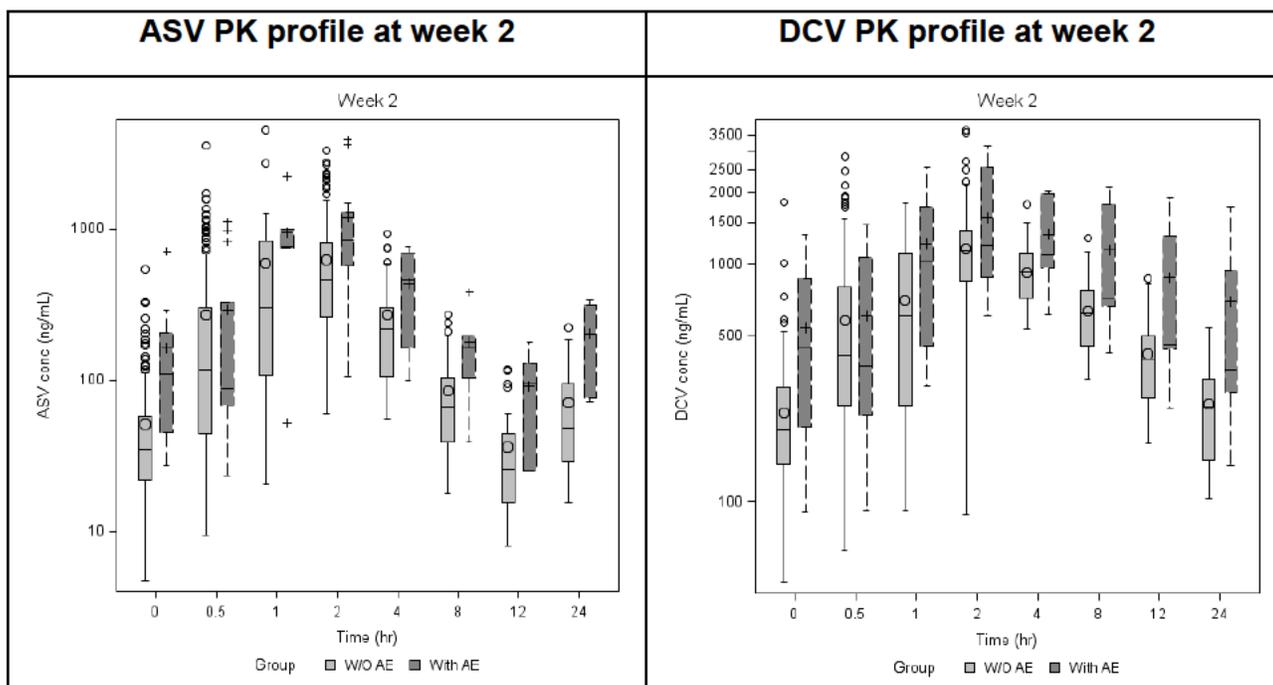
Exposure-Response for Pyrexia and Eosinophilia and Hepatic Safety

The FDA exposure-response analysis for safety focused only on phase 3 DUAL trial 7026 and 7028 to rule out confounding effects from pegIFN/RBV treatment. Please refer to Table 24 and Figure 22 below. ASV and DCV exposures in subjects with AEs of interest (pyrexia and eosinophilia within 2 weeks with or with liver function abnormalities) were elevated at Week 2 compared to subjects without the AEs of interest over the same time period. However, these differences in exposures were not observed as treatment continued beyond Week 2. Of note, the small number of subjects precludes determination of an exposure-response relationship for the AEs of interest. In addition, the ASV and DCV exposures for the 16 subjects were within the range of predicted concentrations for the 7026 and 7028 trials. The differences in ASV or DCV exposures do not appear to play a major role in contributing to the reported AEs of interest. Overall from the phase 3 data, no relationship was identified between ASV or DCV exposures and the AE events of interest.

Table 24: Comparison of Model-Estimated ASV and DCV exposure

Group	N	ASV AUC _(0-tau) (ng*hr/mL) Mean (SD)	DCV AUC _(0-tau) (ng*hr/mL) Mean (SD)
Trial 7026 (Japan) Pyrexia & Eosinophilia Within 2 Weeks	16	2221 (915)	14100 (5544)
Trial 7026 (Japan) No Pyrexia But increased eosinophils	206	1760 (732)	12216 (3378)
Trial 7028 (Global)	641	1560 (855)	12289 (4411)

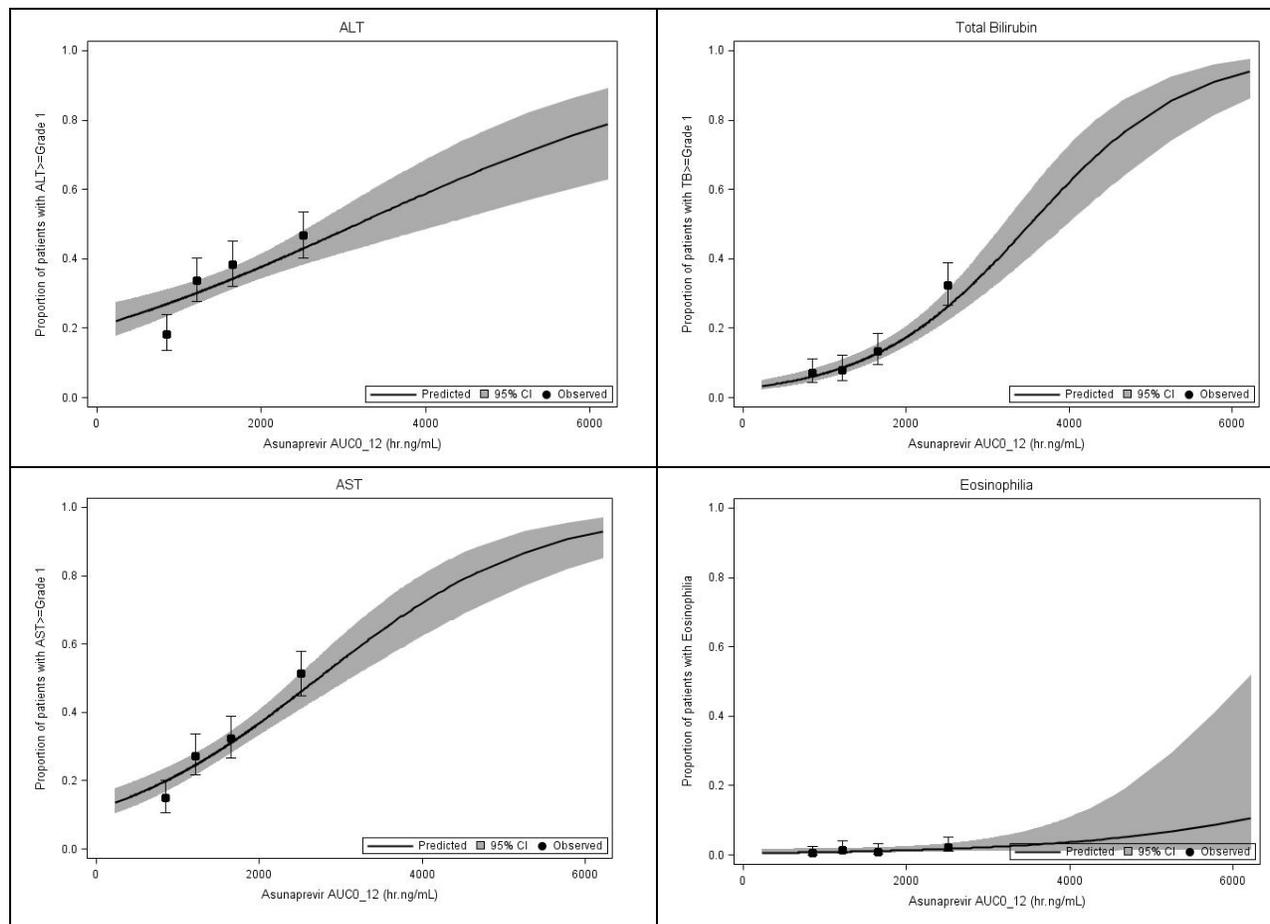
Figure 22: PK Profile at Week 2 Categorized by Occurrence of AEs of Interest in Japanese Subjects



Grade 3 or higher elevations in liver enzyme measurements were predominantly only observed with ASV exposures following administration of 600 mg twice daily dosing used during phase 2. The limited number of grade 3 or higher elevations in liver enzymes (45/867 [5.2%] for ALT and 32/867 [3.7%] for AST) in subjects receiving ASV and DCV combination treatment from the phase 3 studies precludes evaluation of an exposure-response relationship between ASV exposures and these adverse events. Significant exposure-response relationships were identified between lower grade (1 or 2) liver enzyme abnormalities (ALT, AST and TB) and ASV exposure (Figure 23). By contrast,

DCV exposures were not found to be associated with an increase in ALT, AST, or total bilirubin AE incidence (graphs not shown). Additionally, no relationship between either ASV or DCV exposure and eosinophilia could be identified from the phase 3 data.

Figure 23: Exposure-Reponses Relationships Between ASV Exposures (AUC) and the Proportion of Subjects with Grade 1 and 2 Liver Enzyme (ALT, AST, Total Bilirubin) Abnormalities or Eosinophilia



Note: The points are observed quartile mean. The shaded areas are model-estimated 95% CI based on a logistic analysis.

Quantitative Structure Activity Relationship (QSAR) assessment of ASV

Based on the hepatotoxicity safety issues identified with ASV, FDA conducted analysis of the structure activity relationship to determine whether the cyclopropylamine group identified in asunaprevir may be involved in hepatotoxicity observed in the clinical trials. Due to structural similarities, between asunaprevir and trovafloxacin further inquiry with FDA QSAR was completed. The mechanism for trovafloxacin toxicity is proposed to be related to (b) (4) and reactive

intermediates. The QSAR modeling suggests that it is unlikely that ASV forms the same reactive intermediates originating from the (b) (4). An excerpt of the QSAR assessment is provided below (additional details can be found in the pharmacology/toxicology review of ASV):



Summary of Hepatic Safety Assessment of DCV and ASV in the DUAL and QUAD Regimens

In summary, the following points are highlighted from the preceding data presentations:

- A concern for dose-related hepatotoxicity was identified for asunaprevir during a phase 2 dose-finding trial
- Phase 2 data for DCV in combination with PegIFN/RBV and DCV in combination with sofosbuvir did not identify a specific hepatotoxicity signal
- An initial case of pyrexia, eosinophilia and hepatotoxicity was identified in the Japanese DUAL trial 7026 (Subject AI447026-2-10122)
- Liver transaminase elevations often occur without bilirubin involvement; however, there are some cases of significant ALT and bilirubin elevations (cases that met Hy's Law laboratory criteria) that are concerning for drug-induced liver injury. Additionally, cases with significant increases in ALT without bilirubin elevations were also observed.
- Generally subjects with liver biochemistry laboratory abnormalities remained on treatment, with improvement of liver biochemistries. For those who discontinued, the majority achieved SVR12 and did not require treatment for the hepatic events.
- All subjects who discontinued treatment or had significant liver biochemistry abnormalities resolved their liver biochemistry abnormalities (usually within 2-4 weeks); further, there were no deaths, and the majority of subjects were asymptomatic.

- Analyses of the Japanese and non-Japanese data revealed the majority of cases were in Japanese subjects. Japanese subjects had higher proportions of pyrexia, elevated liver biochemistries and eosinophilia. Additionally, a pattern of transiently elevated eosinophils occurring early in treatment with and without pyrexia was seen in Japanese subjects compared to non-Japanese subjects where this pattern wasn't apparent.
- Overall, no relationship was identified between ASV or DCV exposure and pyrexia/eosinophilia with or without liver abnormalities
- QSAR modeling suggests that it is unlikely that ASV forms the same reactive intermediates originating from the (b) (4)

The identification of these additional safety concerns of pyrexia/eosinophilia with and without liver involvement and the overall safety signal for hepatotoxicity prompted the decisions to seek additional FDA expert consultation and led to the decision to hold an Advisory Committee meeting late in the review cycle. Additionally, while the bulk of the evidence suggests that asunaprevir is likely the drug associated with the liver toxicity, it remains uncertain the extent of the contribution DCV provides to these safety events. Any cases of abnormal liver biochemistries in subjects exposed to DCV have also included either ASV, ASV/pegIFN/RBV or peg/IFN in combination therapy. Therefore, currently, unanswered questions remain regarding the overall safety profile of DCV and ASV in combination and further exploration into the identified safety issues is warranted and underway. Therefore, at the time of the writing of this review, a full risk-benefit assessment is not possible as additional important information and consultation is expected. An addendum to this review is expected and will address the risk-benefit assessment at that time.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In order to evaluate the potential common AEs observed with use of DCV and ASV in combination, analysis of AEs from the DUAL exposed subjects in trials 7026 and 7028, compared to the placebo arm of trial 7028 were done. The placebo arm was included in trial 7028 specifically to allow for a direct safety comparison. The QUAD trial was excluded from this analysis because, as has been demonstrated in multiple AE analyses throughout this review, the pegIFN/RBV component of the combination drives the reported AEs and makes assessment of the DCV/ASV component of the regimen difficult. Analysis of the common AEs from the QUAD regimen is provided separately below.

One caveat to the analysis of the common AEs is the fact that placebo subjects in 7028 received a 12 week duration, while on-treatment duration for the DUAL exposed subjects was 24 weeks. Analysis was completed to determine if there was disproportionate reporting of AEs during Weeks 12 – 24 compared to Weeks 1 – 12 for subjects in the DUAL trials. Table 25 summarizes the results. Overall, an additional 28 subjects (13%) and 33 subjects (5%) reported AEs after Week 12 in trials 7026 and 7028, respectively. Therefore, the majority of AEs were reported within the first 12 weeks of

treatment with the DUAL regimen and is appropriate to include the 12 week placebo arm in comparison to the DUAL arms to identify safety trends.

Table 25: Difference in Adverse Event Reporting From Phase 3 DUAL Trials for Weeks 12 – 24

	AI447026	AI447028	
	DCV 60 mg QD + ASV 100 mg BID (24 W) N=222	DCV 60 mg QD + ASV 100 mg BID (24W) N=645	PLACEBO (12W) N=102
<i>Subjects with any AE through Week 12</i>	165 (74%)	514 (80%)	74 (73%)
<i>Subjects with any AE through Week 24</i>	193 (87%)	547 (85%)	74 (73%)
Week 24 –Week 12 Difference	28 (13%)	33 (5%)	n/a

Source: AE and ADSL datasets

Common AEs were evaluated by inclusion of all grades, all cause events occurring on-treatment across the DUAL trials that were observed in 10% or more of subjects from any treatment arm. Laboratory-related events that were reported as AEs are excluded from this analysis because a more objective analysis of laboratory events in all subjects was conducted (Sections 7.3.5 Submission Specific Primary Safety Concerns and 7.4.2 Laboratory Findings). Results of this analysis are summarized in Table 26. Headache, pyrexia, fatigue, diarrhea and nasopharyngitis were the most common AEs reported by more subjects exposed to DUAL from either trial 7026 or 7028 compared to placebo subjects. Only nausea and dizziness were reported at the same rate or at a lower rate for DUAL subjects than placebo subjects. Overall, generally subjects tolerated the DUAL regimen well over 24 weeks of treatment. Table 26 allows for a direct comparison of DUAL safety to placebo which is important for clinicians for assessment of potential drug-related toxicity.

Reviewer Comment: FDA proposal for the product labeling for the Adverse Reactions table for DUAL regimen will include trial 7028 from Table 26 and not trial 7026. Differences in the reported rates of events from trial 7026 for pyrexia and nasopharyngitis may be provided in text; however inclusion of trial 7026 does not provide additional safety information compared to the placebo controlled trial 7028. Additionally, only events that occurred at a rate of 10% or higher and greater than placebo will be included in the Adverse Reactions table for trial 7028 (e.g. headache, fatigue and diarrhea will be included and pyrexia, nasopharyngitis, nausea and dizziness will not be included in the proposed table)

Table 26: All Cause, Any Grade Most Common AEs reported in 10% In Any Arm - Phase 3 DUAL Trials

MedDRA PT	AI447026	AI447028	
	DCV 60 mg QD + ASV 100 mg BID (24 W) N=222	DCV 60 mg QD + ASV 100 mg BID (24W) N=645	PLACEBO (12W) N=102
Subjects with any AE	193 (87%)	547 (85%)	74 (73%)
HEADACHE	37 (17%)	159 (25%)	17 (17%)
PYREXIA	28 (13%)	24 (4%)	1 (1%)
FATIGUE	12 (5%)	139 (22%)	18 (18%)
DIARRHOEA	24 (11%)	103 (16%)	10 (10%)
NAUSEA	13 (6%)	75 (12%)	12 (12%)
DIZZINESS	2 (1%)	51 (8%)	10 (10%)
NASOPHARYNGITIS	68 (31%)	47 (7%)	7 (7%)

Source: AE and ADSL datasets

Similar analyses were conducted for the QUAD trial. Analysis of all cause, all grades, treatment-emergent AEs reported in $\geq 15\%$ of subjects from any treatment arm are provided in the Table 27 below. The most commonly ($>20\%$) reported AEs from the QUAD trial are all labeled AEs for pegIFN and/or RBV including: fatigue, headache, pruritus, asthenia, insomnia, influenza-like illness and rash. Nasopharyngitis is the only event that was reported more frequently in subjects exposed to DUAL, but this was only observed in trial 7026 and not trial 7028.

Table 27: All Cause, All Grade AEs Reported in ≥15% of Subjects From Any Treatment Arm -- Phase 3 Trials

Preferred Term	AI447026	AI447028	AI447029	
	DCV 60mg QD + ASV 100 mg BID (24W) N=222	DCV 60mg QD + ASV 100 mg BID (24W) N=645	PLACEBO (12W) N=102	DCV 60mg + ASV 100mg BID+ PegIFN + RBV (24W) N=398
Subjects with any AE	193 (87%)	547 (85%)	74 (73%)	393 (99%)
FATIGUE	12 (5%)	140 (22%)	18 (18%)	165 (41%)
HEADACHE	37 (17%)	159 (25%)	17 (17%)	124 (31%)
PRURITUS	11 (5%)	40 (6%)	8 (8%)	104 (26%)
ASTHENIA	1 (<1%)	41 (6%)	1 (1%)	96 (24%)
INSOMNIA	10 (5%)	45 (7%)	3 (3%)	89 (22%)
INFLUENZA LIKE ILLNESS	2 (1%)	23 (4%)	6 (6%)	89 (22%)
RASH	12 (5%)	21 (3%)	2 (2%)	82 (21%)
COUGH	2 (1%)	52 (8%)	5 (5%)	73 (18%)
DRY SKIN	3 (1%)	19 (3%)	3 (3%)	71 (18%)
DIARRHOEA	24 (11%)	103 (16%)	10 (10%)	70 (18%)
NAUSEA	13 (6%)	75 (12%)	12 (12%)	66 (17%)
PYREXIA	28 (13%)	24 (4%)	1 (1%)	64 (16%)
ALOPECIA	5 (2%)	31 (5%)	3 (3%)	64 (16%)
IRRITABILITY	0	15 (2%)	0	64 (16%)
MYALGIA	0	42 (7%)	4 (4%)	61 (15%)
NASOPHARYNGITIS	68 (31%)	47 (7%)	7 (7%)	6 (2%)

Source: AE and ADSL datasets

The Applicant has proposed in product labeling to include the most common adverse reactions (frequency of 15% or greater) for the QUAD regimen. This proposal includes the following AEs and percentages: fatigue (39%), headache (28%), pruritus (25%), asthenia (23%), influenza-like illness (22%), insomnia (21%), anemia (19%), rash (18%), alopecia (16%), irritability (16%), and nausea (15%). This assessment of adverse reactions compared to the above all cause assessment (Table 27) omits cough, dry skin, diarrhea, pyrexia and myalgia from the QUAD safety profile. Anemia is not included in Table 27 as it is considered a laboratory-related event and because of variable adverse event reporting of laboratory-related events, will be included in the laboratory section of product labeling.

7.4.2 Laboratory Findings

The following tables provide treatment-emergent graded laboratory abnormalities for hematology and chemistry parameters where any treatment arm had a rate of 5% or higher. These analyses represent any change after baseline and a subject could have more than one event for a given laboratory parameter and could have more than one treatment emergent laboratory abnormality (e.g. ALT, AST and total bilirubin). The denominator used is the total number of subjects per trial or arm as indicated and not by the number of subjects with available data which was the method used by the Applicant. For subjects who received 'rescue' therapy with pegIFN/RBV added to DCV/ASV in the DUAL trials laboratory data were excluded only after the start of pegIFN/RBV. It is important to recall that the duration of the DUAL regimen was 24 weeks and the duration of the placebo was 12 weeks which may account for some of the differences observed between the DUAL treatment arms compared to placebo. Additionally, the placebo arm only includes 102 subjects for comparison.

Graded chemistry parameters that were observed in $\geq 5\%$ of subjects from the phase 3 trials are summarized in Table 28. Grade 3 and 4 ALT and AST events were observed more frequently in subjects on the DUAL regimen and in greater proportion from the DUAL trial 7026 where all subjects were Japanese, when compared to placebo or the QUAD regimen. Grade 3 total bilirubin events were similar for the DUAL, QUAD and placebo subjects. Further discussions of liver biochemistry analyses, significant cases, and the observed differences in trial 7026, are integrated into the safety discussion in Section 7.3.5. As noted in Table 28, albumin, INR, lipase, uric acid, total cholesterol, creatinine and fasting glucose also met the 5% cut point for either grade 1 or 2 events. Generally, these grade 1 and 2 chemistry laboratory events did not have any significant clinical impact on study treatment, there was no clinical indication for routine monitoring of these laboratory events during treatment and subjects did not discontinue therapy due to these mild laboratory changes. Additionally, excluding abnormal liver biochemistries, few subjects had grade 3 or 4 chemistry laboratory abnormalities across the phase 3 program: grade 3/4 INR in 2 subjects from 7028 and 2 subjects from 7029, grade 3 creatinine in 1 subject from 7026 (subject also had acute pyelonephritis) and grade 3 fasting glucose in 1 subject from 7028 (on insulin) and 2 subjects from 7029 (1 subject with type 2 diabetes with elevated fasting glucose and 1 subject with low fasting glucose). All the subjects with grade 3 or 4 INR elevations continued therapy with improvement in INR and completed therapy.

Table 28: Treatment-emergent Graded Chemistry Laboratory Abnormalities ≥5% From Any Arm -- Phase 3 Trials

Lab Test and Emergent Toxicity Grade*		AI447026	AI447028	AI447029	
		DCV 60mg QD + ASV 100 mg BID (24W) N=222	DCV 60mg QD + ASV 100 mg BID (24W) N=645	PLACEBO (12W) N=102	DCV 60mg + ASV 100mg BID+ PegIFN + RBV (24W) N=398
ALT	GRADE 1	18 (8%)	51 (8%)	17 (17%)	28 (7%)
	GRADE 2	23 (10%)	33 (5%)	9 (9%)	24 (6%)
	GRADE 3	12 (5%)	9 (1%)	2 (2%)	12 (3%)
	GRADE 4	6 (3%)	8 (1%)	0	0
AST	GRADE 1	21 (9%)	39 (6%)	13 (13%)	34 (9%)
	GRADE 2	11 (5%)	21 (3%)	6 (6%)	24 (6%)
	GRADE 3	8 (4%)	8 (1%)	1 (1%)	13 (3%)
	GRADE 4	3 (1%)	4 (1%)	0	0
Alkaline Phosphatase	GRADE 1	17 (8%)	13 (2%)	0	8 (2%)
	GRADE 2	1 (<1%)	0	0	0
Total Bilirubin	GRADE 1	35 (16%)	38 (6%)	7 (7%)	89 (22%)
	GRADE 2	8 (2%)	16 (2%)	2 (2%)	33 (8%)
	GRADE 3	1 (<1%)	2 (<1%)	1 (1%)	4 (1%)
Albumin	GRADE 1	47 (21%)	25 (4%)	1 (1%)	30 (8%)
	GRADE 2	0	0	0	3 (1%)
INR	GRADE 1	6 (3%)	53 (8%)	1 (1%)	23 (6%)
	GRADE 2	0	5 (1%)	1 (1%)	3 (1%)
	GRADE 3	0	1 (<1%)	0	2 (1%)
	GRADE 4	0	1 (<1%)	0	0
Lipase	GRADE 1	21 (9%)	157 (24%)	11 (11%)	56 (14%)
	GRADE 2	18 (8%)	55 (9%)	9 (9%)	33 (8%)
	GRADE 3	1 (0%)	10 (2%)	2 (2%)	7 (2%)
	GRADE 4	0 (0%)	6 (1%)	1 (1%)	4 (1%)
Uric Acid	GRADE 1	0	73 (11%)	8 (8%)	87 (22%)
	GRADE 2	0	0	0	0
	GRADE 3	0	1 (<1%)	0	1 (<1%)
	GRADE 4	0	0	0	2 (1%)
Total Cholesterol	GRADE 1	0	55 (9%)	2 (2%)	6 (2%)
	GRADE 2	0	21 (3%)	0	4 (1%)
	GRADE 3	0	4 (1%)	0	0 (0%)
Creatinine	GRADE 1	18 (8%)	2 (<1%)	0	2 (1%)
	GRADE 2	1 (<1%)	0	0	1 (<1%)
	GRADE 3	1 (<1%)	0	0	0
Glucose, Fasting	GRADE 1	0	32 (5%)	0	20 (5%)
	GRADE 2	0	32 (5%)	1 (1%)	23 (6%)
	GRADE 3	0	1 (<1%)	0	2 (1%)

Source: laboratory and ADSL datasets

Because of the known hematologic toxicities of pegIFN/RBV, subjects exposed to pegIFN/RBV in the QUAD regimen in trial 7029 had a higher proportion of treatment-emergent hematologic laboratory abnormalities (Table 29). Overall, the subjects exposed to the DUAL regimen had lower rates of hematologic events. However, again subjects from the DUAL trial 7026 had higher frequency and grade events compared to subjects from the DUAL trial 7028 or the placebo arm. This difference may be related to the overall enrolled populations; trial 7026 had a higher proportion of subjects above age 65 years and more females (which may contribute to higher rate of lower hemoglobin), both of which could contribute to the observed differences.

Table 29: Treatment-emergent Graded Hematology Laboratory Abnormalities ≥5% From Any Arm -- Phase 3 Trials

Lab Test and Emergent Toxicity Grade*		AI447026		AI447028		AI447029	
		DCV 60mg QD + ASV 100 mg BID (24W) N=222	DCV 60mg QD + ASV 100 mg BID (24W) N=645	PLACEBO (12W) N=102	DCV 60mg + ASV 100mg BID+ PegIFN + RBV (24W) N=398		
WBC (low)	GRADE 1	10 (5%)	4 (1%)	1 (1%)	173 (43%)		
	GRADE 2	3 (1%)	3	0	112 (28%)		
	GRADE 3	0	0	0	36 (9%)		
	GRADE 4	0	0	0	2 (1%)		
Hb (low)	GRADE 1	15 (7%)	12 (2%)	0	126 (32%)		
	GRADE 2	14 (6%)	4 (1%)	0	59 (15%)		
	GRADE 3	10 (5%)	0	0	21 (5%)		
	GRADE 4	0	0	1 (1%)	0		
Platelets (low)	GRADE 1	22 (10%)	18 (3%)	2 (2%)	141 (35%)		
	GRADE 2	14 (6%)	18 (3%)	2 (2%)	105 (26%)		
	GRADE 3	3 (1%)	3 (<1%)	0	10 (3%)		
Leukocytes	GRADE 1	20 (9%)	19 (3%)	1 (1%)	234 (59%)		
	GRADE 2	4 (2%)	9 (1%)	0	152 (38%)		
	GRADE 3	0	1 (<1%)	0	49 (12%)		
	GRADE 4	0	0	0	4 (1%)		
Lymphocytes	GRADE 1	11 (5%)	7 (1%)	1 (1%)	77 (19%)		
	GRADE 2	10 (5%)	5 (1%)	1 (1%)	80 (20%)		
	GRADE 3	5 (2%)	4 (1%)	0	58 (15%)		
	GRADE 4	2 (1%)	3 (<1%)	0	13 (3%)		
Neutrophils + Bands (absolute)	GRADE 1	23 (10%)	36 (6%)	6 (6%)	233 (59%)		
	GRADE 2	14 (6%)	11 (2%)	2 (2%)	169 (42%)		
	GRADE 3	3 (1%)	3 (<1%)	0	84 (21%)		
	GRADE 4	0	5 (1%)	0	16 (4%)		

Source: laboratory and ADSL datasets

Reviewer Comment: The most significant and clinically relevant laboratory findings from the phase 3 trials are related to the liver (ALT, AST, alkaline phosphatase and total bilirubin). However, generally the majority of subjects had improvement of their liver laboratory parameters with treatment with either the DUAL or QUAD regimen and there were no events of irreversible liver injury.

FDA is awaiting internal and external consultation prior to the determination of a complete benefit-risk assessment. And, while currently the risk of serious irreversible liver damage or liver failure remains unquantified, it is advisable to assume that this may occur in a broader population of chronic hepatitis C patients. However, the risk of liver injury may be mitigated by routine monitoring of liver laboratories during treatment and by providing recommended discontinuation criteria. The Applicant's expert panel recommended that patients on DCV/ASV containing regimens have ALT be monitored at Weeks 2 and 4 and then monthly for the duration of therapy. No specific discontinuation criteria were recommended by the Applicant's panel. FDA's proposal for the laboratory section of the product labeling will include a discussion of liver laboratory findings and recommendations for clinical and laboratory monitoring. Further input from experts will be considered for recommendations in labeling for discontinuation criteria.

In contrast, the other chemistry and hematologic laboratory parameters do not have clinical recommendations for routine monitoring or interventions other than what is provided in the pegIFN/RBV product labeling and would be pertinent only to the QUAD regimen. Therefore, these laboratory parameters will not be recommended for inclusion in a table in the product labels for the laboratory section. Text will be proposed by treatment regimen and trial to describe the more significant laboratory abnormalities (grades 3/4) that are most clinically relevant.

7.4.3 Vital Signs

Analyses were completed for changes over the on-treatment duration for mean heart rate, systolic blood pressure and diastolic blood pressure. There were no trends observed for clinically meaningful increases or decreases for these vital sign parameters and no adverse events related to blood pressure abnormalities.

7.4.4 Electrocardiograms (ECGs)

Trial 7026

During the study, no trends in ECG abnormalities were observed and no subject discontinued treatment due to an ECG abnormality. The most frequent on-treatment ECG interval abnormality was QTcF interval prolongation. Overall, 10 subjects (5%) had a maximum on-treatment QTcF interval between 450-480 msec. Among these 10 subjects, 3 subjects had baseline QTcF interval prolongation between 450 and 480 msec. There were no on-treatment QTcF interval prolongations greater than 480 msec.

One subject had an ECG abnormality reported as an AE by the investigator:

AI447026-7-20236: a 69 year old Japanese male with a history of hypertension has an SAE of myocardial infarction (grade 3) noted on his Week 24 ECG, following his last dose of study medication. The subject was asymptomatic and was prescribed isosorbide and aspirin. The

cardiologist considered the findings of the ECG at Week 24 to be significantly different from those at Week 12 (probable inferior infarct; sinus tachycardia) and that the event of myocardial infarction occurred during this 3-month period. It should be noted that, in retrospect, the cardiologist indicated that the ECG at Week 4 had shown cardiac ischemia (with sinus tachycardia), ventricular premature complex, and abnormal T wave; however, it was not considered clinically significant as the subject had no symptoms, so study therapy was not discontinued at that time. The AE was considered not drug-related.

Reviewer Comment: This 69 yo subject suffered an asymptomatic myocardial infarction while on DUAL therapy. While in retrospect, the cardiologist noted significant changes on the ECG done at Week 4, the subject apparently remained asymptomatic throughout or did not report any significant symptoms. The subject was continued on study therapy. I agree with the causality assessment that this case does not appear to represent a drug-related event, and most likely the subject had pre-existing coronary artery disease based on his risk factors of age, male gender and history of hypertension.

Trial 7028

A total of 220 subjects (30%) had abnormal ECGs pre-treatment. An on-treatment ECG abnormality was reported for 1 (0.2%) subject:

AI447028-111-80406: a 58-year-old white female in the intolerant/ineligible group with a medical history of hypertension, Type 2 diabetes mellitus, hypothyroidism, and sarcoidosis, reported multiple AEs of prolonged QT (grade 2 on-treatment but worst grade of grade 4, 4 days after stopping therapy) considered not related to study treatment by the investigator (thought to be related other concomitant medications, the subject was taking Monopax, a homeopathic medication, oxycodone, insulin and spironolcatone), leading to treatment interruption and discontinuation on Study Day 160 (Week 24). The subject had also reported grade 1 angina pectoris on Day 127 that was considered not drug-related and did not lead to any change in study drugs.

Reviewer Comment: It is unclear whether Monopax, or the other concomitant medications this subject was taking contributed to the AE of prolonged QT. Because the QT prolongation worsened off treatment, it seems less likely to be related to study drug. Additionally, both DCV and ASV had negative thorough QT trials as is discussed below in Section 7.4.5.

Trial 7029

A total of 120 (30%) subjects had abnormal ECGs pre-treatment. No on-treatment or follow-up ECGs were routinely collected in this trial. There were no elective on-treatment ECG abnormalities reported as AEs for any subject in this trial.

7.4.5 Special Safety Studies/Clinical Trials

Thorough QT (TQT) trials were completed for both DCV and ASV. Both drugs were not associated with QTc prolongation or clinically meaningful effects on other ECG intervals.

Daclatasvir

Fifty-six subjects received daclatasvir 60 mg, 180 mg, placebo and moxifloxacin 400 mg. No significant QTc prolongation effects of daclatasvir doses of 60 mg and 180 mg) were detected in the TQT trial. The largest upper bounds of the 2-sided 90% CI for the mean differences between BMS-790052 60 mg and placebo, and between BMS-790052 180 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, indicating that assay sensitivity was established.

Asunaprevir

One hundred and twenty healthy subjects received ASV 300 mg BID, placebo, and a single oral dose of moxifloxacin 400 mg.

No significant QTc prolongation effect of asunaprevir (ASV) 300 mg BID was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between ASV 300 mg BID and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated, indicating that assay sensitivity was established.

7.4.6 Immunogenicity

Because both DCV and ASV are small molecules and not a peptides, immunogenicity effects were not anticipated and therefore not specifically assessed during the clinical trials.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Only DCV 60 mg once daily dosing and ASV 100 mg BID dosing were used in all 3 pivotal phase 3 trials. These are the proposed doses for use if the marketing application is approved. Dose adjustment for DCV for 30 mg and 90 mg are proposed for DDI. Please see Section 7.5.5.

7.5.2 Time Dependency for Adverse Events

The duration for the phase 3 trials was 24 weeks, as is the proposed dosing indication; therefore no duration dependency evaluation for AEs was performed. However, as discussed in the safety section, the majority of AEs during the DUAL trials occurred in the first 12 weeks of the regimen. Overall, 193 subjects (87%) in 7026 and 547 (85%) subjects in 7028 reported any AE through 24 weeks on the DUAL regimen; only 28 subjects (13%) and 33 subjects (5%) in 7026 and 7028 respectively, reported AEs occurring between Weeks 12 and 24 on-treatment.

7.5.3 Drug-Demographic Interactions

Multiple analyses were completed to evaluate AEs in relation to baseline demographic factors including age, gender, and race. Section 7.3.5 has in-depth discussion regarding analyses of racial differences observed in the Japanese subjects in comparison to other racial groups exposed to the DUAL regimen.

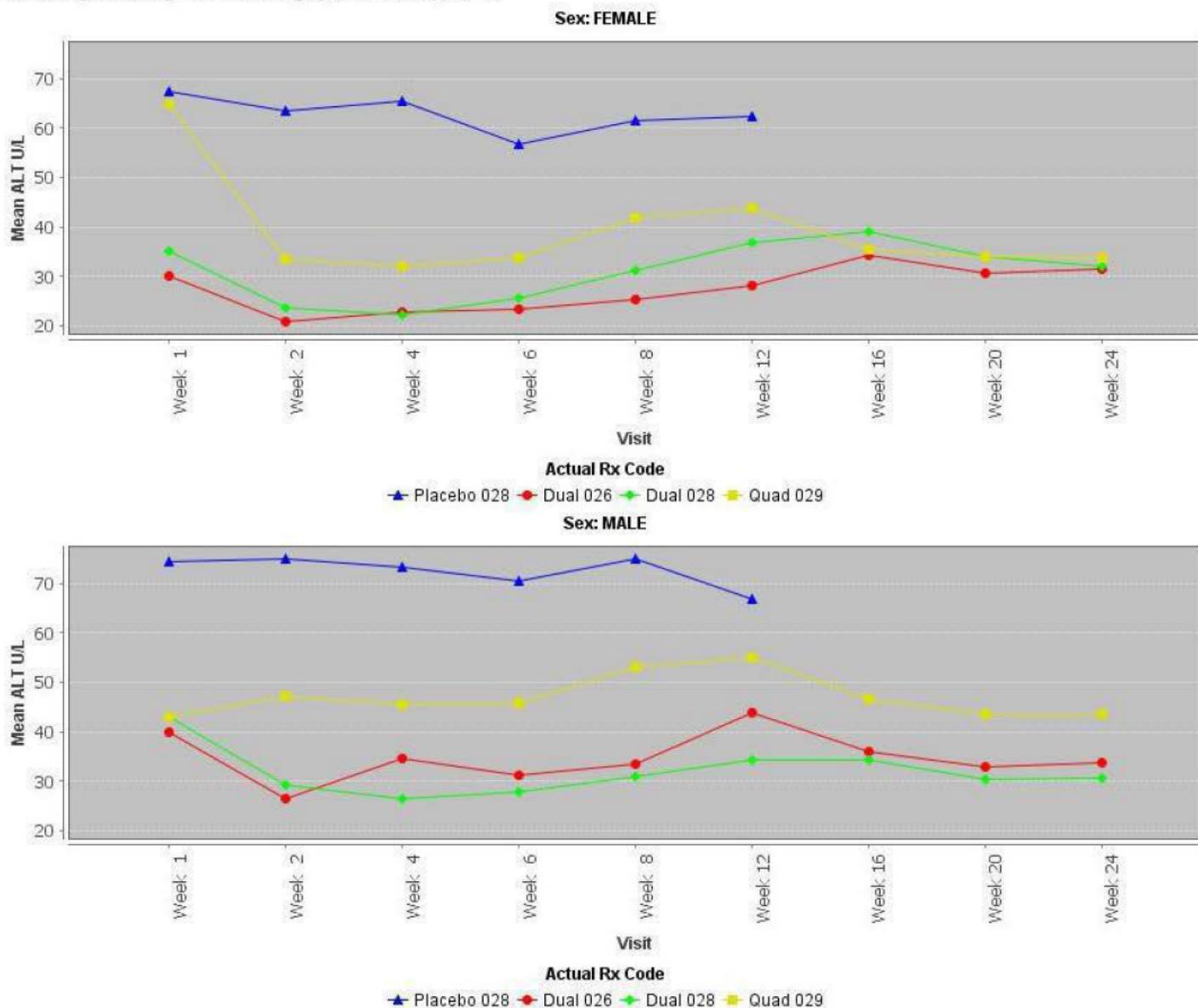
Analyses of AEs related to age (<65 years or ≥ 65 years) did not reveal any trends for safety events occurring more frequently in an elderly population. It is important to note that a significant number of subjects were enrolled who were ≥ 65 years of age: 40% in trial 7026; 21% in trial 7028 and 9% in trial 7029.

Historically, females are often under-represented in clinical trials. The phase 3 trials for DCV and ASV enrolled an overall large proportion of females compared to some other HCV development programs. Females made up 65% of trial 7026, 52% of trial 7028 and 9% of trial 7029. Analyses of AEs, both all cause and related, did not show any obvious trends for any particular safety events across the phase 3 database. However, across the DUAL trials 7026 and 7029 there was a higher proportion of female subjects compared to males who reported nausea (5% of females and 1 % of males in 7026 and 9% of female versus 3% of males in 7028); compared to 7% of females versus 5% of males from the placebo arm of 7028. Nausea was reported by 9% of female subjects and 7% of male subjects exposed to QUAD in 7029. Additionally, nasopharyngitis was reported by more females compared to males across the DUAL trials (predominantly in 7026); however, this AE was rarely considered drug-related.

There was no striking gender difference in the rate of liver-related AEs or liver biochemistries across the phase 3 trials. In trial 7026, 11% of female (n=24) subjects were reported with increased ALT (all grades, related) compared to 5% of male (n=12) subjects. The gender difference is smaller for grade 3 or 4 related increased ALT: 5% of females compared to 3% of males from trial 7026. This trend was not observed in either trial 7028 or 7029; however rates of increased ALT were less frequently reported from both of these trials and more females were enrolled in trial 7026 compared to 7028 and 7029, both of which likely contributes to the difference. Additionally, these trials are not powered to determine statistical differences for safety events; these are general observations of the trends in data. Laboratory analyses of liver biochemistries did not find any clinically meaningful difference between females and males. Figure 24 provides a summary of mean ALT by study visit and gender. There are no clinically significant differences in the ALT trends over time while on treatment between males and females exposed to DUAL or QUAD. Compared to placebo, the mean ALT was lower for both the DUAL and QUAD treatment regimens. Overall, other than small differences in AE reporting of nausea and nasopharyngitis, there is no apparent gender difference for safety events from the phase 3 database for DCV and ASV. In particular, there is no evidence of a significant difference for liver-related AEs or liver biochemistries by gender from the phase 3 trials.

Figure 24: Mean ALT by Study Visit and Gender – DUAL Trials 7026 and 7028

mean ALT by visit and gender line sum graph - Subset of patients



Patient Selection Criteria: Subject-Level Analysis Dataset.Safety Population Flag =Y
 Output Filter: Laboratory Results with US Units.Drv: Analysis Flag =YES AND Laboratory Results with US Units.Drv: Lab Test or Examination Code =Alanine Ami...
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7.5.4 Drug-Disease Interactions

Multiple analyses were completed to evaluate AEs for any patterns where subjects with baseline cirrhosis may have increased risk for particular safety events across the phase 3 trials. There were no events that occurred in a higher proportion of subjects with baseline cirrhosis compared to those without cirrhosis. Additional analyses also focused on liver-related AEs and laboratory abnormalities,

again no difference was found for subjects with or without baseline cirrhosis which is consistent with the Applicant's findings.

Evaluation of both DCV and ASV in subjects with hepatic and renal impairment was also completed. See Section 4.4.3 Pharmacokinetics for details.

7.5.5 Drug-Drug Interactions

Please refer to the Clinical Pharmacology Review for detailed assessment of the phase 1 drug-drug interaction trials and labeling considerations. This section summarizes notable findings.

The concomitant use of asunaprevir and daclatasvir was evaluated in a drug-drug interaction trial without significant pharmacokinetic interactions. No efficacy or safety issues were identified in clinical trials that were considered related to concurrent use of these medications. Similarly, while a drug-drug interaction trial was not conducted for asunaprevir coadministered with daclatasvir plus pegylated interferon alpha and ribavirin, no efficacy or safety issues were identified in clinical trials considered related to the concurrent use of these medications. The in vitro study results indicate that CYP3A is the primary cytochrome P450 enzyme system responsible for asunaprevir or daclatasvir metabolism.

Cytochrome P450 enzymes

Asunaprevir

(b) (4)

Daclatasvir

For daclatasvir's effects on other medications, the in vitro information indicates a potential drug-drug interaction with CYP3A inhibition and induction. Daclatasvir is also a CYP3A substrate.

Transporters

Asunaprevir

(b) (4)

Daclatasvir

For daclatasvir' s effects on transporters the in vitro information indicated a potential drug-drug interaction with P-gp, BCRP, OATP1B1 and OATP1B3 substrates. Daclatasvir is also a P-gp substrate.

The Applicant is proposing the following dosing recommendation to address potential drug-interaction issues:

Daclatasvir (in the absence of concomitant use of ASV)

- Strong CYP3A inhibitors: **decrease** daclatasvir dose to **30 mg once daily**: (b) (4)
- Moderate CYP3A inducers: **increase** daclatasvir dose to **90 mg once daily**: (b) (4)

Contraindicate use of certain medications in combination with ASV or DCV:

Asunaprevir

(b) (4)

Daclatasvir

- Strong CYP 3A inducers: (b) (4)

Reviewer Comment:

(b) (4)
Labeling negotiations are ongoing at the time of the writing of this review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The maximum study duration of the DCV and ASV clinical trials (majority of data at 24 weeks duration and limited 48 weeks duration) limits the assessment for oncologic events. Most of the reported malignancies are those consistent with the patient population (e.g. hepatocellular carcinoma) and no clustering of any particular events was noted.

7.6.2 Human Reproduction and Pregnancy Data

In nonclinical data, there was no evidence of selective developmental toxicity associated with DCV or ASV across the standard battery of reproductive toxicity studies.

Developmental toxicities were observed in both rats and rabbits exposed to DCV (not ASV) in the presence of maternal toxicity. DCV and ASV were both shown to cross the placenta in limited amounts and both were excreted into milk in rodent studies. These results suggest that both the fetus and nursing infants of women receiving DCV and/or ASV may be exposed to DCV and/or ASV and their metabolites.

There are no adequate and well-controlled trials of DCV and/or ASV in pregnant and lactating women. Pregnant and lactating women were excluded from DCV and ASV clinical trials.

Pregnancies in the Phase 3 Trials

There were no positive pregnancy tests for study subjects during the on-treatment period of all of the phase 3 trials. However, there were 3 reported positive pregnancy tests:

- 1 enrolled subject from trial 7028 who did not enter treatment due to a positive pregnancy test
- 1 female partner of a study subject (AI447028-29-80369) was reported as pregnant with an approximate date of conception 4 days prior to the subjects' last doses of study drugs.
- 1 female study subject (AI447029-45-90368) exposed to QUAD, reported a positive pregnancy test approximately 1.5 months after her last dose of study therapy. The subject had elective termination of pregnancy.

Pregnancies in the Overall DCV Safety Database

Overall, a total of 31 pregnancies of study subjects or female partners were reported in the total DCV safety database for the NDA. The following table provides a summary of the available data as of April 1, 2014. Of note, 3 spontaneous abortions were reported. The DCV Safety Update Report included one additional pregnancy for a female partner of a subject who received DCV/pegIFN/RBV in a non-BMS-sponsored trial. No outcome information is available for this pregnancy.

Table 30: Pregnancies in the Overall DCV Safety Database

Appendix 1: *Updated Summary of Pregnancies in Study Subjects or Female Partners of Study Subjects For Complete and Ongoing Studies with Any Daclatasvir Treatment Groups As of 01-Apr-2014*

Subject PID ^a (Age/Gender/Race)	Study Subject or Female Partner (Age/Race)	Subject Treatment Assignment	Dates of Study Therapy	Approximate Date of Conception	Outcome
AI444010-68-106 (27/Female/White)	Study Subject	DCV 60 mg QD/ pegIFN α /RBV	23-Aug-2010 - 06-Feb-2011	12-Apr-2011	Elective termination
AI444010-33-382 (28/Male/White)	Female Partner (30/White)	DCV 20 mg QD/ pegIFN α /RBV	11-Oct-2012 - 23-Nov-2010	Not provided (reported Dec-2012)	Not provided
AI444010-33-384 ^b (31/Male/White)	Female Partner (Unknown/Unknown)	DCV 60 mg QD/ pegIFN α /RBV	06-Oct-2010 - 22-Mar-2011	Feb-2012	Fetal malformation (renal agenesis, unviable) at Week 24
AI444031-10-152 (40/Male/White)	Female Partner (Unknown/Unknown)	DCV 60 mg QD (16 WK)/pegIFN α /RBV	08-Apr-2011 - 29-Jul-2011	24-Sep-2011	Elective termination
AI444031-8-81 (45/Male/White)	Female Partner (36/White)	Placebo/pegIFN α /RBV	16-Mar-2011 - 28-Aug-2011	25-Nov-2011	Elective termination
AI444038-10-398 (19/Male/White)	Female Partner (Unknown/Unknown)	DCV 60 mg QD/ pegIFN α /RBV	07-Jun-2012 - 21-Nov-2012	Feb-2013	Healthy male infant delivered at unknown week (b) (6)
AI444038-17-438 (58/Male/White)	Female Partner (51/Unknown)	DCV 60 mg QD/ pegIFN α /RBV	20-Jul-2012 - 06-Dec-2012	Not provided	Elective termination
AI444038-29-434 (37/Female/White)	Study Subject	DCV 60 mg QD/ pegIFN α /RBV	23-Jul-2012 - 08-Jan-2013	25-May-2013	Unknown
AI444040-5-285 (28/Female/White)	Study Subject	DCV 60 mg QD/ SOF 400 mg QD/RBV	14-Mar-2012 - 06-Jun-2012	01-Jul-2012	Healthy male infant delivered at Week 35 (b) (6)
AI444040-10-72 (43/Female/White)	Study Subject	DCV 60 mg QD/ SOF 400 mg QD	28-Jul-2011 - 10-Jan-2012	25-Jul-2012	Spontaneous abortion Week 5 (24-Aug-2012)
AI444042-4-1 (44/Male/Black/ African American)	Female Partner (40/Black/African American)	DCV 60 mg QD/ pegIFN α /RBV	20-Jan-2012 - 05-Jul-2012	05-Nov-2011	Healthy male infant delivered at Week 40 (b) (6)
AI444042-115-89 (40/Female/White)	Study Subject	DCV 60 mg QD/ pegIFN α /RBV	11-Jun-2012 - 22-Jul-2012	25-Nov-2012	Healthy male infant delivered at week 38.5 (b) (6)
(b) (4)-3-252 (53/Male/White)	Female Partner (43/White)	DCV 30 mg QD/ pegIFN α /RBV	14-May-2012 - 29-Oct-2012	Apr-2012	Healthy male infant delivered at Week 39 (b) (6)

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NDA 206-843 and NDA 206-844
Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Appendix 1: Updated Summary of Pregnancies in Study Subjects or Female Partners of Study Subjects For Complete and Ongoing Studies with Any Daclatasvir Treatment Groups As of 01-Apr-2014

Subject PID/ ^a (Age/Gender/Race)	Study Subject or Female Partner (Age/Race)	Subject Treatment Assignment	Dates of Study Therapy	Approximate Date of Conception	Outcome
(b) (4)-107-315 (30/Female/White)	Study Subject	DCV 60 mg QD/ pegIFNα/RBV	28-Jun-2012 - 13-Dec-2012	Jul-2013	Not provided
A1444052-49-553 (37/Female/Asian)	Study Subject	DCV 60 mg QD/ pegIFNα/RBV	31-Aug-2012 - 14-Feb-2013	23-Jul-2013	Not provided
A1444052-81-385 (45/Male/White)	Female Partner (26/White)	DCV 60 mg QD/ pegIFNα/RBV	18-Jul-2012 - 01-Jan-2013	Apr-2012	Healthy infant (gender unknown) delivered at unknown week (b) (6)
A1444052-98-580 (34/Male/White)	Female Partner (27/White)	TVR 750 mg TID/ pegIFNα/RBV	04-Sep-2012 - 18-Feb-2013 (TVR end date: 26-Nov-2012)	Not provided	Not provided
A1444052-124-556 (23/Male/White)	Female Partner (21/White)	DCV 60 mg QD/ pegIFNα/RBV	29-Aug-2012 - 12-Feb-2013	24-May-2013	Elective termination
A1444052-61-00780 (30/Female/White)	Study Subjects	DCV 60 mg QD/ pegIFNα/RBV	22-Oct-2012 - 09-Apr-2013	Jun-2013	Spontaneous abortion (29-Aug- 2013)
A1447028-29-80369 (26/Male/White)	Female Partner (Unknown/Unknown)	DCV 60 mg QD/ ASV 100 mg BID	25-Sep-2012 - 14-Mar-2013	18-Mar-2013	Healthy male infant delivered at Week 41 (b) (6)
A1447029-45-90368 (42/Female/White)	Study Subject	DCV 60 mg QD/ ASV 100 mg BID/ pegIFNα/RBV	18-Oct-2012 - 4-Apr-2013	28-May-2013	Elective termination at unknown Week (29-Jun-2013)
A1447031-23-10166 (46/Male/Japanese)	Female Partner (29/Asian)	DCV 60 mg QD/ ASV 100 mg BID	12-Feb-2013 - 28-Jul-2013	Not provided	Not provided
A1447031-36-10252 (26/Female/Japanese)	Study Subject	DCV 60 mg QD/ ASV 100 mg BID	13-Mar-2013 - 30-Jul-2013	14-Jul-2013	Not provided
A1443014-3-74 (46/Male/White)	Female Partner (34/White)	DCV 60 mg QD/ ASV 200 mg/BID/ BMS-791325 75 mg BID	26-Jan-2012 - 19-Apr-2012	Mar-2012	Healthy female infant delivered at Week 39 (b) (6)

Appendix 1: Updated Summary of Pregnancies in Study Subjects or Female Partners of Study Subjects For Complete and Ongoing Studies with Any Daclatasvir Treatment Groups As of 01-Apr-2014

Subject PID/ ^a (Age/Gender/Race)	Study Subject or Female Partner (Age/Race)	Subject Treatment Assignment	Dates of Study Therapy	Approximate Date of Conception	Outcome
A1443014-20-552 (29/Male/White)	Female Partner (22/White)	DCV 30 mg/BID/ ASV 200 mg/BID/ BMS-791325 150 mg BID	12-Mar-2013 - 03-Jun-2013	21-Jul-2013	Spontaneous abortion Week 6 (2-Sep-2013)
A1443014-29-342 (56/Male/White)	Female Partner (Unknown/Unknown)	DCV 30 mg BID/ ASV 200 mg/BID/ BMS-791325 75 mg BID	5-Feb-2013- 28 April 2013	unknown	Healthy female infant delivered at unknown week (b) (6)
A1443102-31-270 (31/Female/White)	Study Subject	DCV 30 mg BID/ ASV 200 mg BID/ BMS-791325 75 mg BID	24-Jan-2014-7- Mar-2014	15-Feb-2014	Unknown
A1452017-67-230 (37/Male/White)	Female Partner (Unknown/Unknown)	Blinded: DCV 60 mg QD or Placebo/ Blinded: pegIFNλ/RBV or pegIFNα/RBV	21-Jan-2013 - 11-Feb-2013	Not provided	Not provided
A1452017-60-24 (41/Male/White)	Female Partner (42/White)	Blinded: DCV 60 mg QD or Placebo/ Blinded: pegIFNλ/RBV or pegIFNα/RBV	03-Oct-2012 - 17-Mar-2013 (DCV/PBO end date: 26-Dec-2012)	07-May-2013	Pregnancy ongoing (expected date of delivery 30-Jan-2014)
A1452017-145-1002 (46/Male/Japanese)	Female Partner (30/Asian)	Blinded: DCV 60 mg QD or Placebo/ Blinded: pegIFNλ/RBV or pegIFNα/RBV	14-May-2013 - 22-Aug-2013	21-Jul-2013	Elective termination
A1452017-156-477 (32/Male/Japanese)	Female Partner (32/Asian)	Blinded: DCV 60 mg QD or Placebo/ Blinded: pegIFNλ/RBV or pegIFNα/RBV	20-Feb-2013 - 10-Jun-2013	Unknown	Male pre-term infant delivered at unknown week (b) (6)

Clinical Review
Wendy Carter, D.O.
NDA 206-843 and NDA 206-844
Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Appendix 1: Updated Summary of Pregnancies in Study Subjects or Female Partners of Study Subjects For Complete and Ongoing Studies with Any Daclatasvir Treatment Groups As of 01-Apr-2014

Subject PID/ ^a (Age/Gender/Race)	Study Subject or Female Partner (Age/Race)	Subject Treatment Assignment	Dates of Study Therapy	Approximate Date of Conception	Outcome
A1452017-163-171 (25/Male/Japanese)	Female Partner (27/Asian)	Blinded: DCV 60 mg QD or Placebo/ Blinded: pegIFNλ/RBV or pegIFNα/RBV	12-Dec-2012 - 03-Mar-2013	23-Jun-2013	Pregnancy ongoing (estimated date of delivery Apr-2014)

Note: New, updated data as of 01-Apr-2014, and since the DCV SCS (01-Aug-2013) are denoted with bold italicized font.

^a As of 01-Apr-2014, there was one additional report of a pregnancy for a female partner of a patient who received DCV/pegIFNα/RBV in a non-BMS-sponsored study. At the time of this report, no further information is available for this case.

^b Conception occurred approximately 11 months after last dose of DCV/Peg/RBV.

Abbreviations: ASV - asunaprevir, BID - twice daily, DCV - daclatasvir, pegIFNα/RBV - pegylated interferon alfa + ribavirin, pegIFNλ/RBV - pegylated interferon lambda + ribavirin; PID - patient identification number, Q12 - every twelve hours, QD - once daily

Source: BMS internal safety database as of 01-Apr-2014

Source: DCV Safety Update Report – Appendix 1

Pregnancies in the Overall ASV Safety Database

Overall, a total of 13 pregnancies of study subjects or female partners were reported in the total ASV safety database for the NDA. The following table provides a summary of the available data. Of note, 2 spontaneous abortions were reported. The ASV Safety Update Report included one additional study subject with pregnancy from an ongoing clinical trial of DCV/ASV and BMS-791325 (an investigational non-nucleoside NS5B inhibitor); the outcome for the pregnancy is unknown at the time of the database cut point (April 1, 2014).

Table 31: Pregnancies in the Overall ASV Safety Database

Appendix 1: Updated Summary of Pregnancies in Study Subjects or Female Partners of Study Subjects in Studies with Any Asunaprevir Treatment Groups As of 01-Apr-2014

Subject PID/ (Age/Gender/Race)	Study Subject or Female Partner (Age/Race)	Subject Treatment Assignment	Dates of Study Therapy	Approximate Date of Conception	Outcome
AI447007-1-14 (31/Male/Other)	Female Partner (25/White)	ASV 600 mg Q12 hr/ Midazolam 5 mg (2 doses)	24-Feb-2009 - 03-Mar-2009	May-2009	Estimated date of delivery 22-Jan 2010 (Subject lost to follow up)
AI447016-15-10014 (39/Female/White)	Study Subject	Placebo/pegIFN α /RBV	Never treated	Unknown	Unknown
AI447016-15-10022 (47/Male/White)	Female Partner (41/Unknown)	Placebo/pegIFN α /RBV	18-Mar-2010 - 16-Feb-2011	10-Mar-2010	Healthy male infant delivered (b) (6)
AI447016-30-20087 (32/Male/White)	Female Partner (27/White)	ASV 200 mg BID/ pegIFN α /RBV	14-Feb-2011 - 01-Aug-2011	21-Apr-2011	Spontaneous abortion Week 9 (16-Jun-2011)
AI447028-29-80369 (26/Male/White)	Female Partner (Unknown/Unknown)	DCV 60 mg QD/ ASV 100 mg BID	25-Sep-2012 - 14-Mar-2013	18-Mar-2013	Healthy male infant delivered at Week 41 (27-Dec-2013)
AI447029-45-90368 (42/Female/White)	Study Subject	DCV 60 mg QD/ ASV 100 mg BID/ pegIFN α /RBV	18-Oct-2012 - 04-Apr-2013	28-May-2013	Elective termination at unknown Week (29-Jun-2013)
AI447030-1-20002 (26/Male/White)	Female Partner (Unknown/Unknown)	ASV 100 mg and 200 mg softgel capsule (1 dose) ASV 100 mg BID (9 days + 1 dose)	25-Apr-2012 - 14-May-2012	15-Jul-2012	Not provided
AI447031-23-10166 (46/Male/Japanese)	Female Partner (29/Asian)	DCV 60 mg QD/ ASV 100 mg BID	12-Feb-2013 - 28-Jul-2013	Not provided	Not provided
AI447031-36-10252 (26/Female/Japanese)	Study Subject	DCV 60 mg QD/ ASV 100 mg BID	13-Mar-2013 - 30-Jul-2013	14-Jul-2013	Not provided
AI447034-1-3 (20/Female/Asian)	Study Subject	ASV or placebo 100 mg QD (1 dose) followed by ASV or placebo 100 mg BID (14 days)	3-Sep-2013 - 11- Sep-2013	29-Aug-2013	Elective termination at Week 6 (23-Sep-2013)

Appendix 1: Updated Summary of Pregnancies in Study Subjects or Female Partners of Study Subjects in Studies with Any Asunaprevir Treatment Groups As of 01-Apr-2014

Subject PID/ (Age/Gender/Race)	Study Subject or Female Partner (Age/Race)	Subject Treatment Assignment	Dates of Study Therapy	Approximate Date of Conception	Outcome
AI443014-3-74 (46/Male/White)	Female Partner (34/White)	DCV 60 mg QD/ ASV 200 mg/BID/ BMS-791325 75 mg BID	26-Jan-2012 - 19-Apr-2012	Mar-2012	Healthy female infant delivered at Week 39 (5-Dec-2012)
AI443014-20-552 (29/Male/White)	Female Partner (22/White)	DCV 30 mg/BID/ ASV 200 mg/BID/ BMS-791325 150 mg BID	12-Mar-2013 - 03-Jun-2013	21-Jul-2013	Spontaneous abortion Week 6 (2-Sep-2013)
AI443014-29-342 (56/Male/White)	Female Partner (Unknown/Unknown)	DCV 30 mg BID/ ASV 200 mg/BID/ BMS-791325 75 mg BID	5-Feb-2013 - 28-Apr-2013	Unknown	Healthy female infant delivered at unknown week (27-Jan-2014)
AI443102-31-270 (31/Female/White)	Study Subject	DCV 30 mg BID/ ASV 200 mg BID/ BMS-791325 75 mg BID	24-Jan-2014- 7-Mar-2014	15-Feb-2014	Unknown

Note: New, updated data as of 01-Apr-2014, and since the ASV SCS (16-Dec-2013) are denoted with bold italicized font.

Abbreviations: ASV - asunaprevir, BID - twice daily, DCV - daclatasvir, pegIFN α /RBV - pegylated interferon alfa + ribavirin, PID - patient identification number, Q12 - every twelve hours, QD - once daily

Source: BMS internal safety database as of 01-Apr-2014

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and efficacy of DCV and/or ASV have not been established in the pediatric population.



Pediatric Study Plans for DCV and ASV



7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Experience regarding the effects of DCV and/or ASV overdose in humans is limited. Events typically represented inadvertent single extra doses of study medication and did not result in clinical symptoms or require treatment intervention.

The potential for drug abuse, withdrawal or rebound for DCV/ASV, DCV/SOF, DCV/ASV/pegIFN/RBV, DCV/pegIFN/RBV or ASV/pegIFN/RBV therapy was not studied. Risk for abuse or dependent potential or withdrawal or rebound is not anticipated.

7.7 Additional Submissions / Safety Issues

The Sponsor submitted a 2 month safety update reports (SUR) for both NDAs including safety data from all ongoing clinical trials. Predominantly, trials were in the follow up periods where subjects were no longer receiving DCV or ASV or control therapy. No additional safety issues were identified in the review of the SUR which have not already been discussed in the preceding text.

8 Postmarket Experience

DCV and ASV were approved in Japan on July 7, 2014, which was during this review cycle. Additionally, CHMP on June 27, 2014, recommended granting a marketing authorization for daclatasvir in combination with other medicines for the treatment of chronic hepatitis C virus infection in adults. Data in support of asunaprevir was not submitted to CHMP. As such, there is minimal postmarketing experience at this time for either DCV or ASV.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Labeling negotiations are ongoing. Below are general clinical recommendations for proposed labeling. Major labeling recommendations or changes will be further summarized in the clinical review addendum as warranted.



Clinical Review
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NDA 206-843 and NDA 206-844
Daklinza (daclatasvir) and (b) (4) (asunaprevir)

(b) (4)



Clinical Review
Wendy Carter, D.O.
NDA 206-843 and NDA 206-844
Daklinza (daclatasvir) and (b) (4) (asunaprevir)

(b) (4)

9.3 Advisory Committee Meeting

(b) (4)

Appendix A

Clinical Investigator Financial Disclosure Review Template

Application Number: 206843

Submission Date(s): 3/31/2014

Applicant: Bristol Myers Squibb Company

Product: Daclatasvir

Reviewer: Wendy Carter, D.O.

Date of Review: May 1, 2014

Covered Clinical Study (Name and/or Number): (b) (4)
AI444010, (b) (4)
AI444011, AI444012, AI444013, AI444014, (b) (4)
AI444040, (b) (4) AI444046, (b) (4)
AI447026, AI447028, AI447029, (b) (4)

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>3,580 unique individuals served as either PIs or Sub-Is in the covered studies</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>5</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>1; This investigator received \$1,600.00 in compensation on a BMS Advisory Board and while this amount</u>		

<p>does not exceed the 25,000 category, it was reported due to his institutions (b) (6) requirement that any interaction regardless of compensation amount be recorded.</p> <p>Significant payments of other sorts: 0</p> <p>Proprietary interest in the product tested held by investigator: 0</p> <p>Significant equity interest held by investigator in sponsor of covered study: 0</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

BMS has adequately disclosed financial interests/arrangements with clinical investigators in accordance with 21CFR Part 54. The Applicant provided certification (Form 3454) which indicates that the vast majority of investigators and sub-investigators who participated in BMS studies had no financial arrangements with the Applicant. There were a very small number of BMS employees (5; 1 as a Principal Investigator and 4 as sub-Investigators) who participated in phase 1 studies at a BMS Clinical Pharmacology Unit prior to it being closed and only 1 investigator with disclosable financial information; however, the financial amount was \$1,600 which does not exceed the 25,000 category, and it was reported due to his institution's (b) (6) requirement that any interaction regardless of compensation amount be recorded. Based on the low proportion of investigators with a financial interest and the objective nature of the pivotal and supportive trial designs (randomized and placebo controlled or open label with central laboratory HCV RNA PCR based efficacy endpoints), the likelihood that trial results were substantively biased based on financial interest is minimal.

Clinical Review
 Wendy Carter, D.O.
 NDA 206-843 and NDA 206-844
 Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Clinical Investigator Financial Disclosure
 Review Template

Application Number: 206844
 Submission Date(s): 3/31/2014
 Applicant: Bristol Myers Squibb Company
 Product: Asunaprevir

Reviewer: Wendy Carter, D.O.

Date of Review: May 1, 2014

Covered Clinical Study (Name and/or Number): (b) (4), AI444014, AI444026, AI444046, (b) (4), AI447026, AI447027, AI447028, AI447029, (b) (4), AI447040, and AI447043.

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>2,165</u> unique individuals served as either PI's or Sub-I's in the covered studies		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>5</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request details from applicant)- Not applicable as no investigators other than the 5 BMS employees were

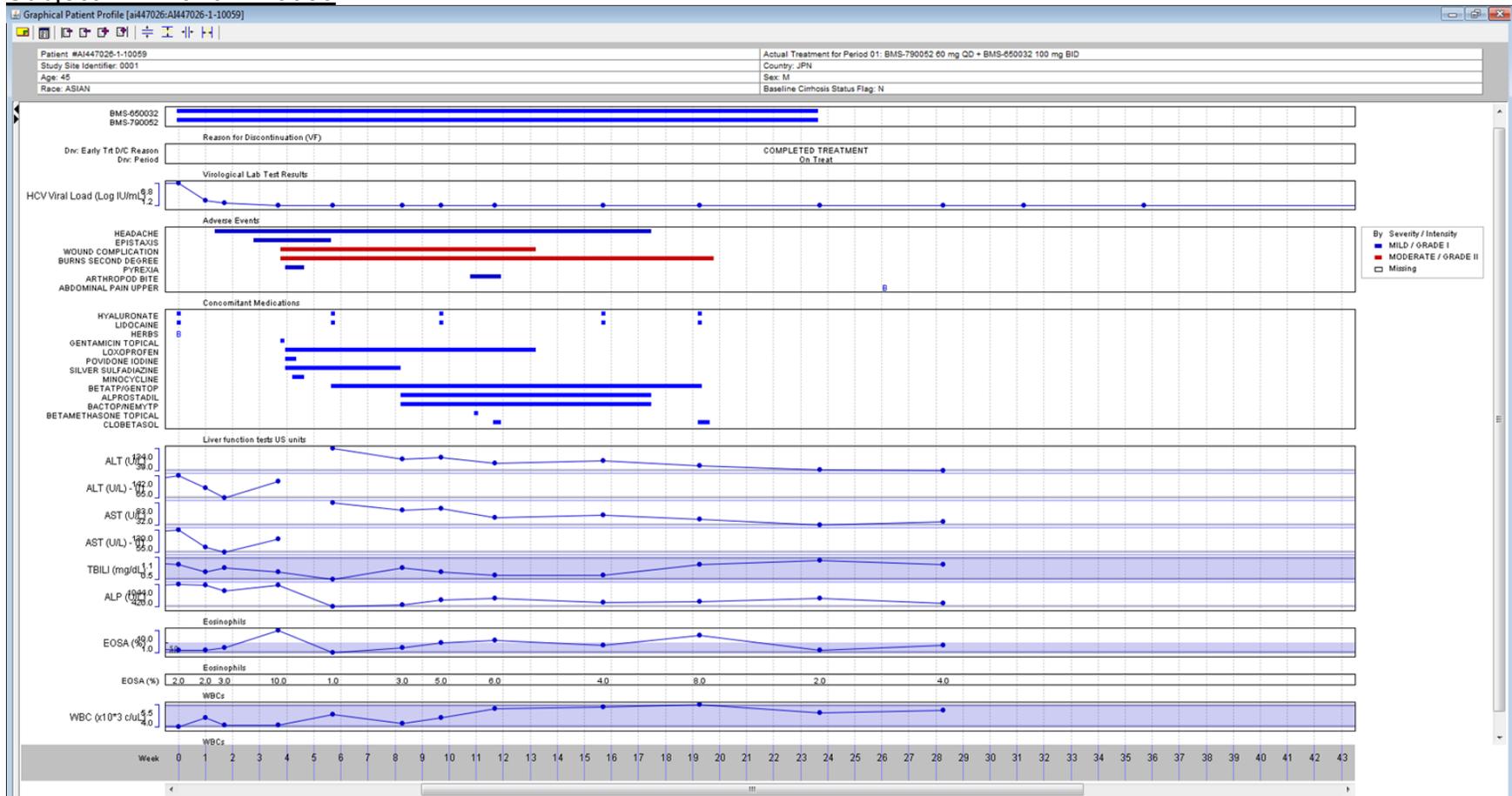
Clinical Review
 Wendy Carter, D.O.
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		identified with disclosable financial interests
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request information from applicant)- Not applicable as no investigators other than the 5 BMS employees were identified with disclosable financial interests
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>1</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

BMS has adequately disclosed financial interests/arrangements with clinical investigators in accordance with 21CFR Part 54. The Applicant provided certification (Form 3454) which indicates that the vast majority of investigators and sub-investigators who participated in BMS studies had no financial arrangements with the Applicant. There were a very small number of BMS employees (5; 1 as a Principal Investigator and 4 as sub-Investigators) who participated in phase 1 studies at a BMS Clinical Pharmacology Unit prior to it being closed and no investigators with disclosable financial information. Based on the low proportion of investigators with a financial interest and the objective nature of the pivotal and supportive trial designs (randomized and placebo controlled or open label with central laboratory HCV RNA PCR based efficacy endpoints), the likelihood that trial results were substantively biased based on financial interest is minimal.

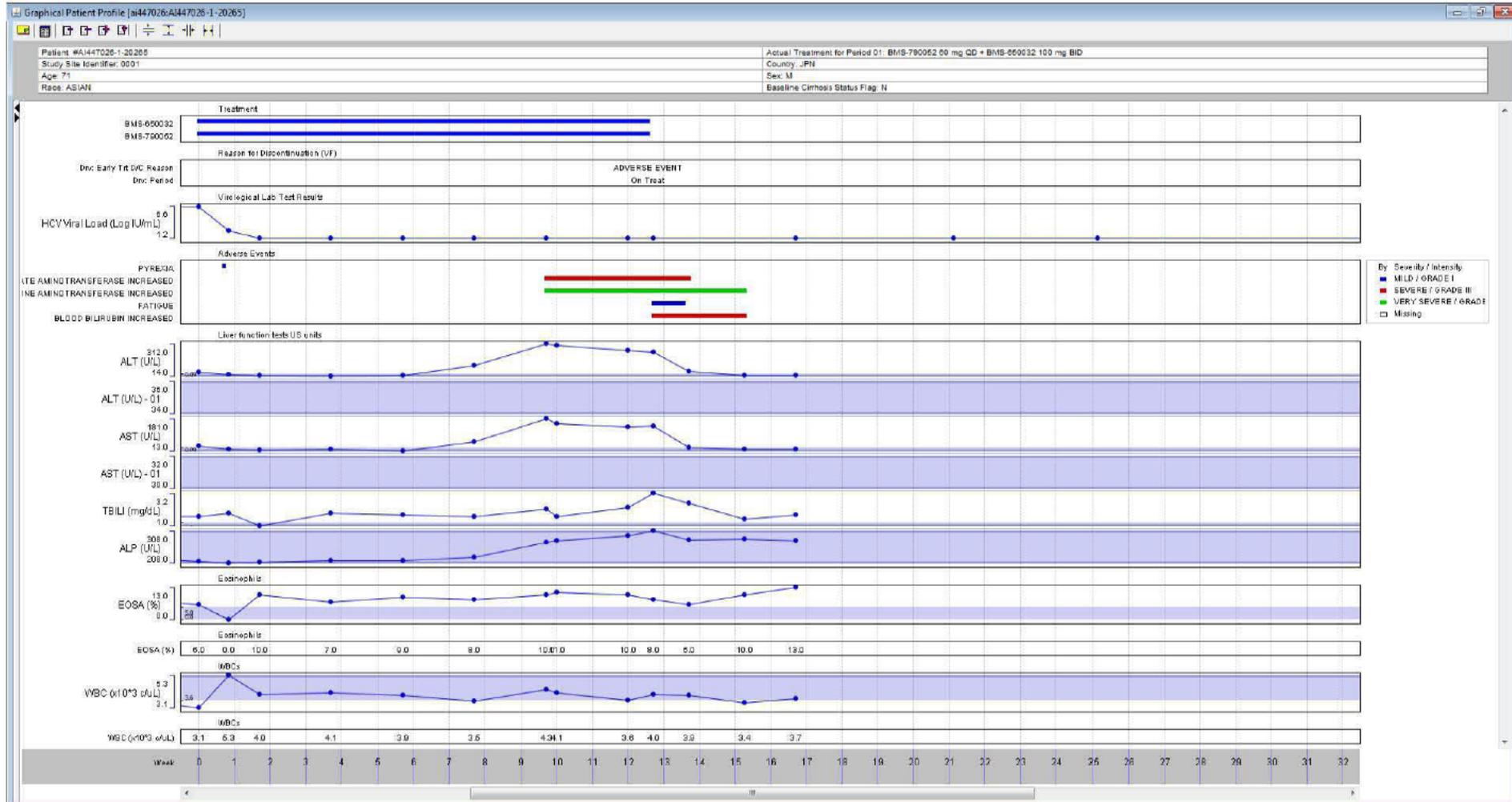
Appendix B: 16 Subjects with Pyrexia and Eosinophilia Within 2 Weeks – Phase 3

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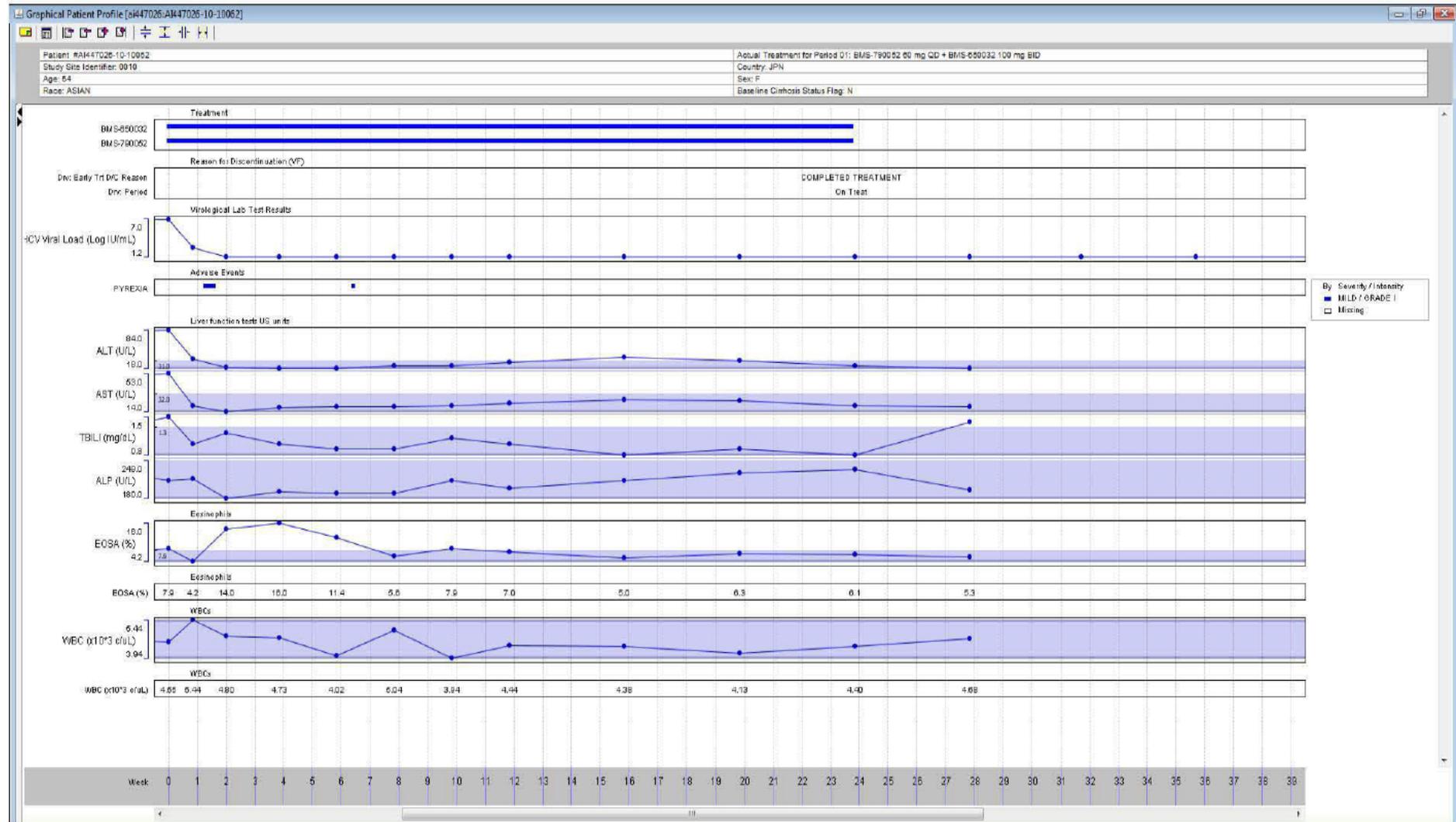
Clinical Review
 Wendy Carter, D.O.
 NDA 206-843 and NDA 206-844
 Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Subject AI447026-1-20265



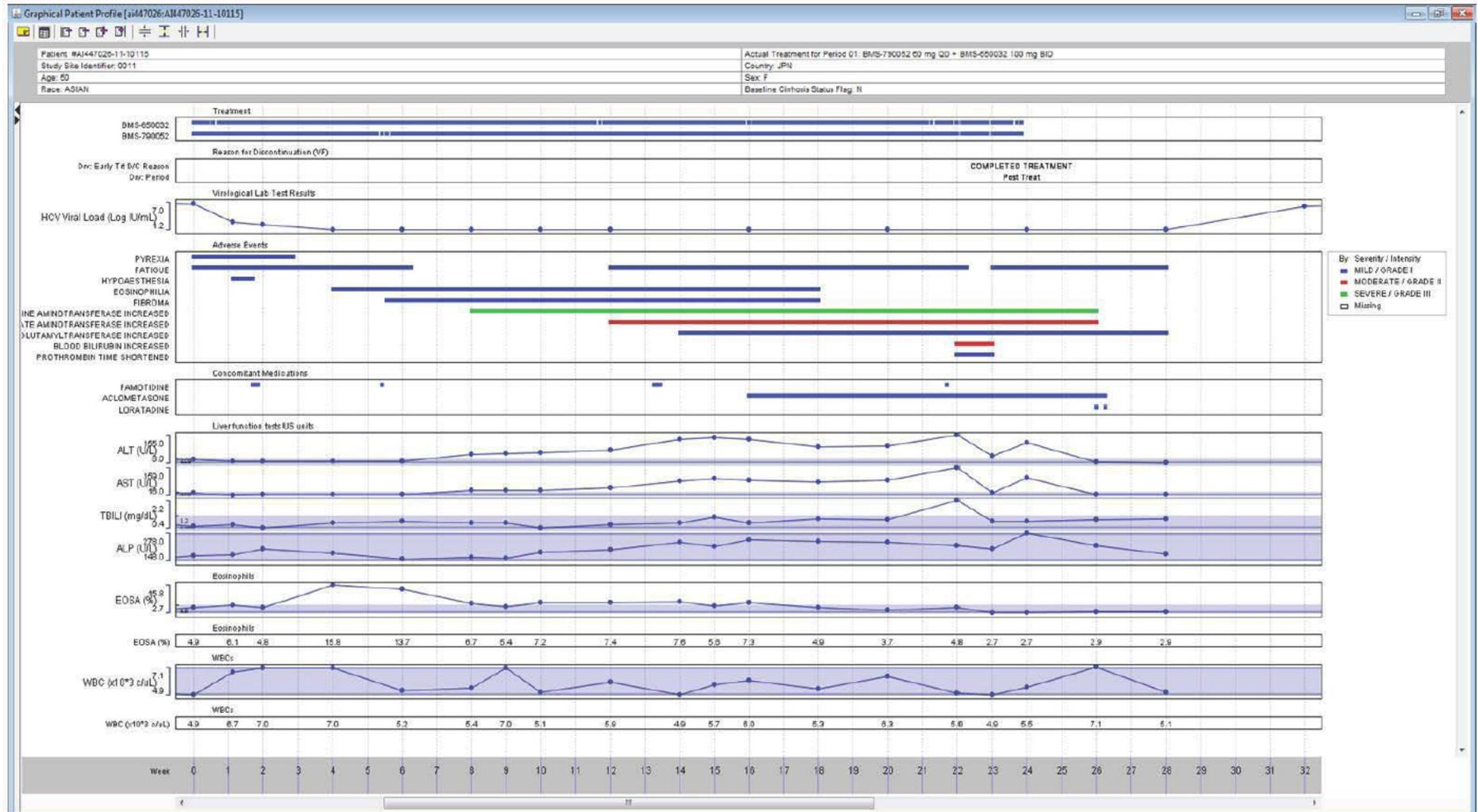
Clinical Review
 Wendy Carter, D.O.
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 Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Subject AI447026-10-10062



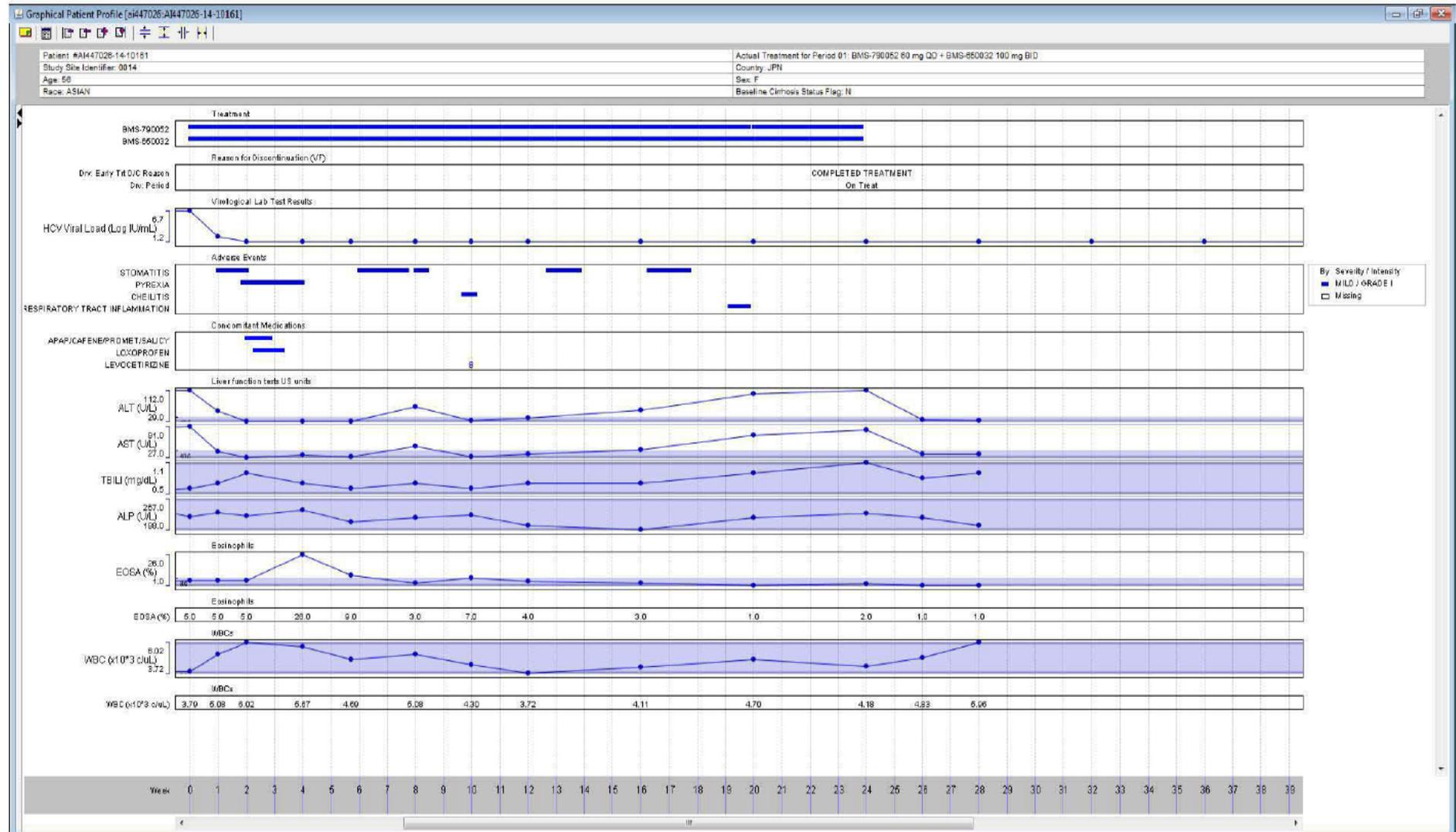
Clinical Review
 Wendy Carter, D.O.
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 Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Subject A1447026-11-10115



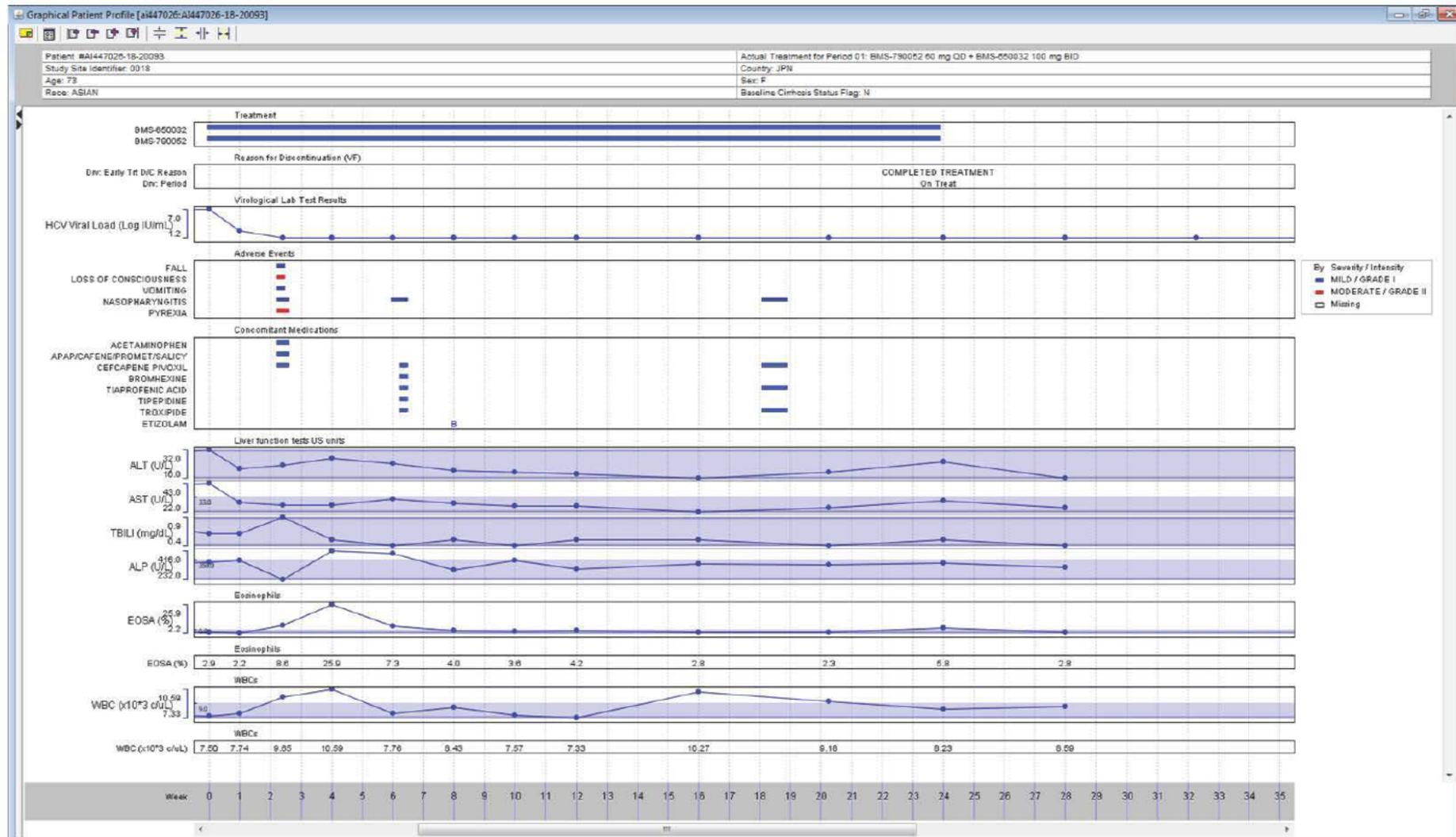
Clinical Review
 Wendy Carter, D.O.
 NDA 206-843 and NDA 206-844
 Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Subject AI447026-14-10161



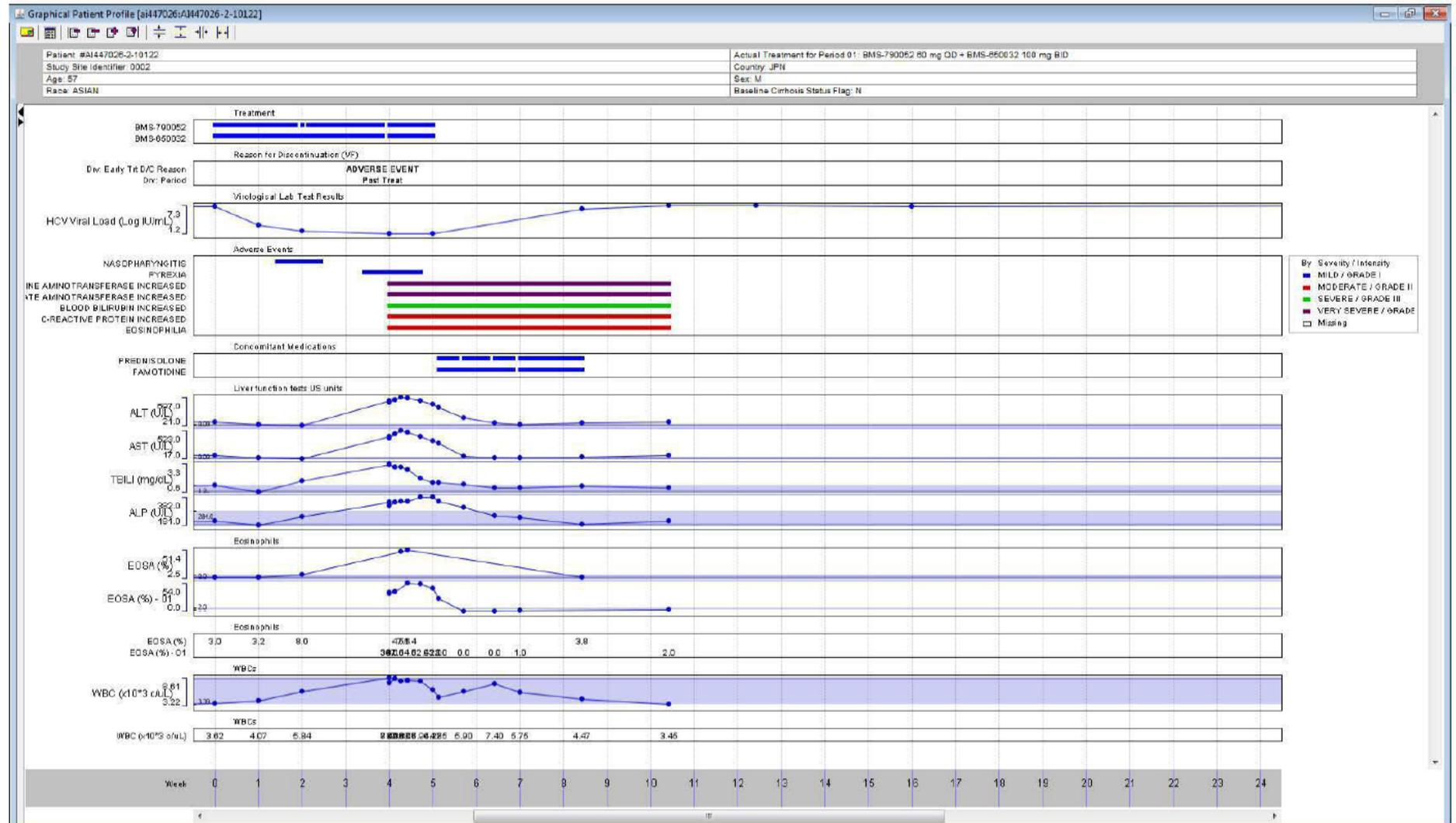
Clinical Review
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 Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Subject AI447026-18-200093



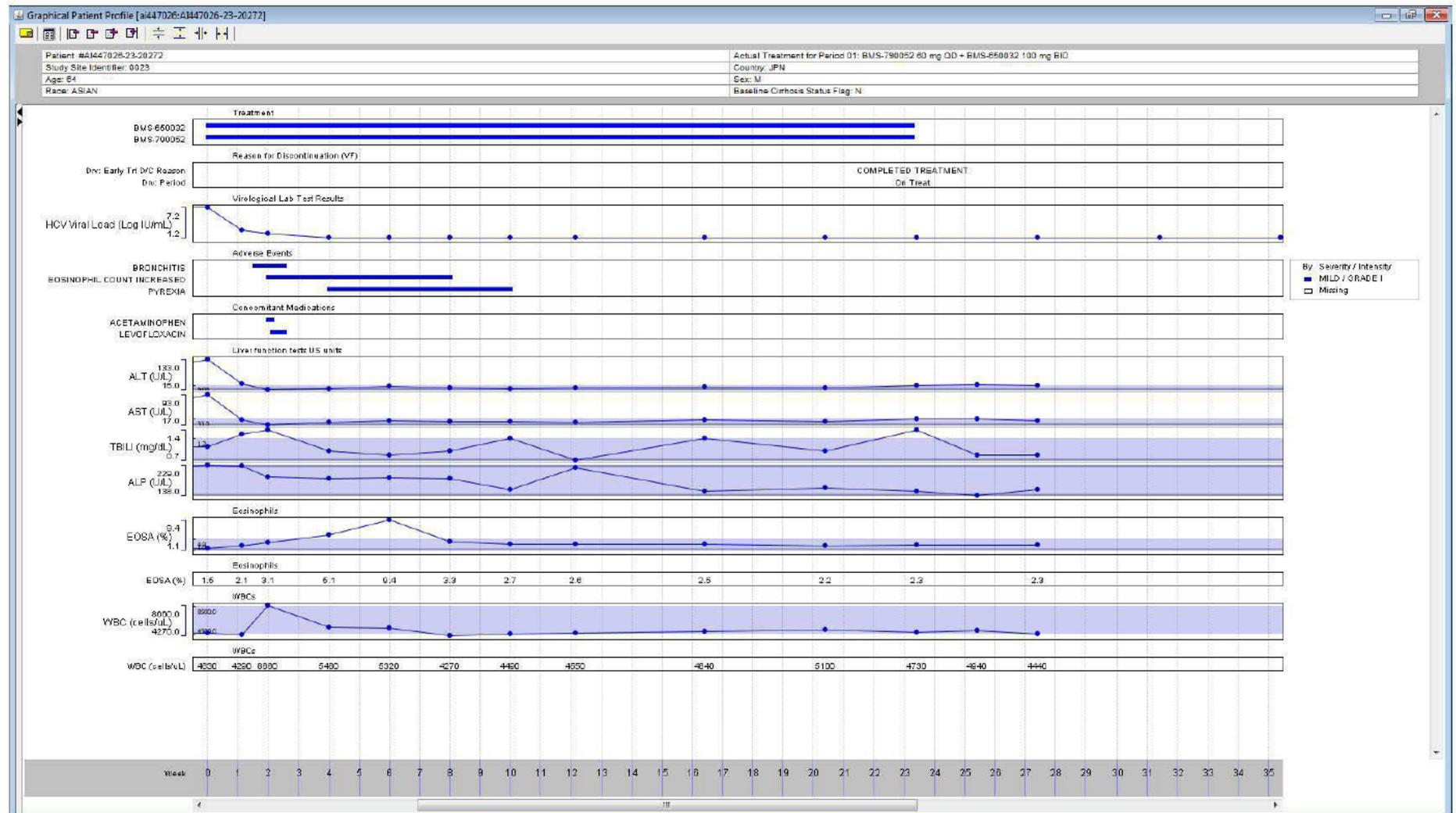
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 NDA 206-843 and NDA 206-844
 Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Subject A1447026-2-10122



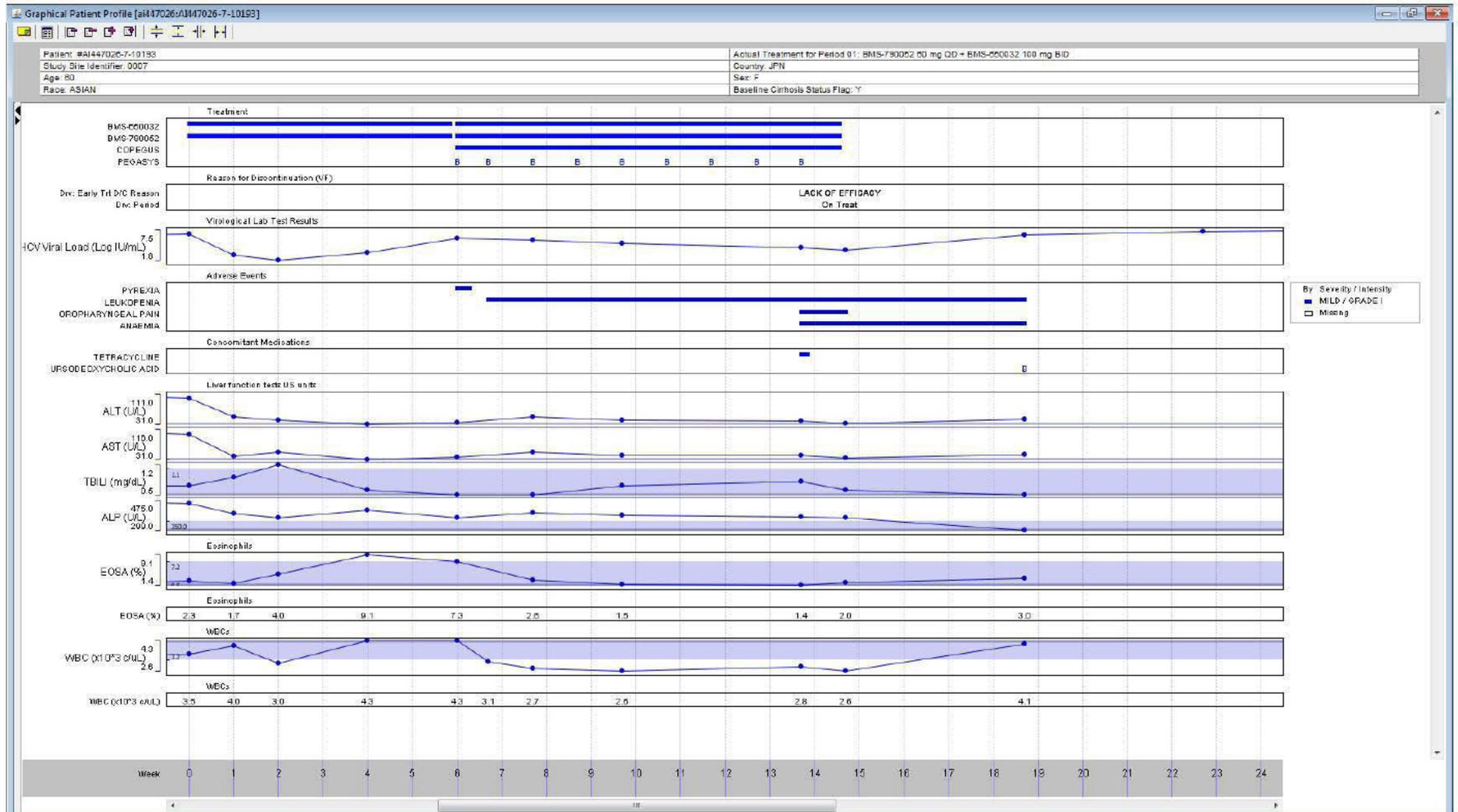
Clinical Review
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 NDA 206-843 and NDA 206-844
 Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Subject AI447026-23-20272



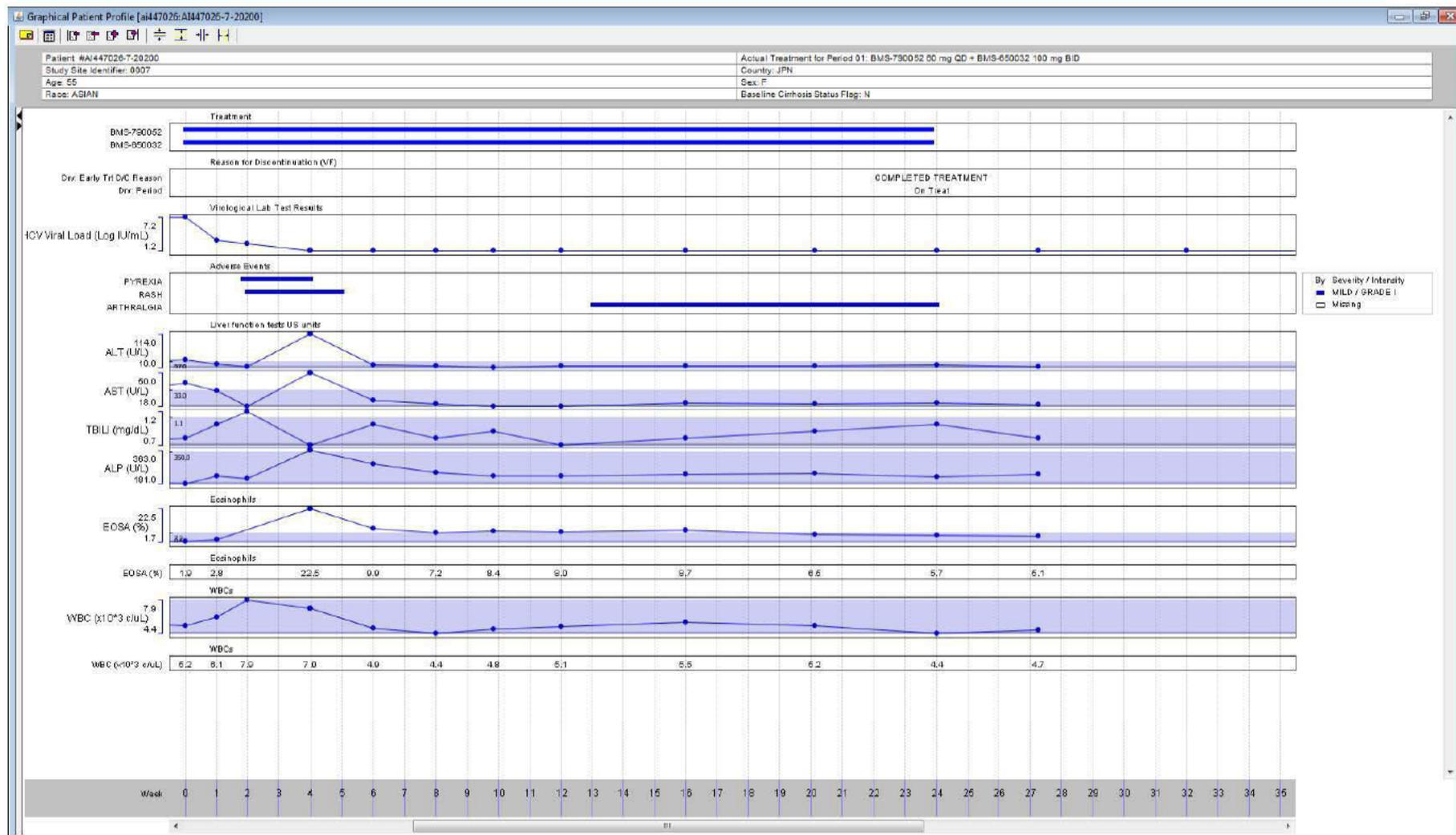
Clinical Review
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 NDA 206-843 and NDA 206-844
 Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Subject A1447026-7-10193



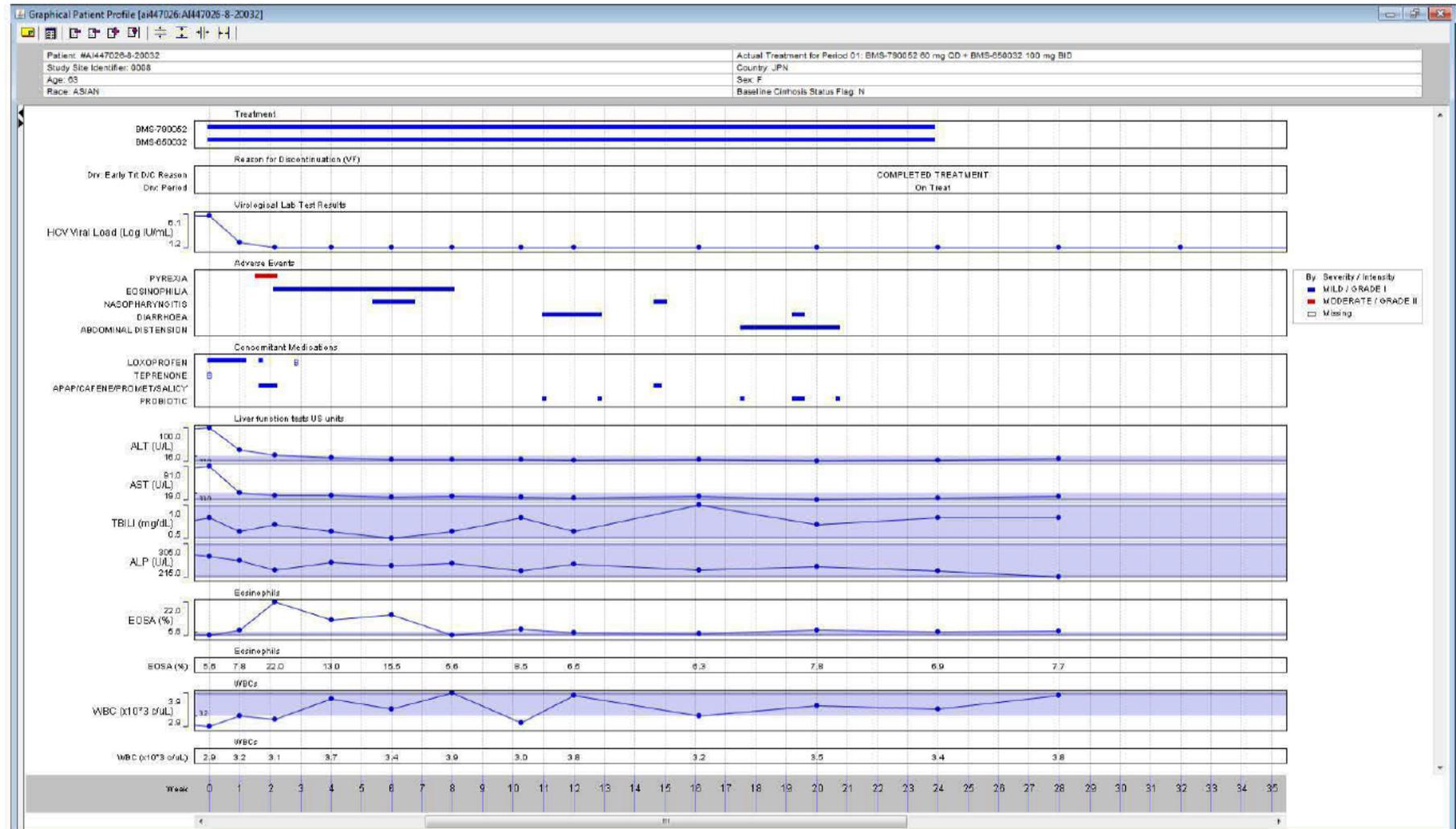
Clinical Review
 Wendy Carter, D.O.
 NDA 206-843 and NDA 206-844
 Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Subject AI447026-7-20200



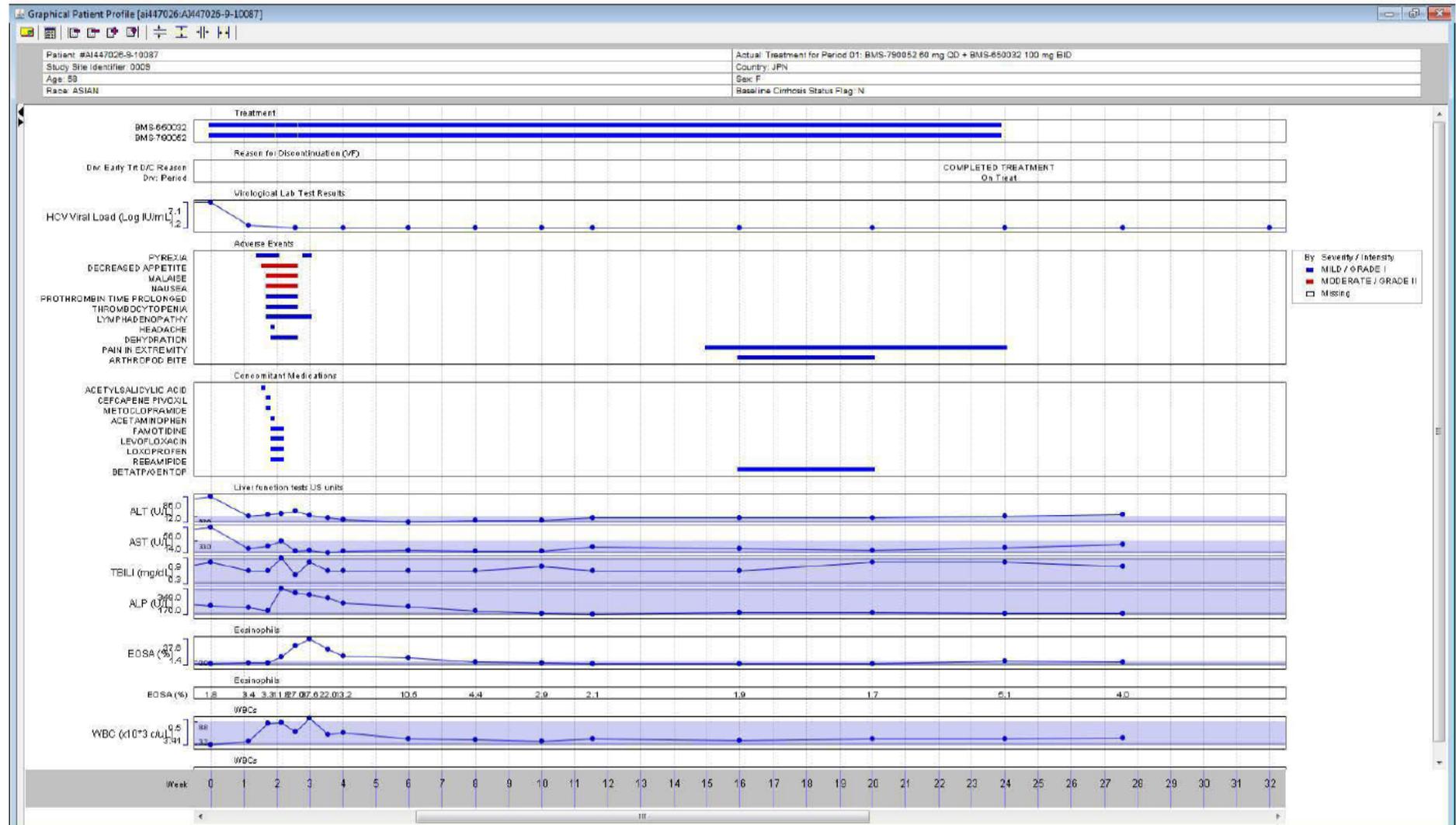
Clinical Review
 Wendy Carter, D.O.
 NDA 206-843 and NDA 206-844
 Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Subject AI447026-8-20032



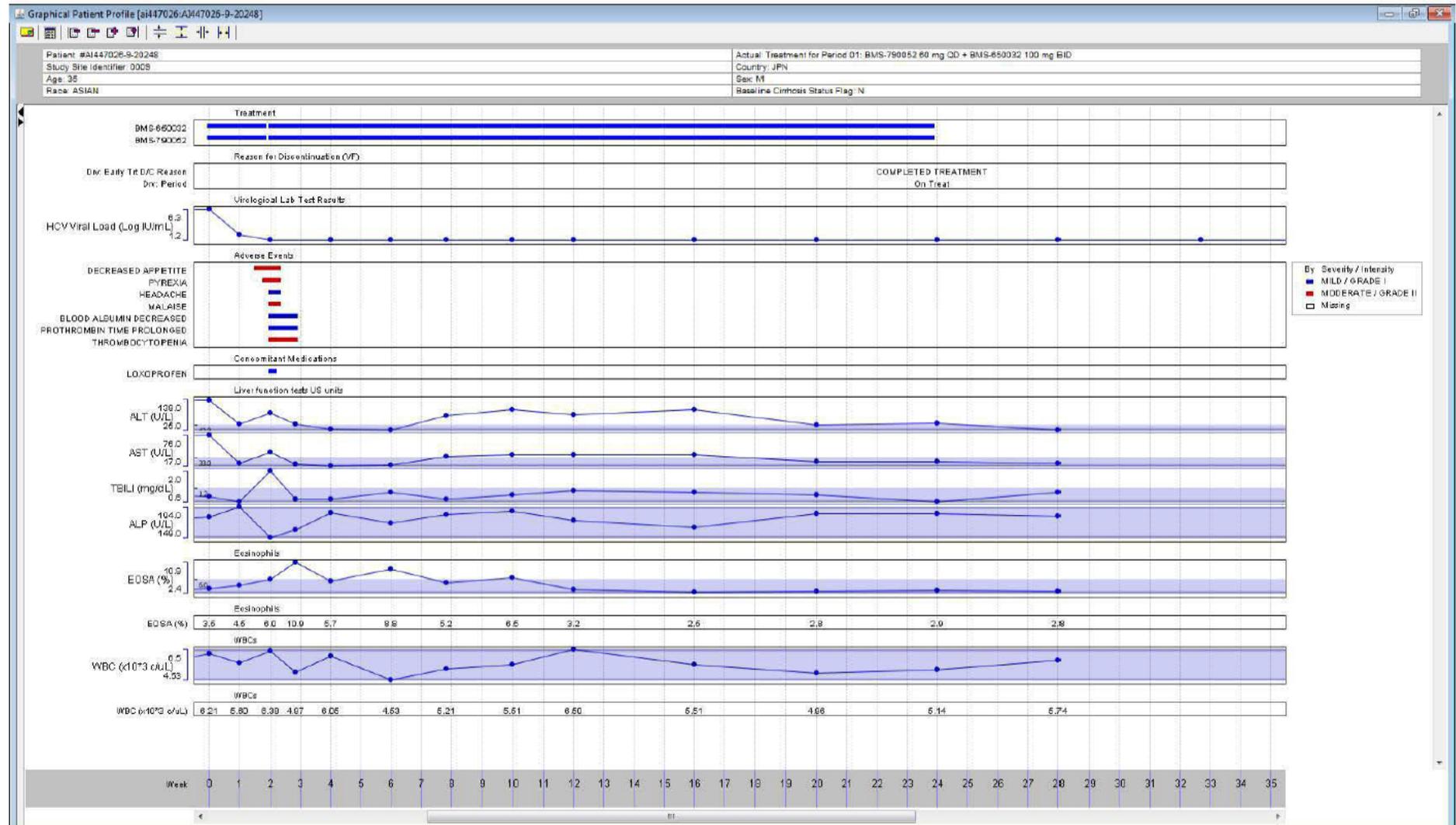
Clinical Review
 Wendy Carter, D.O.
 NDA 206-843 and NDA 206-844
 Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Subject AI447026-9-10087



Clinical Review
 Wendy Carter, D.O.
 NDA 206-843 and NDA 206-844
 Daklinza (daclatasvir) and (b) (4) (asunaprevir)

Subject AI447026-9-20248



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/s/

WENDY W CARTER
08/29/2014

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