

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208261Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review Addendum

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|--|---|
| <b>Date</b>  | January 19, 2015  |
| <b>From</b>  | Adam Sherwat  |
| <b>Subject</b>   | Cross-Discipline Team Leader (CDTL) Review Addendum                       |
| <b>NDA/BLA #</b>   | NDA 208261  |
| <b>Supplement#</b>   |   |
| <b>Applicant</b>   | Merck Sharp & Dohme Corp.   |
| <b>Date of Submission</b>                                      | May 28, 2015  |
| <b>PDUFA Goal Date</b>   | January 28, 2015  |
| <b>Proprietary Name / Non-Proprietary Name</b>                 | Zepatier [Elbasvir (EBR) and Grazoprevir (GZR)]/ MK-5172 and MK-8742      |
| <b>Dosage form(s) / Strength(s)</b>                            | Fixed Dose Combination Tablet 50 mg EBR /100 mg GZR                       |
| <b>Applicant Proposed Indication(s)/Population(s)</b>          | Treatment of chronic hepatitis C genotypes 1, 4, or 6 infection in adults |
| <b>Recommendation on Regulatory Action</b>                     | Approval  |
| <b>Recommended Indication(s)/Population(s) (if applicable)</b> | Treatment of chronic hepatitis C genotypes 1 and 4 infection in adults    |

## Addendum

The intent of this addendum is to briefly discuss the Division's evolution of thought with respect to dosing recommendations for Zepatier-based regimens in GT1a infected patients with key NS5A baseline polymorphisms (defined as polymorphisms at amino acid positions 28, 30, 31, or 93). The reader is directed to the full CDTL review dated 21 December 2016 (and the primary reviews referenced therein) for a complete discussion of the impact of NS5A polymorphisms on clinical efficacy.

The Agency's analyses demonstrated that both treatment-naïve and pegylated interferon/ribavirin-treatment experienced patients who were infected with HCV genotype 1a virus with any key NS5A polymorphism(s) at baseline were significantly less likely to benefit from a 12 week course of Zepatier than subjects infected with HCV genotype 1a virus without key NS5A polymorphisms. Based on the available data from Trial 068 in pegylated interferon/ribavirin-treatment experienced subjects, it appeared that extending

treatment duration to 16 weeks together with the addition of ribavirin (RBV) might overcome the impact of baseline NS5A polymorphisms in HCV GT1a-infected subjects. Specifically, 6/6 GT1a-infected subjects with key baseline NS5A polymorphisms achieved SVR12 after receiving a 16 week regimen of Zepatier + RBV. The specific NS5A polymorphisms observed in these six subjects (including two subjects with cirrhosis) included M28V (n=2), Q30H (n=1), L31M (n=2), or Y93C/H (n=1 each); one subject had two key NS5A resistance-associated polymorphisms (Q30H+Y93H). Secondary support for efficacy with this regimen was based on the absence of reported virologic failure in any of 106 subjects receiving Zepatier + RBV for 16 weeks in Trial 068. It was also notable that the vast majority of virologic failures in the other arms of Trial 068 were relapsers with only one breakthrough reported; therefore, it seemed probable that extending the duration of Zepatier and adding RBV might be beneficial. Furthermore, the Division had examples from other development programs of improvement in efficacy in difficult-to-treat populations related to extending direct acting antiviral treatment duration and/or the addition of RBV.

Based on these data and with my full concurrence, the primary review team presented the following treatment algorithm for GT1a patients to the Sponsor at the Post-Midcycle Meeting on 10 September 2015:

1. Recommend in the product label that all genotype 1a-infected patients are screened for key NS5A resistance-associated polymorphisms prior to initiation of therapy using commercially available assays.
2. GT1a-infected patients without key NS5A polymorphisms will receive Zepatier for 12 weeks.
3. GT1a-infected patients with key NS5A polymorphisms will have one of two options:
  - a. Receive Zepatier + RBV for 16 weeks OR
  - b. Consider alternative treatment options

My view and that of the primary reviewers was that this algorithm would serve to maximize SVR rates for GT1a-infected patients. Our intent was to issue a Post-Marketing Requirement (PMR) for a clinical trial that would confirm the efficacy of a Zepatier regimen of at least 16 weeks in duration combined with RBV in GT1a-infected patients with one or more key baseline NS5A polymorphisms.

However, based on a series of internal discussions, it was determined that the available data were insufficient to support a dosing recommendation in the label

for GT1a-infected patients with any key baseline NS5A polymorphisms. The primary concern was that the available SVR data, although encouraging, were limited in size and therefore might not accurately reflect the actual efficacy of a treatment regimen consisting of 16 weeks of Zepatier + RBV in this patient population. The Division's position was formally conveyed to the Sponsor in the form of our Late Cycle Communication sent on 6 November 2015. However, during the course of the review cycle, it became increasingly clear that the lack of clear guidance in the product label for the management of GT1a-infected patients with key baseline NS5A polymorphisms could lead to suboptimal treatment of some patients by HCV care providers.

The Division concluded that it was imperative to provide clear direction in the product label for the management of GT1a-infected patients both with and without key baseline NS5A polymorphisms. As such, the Division was willing to leverage the available data (including confirmatory SVR24 results from all subjects with NS5A polymorphisms) from Clinical Trial 068 to support a dosing recommendation of Zepatier + RBV for 16 weeks in GT1a-infected patients with key baseline NS5A polymorphisms. This decision was contingent on the provision of confirmatory data in this patient population in the form of a PMR.

The Sponsor was made aware of this change in our position on 8 January 2016. The Sponsor subsequently agreed to the Division's proposed labeling addressing this issue and formally agreed to conduct a PMR with an accelerated timeline to provide confirmation of our current dosing recommendations for this population.

The agreed upon, key revised labeling in Sections 2 and 12.4 is as follows:

## **Section 2.1 Testing Prior to the Initiation of Therapy**

### NS5A Resistance Testing in HCV Genotype 1a-Infected Patients

Testing patients with HCV genotype 1a infection for the presence of virus with NS5A resistance-associated polymorphisms is recommended prior to initiation of treatment with ZEPATIER to determine dosage regimen and duration [*see Dosage and Administration (2.2)*], *Table 1*. In subjects receiving ZEPATIER for 12 weeks, sustained virologic response (SVR12) rates were lower in genotype 1a-infected patients with one or more baseline NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93 [*see Microbiology (12.4)*], *Table 11*.

## Section 2.2 Recommended Dosage in Adults

**Table 1: Recommended Dosage Regimens and Durations for ZEPATIER for Treatment of HCV Genotype 1 or 4 in Patients with or without Cirrhosis**

| Patient Population  | Treatment                   | Duration |
|---|-----------------------------|----------|
| Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* <u>without</u> baseline NS5A polymorphisms <sup>†</sup> | ZEPATIER                    | 12 weeks |
| Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* <u>with</u> baseline NS5A polymorphisms <sup>†</sup>    | ZEPATIER + RBV <sup>‡</sup> | 16 weeks |
| Genotype 1b: Treatment-naïve or PegIFN/RBV-experienced*   | ZEPATIER                    | 12 weeks |
| Genotype 1a <sup>§</sup> or 1b: PegIFN/RBV/PI-experienced <sup>¶</sup>  | ZEPATIER + RBV <sup>‡</sup> | 12 weeks |
| Genotype 4: Treatment-Naïve   | ZEPATIER                    | 12 weeks |
| Genotype 4: PegIFN/RBV-experienced*   | ZEPATIER + RBV <sup>‡</sup> | 16 weeks |

\*Patients who have failed treatment with peginterferon alfa (PegIFN) + ribavirin (RBV).

<sup>†</sup>NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93. See section 2.1 Testing prior to the initiation of therapy, subsection NS5A resistance testing in HCV genotype 1a infected patients.

<sup>‡</sup>For patients with CrCl less than or equal to 50 mL per minute, including patients receiving hemodialysis, refer to the ribavirin tablet prescribing information for the correct ribavirin dosage.

<sup>§</sup>The optimal ZEPATIER-based treatment regimen and duration of therapy for PegIFN/RBV/PI-experienced genotype 1a-infected patients with one or more baseline NS5A resistance-associated polymorphisms at positions 28, 30, 31, and 93 has not been established.

<sup>¶</sup>Patients who have failed treatment with PegIFN + RBV + HCV NS3/4A protease inhibitor (PI): boceprevir, simeprevir, or telaprevir.

## Section 12.4 Microbiology

**Table 11: SVR12 in HCV Genotype 1a-Infected Subjects without or with baseline NS5A Polymorphisms**

| NS5A polymorphism status                                   | ZEPATIER 12 Weeks SVR12 % (n/N) | ZEPATIER + RBV 16 Weeks SVR12 % (n/N) |
|--|---------------------------------|---------------------------------------|
| Without baseline NS5A polymorphism (M28, Q30, L31 or Y93)  | 98% (441/450)                   | 100% (49/49)                          |
| With baseline NS5A polymorphism (M28*, Q30*, L31* or Y93*) | 70% (39/56)                     | 100% (6/6)                            |

\*Any change from GT1a reference.

The agreed upon PMR related to this issue is as follows:

Conduct a trial in hepatitis C virus genotype 1a infected subjects with at least one baseline NS5A polymorphism at amino acid position 28, 30, 31, or 93 to evaluate if treatment with elbasvir/grazoprevir and ribavirin for at least 16 weeks reduces the rate of virologic failure and the rate of treatment-emergent drug resistant viral populations. The trial should have adequate representation of

subjects with baseline NS5A polymorphisms that have been demonstrated to have the greatest impact on elbasvir/grazoprevir efficacy in clinical trials evaluating recommended regimens.

The Sponsor has agreed to submit a final report from this trial no later than 31 December 2018.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ADAM I SHERWAT  
01/19/2016

## Cross-Discipline Team Leader Review

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|---|---|
| <b>Date</b>   | December 20, 2015   |
| <b>From</b>   | Adam Sherwat  |
| <b>Subject</b>  | Cross-Discipline Team Leader (CDTL) Review                                |
| <b>NDA/BLA #</b>                                      | NDA 208261  |
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## 1. Benefit-Risk Assessment

I am in agreement with the Risk-Benefit Assessment as provided in the Clinical Review by Dr. Sarita Boyd and Dr. Prabha Viswanathan; therefore this section closely mirrors that found in the Clinical Review with the exception of relatively minor revisions that do not substantively impact the overall risk-benefit assessment.

### Benefit-Risk Summary and Assessment

Elbasvir (EBR) is a hepatitis C virus (HCV) NS5A inhibitor and Grazoprevir (GZR) is an HCV NS3/4A protease inhibitor. EBR/GZR is a fixed-dose combination tablet with a proposed indication for treatment of chronic HCV genotypes (GTs) 1, 4, or 6 infection in adults. Intended subpopulations include treatment-naïve (TN) and treatment-experienced (TE) patients and patients with advanced chronic kidney disease (CKD), including those receiving hemodialysis.

HCV infection is a serious disease, affecting an estimated 3 million people in the U.S. and over 100 million people worldwide. Although often

asymptomatic in early stages, if untreated, chronic HCV can lead to debilitating and life-threatening liver problems, including hepatocellular carcinoma, liver failure, and death. The current standard of care treatments for HCV GT 1 infection consist of oral direct-acting antivirals (DAAs) that result in sustained virologic response determined 12 weeks after the end of treatment (SVR12; considered a virologic cure) in up to 93-99% of patients. During this NDA review cycle, two interferon (IFN) sparing regimens were approved for the treatment of patients with GT 4 infection with SVR12 rates of 93-100%. However, additional IFN-free treatment options would be beneficial for GT 1 and GT 4 infected patients, and a major treatment gap remains for HCV-infected CKD patients receiving dialysis as no IFN-sparing regimens are currently available for this patient population.

SVR12 rates for EBR/GZR were generally high, but varied depending on the regimen (i.e., duration of treatment, co-administration of RBV), patients' HCV GT, and patients' prior treatment history. Efficacy was similar in patients with or without cirrhosis, with or without HIV coinfection, and with or without CKD. EBR/GZR represents the first IFN-free regimen for treatment of HCV in CKD patients receiving hemodialysis. EBR/GZR is a highly effective RBV-free single tablet once daily treatment option for TN and PR-experienced patients with GT 1 infection and for TN patients with GT 4 infection. EBR/GZR with RBV is a highly effective option for PI/PR-experienced patients with GT 1 infection and PR-experienced patients with GT 4 infection. (b) (4)

Although overall SVR12 rates in the pivotal trials were high, results from GT 1 infected subjects with baseline NS5A polymorphisms were less than optimal. Post-hoc analyses revealed that removal of GT 1a TN and TE subjects who had baseline NS5A polymorphisms decreased the rate of virologic failure by 4-6%. Because these failures resulted in development of additional resistance-associated substitutions and limitation of future treatment options, avoiding EBR/GZR treatment in these patients is recommended. Therefore, baseline NS5A resistance testing should be considered for all GT 1a infected patients. Although increased EBR/GZR treatment duration (i.e. 16 or 18 weeks) and the addition of RBV together appear to overcome the effect of baseline NS5A polymorphisms, (b) (4) Treatment of all GT 1a patients with EBR/GZR and RBV for 16 weeks without screening for baseline NS5A polymorphisms is also not recommended because approximately 90% of these patients would be over-treated and the safety profile is suboptimal compared to 12 weeks of EBR/GZR without RBV. As the impact of baseline NS5A polymorphisms in GT 1b infected subjects was less profound as compared to GT 1a infected subjects, the Agency is not advocating for NS5A genotypic screening for the GT 1b infected patient population.

Late ALT elevation was the major safety issue identified in this review. Incidence was relatively low overall (0.8%) but higher (2-3%) in populations shown to have increased exposures, such as females, Asians, and the elderly (> 65 years of age). None were associated with clinical AEs, and all events completely resolved following cessation of treatment. Late ALT elevation events can be reasonably monitored and managed by hepatic laboratory testing prior to therapy, at scheduled intervals on treatment, and as clinically indicated. No other major safety issues related specifically to EBR/GZR were identified in this review. RBV is associated with common adverse reactions and serious risks, but these safety issues are well known and are not exacerbated by the addition of EBR/GZR based on available data.

Approval of EBR/GZR for treatment of adult patients with HCV GT 1 or 4 infection is fully supported by the available efficacy and safety data.

The following regimens, some of which differ from the Applicant’s proposal, are recommended based on thorough analyses of efficacy, safety, and virology data overall and in each subpopulation:

- (1) TN and PR-experienced GT 1a infected patients without baseline NS5A polymorphisms (12 weeks duration)
- (2) TN and PR-experienced GT 1b infected patients (12 weeks duration)
- (3) PI/PR-experienced GT 1 infected patients (12 weeks duration with RBV)
- (4) TN GT 4 infected patients (12 weeks duration)
- (5) PR-experienced GT 4 infected patients (16 weeks duration with RBV)
- (6) Advanced CKD patients including those on hemodialysis (same regimens as above)

| Dimension                                 | Evidence and Uncertainties  | Conclusions and Reasons  |
|---|---|--|
| <a href="#">Analysis of Condition</a>     | <ul style="list-style-type: none"> <li>• Chronic hepatitis C viral infection (HCV infection) causes inflammation of the liver that can lead to long-term health problems or death.</li> <li>• Globally it is estimated that over 100 million people are infected with HCV, including approximately 3 million people in the United States (U.S.).</li> <li>• The prevalence rate of HCV among patients undergoing hemodialysis has been reported as 7.8%, and it is estimated that over 60,000 HCV-infected patients will require HD by 2020.</li> <li>• There are at least six distinct HCV genotypes (GTs). Most common among U.S. patients is GT 1 (72%), followed by GT 2 (11%), GT 3 (9%), and GT 4 (6%). GTs 5 and 6 occur uncommonly (<math>\leq 1\%</math>) in the U.S. but may predominate in other parts of the world.</li> <li>• HCV infection is typically asymptomatic in its early stages. However, if left untreated, HCV infection can lead to cirrhosis, hepatocellular carcinoma, liver failure, and death. HCV infection is a leading cause of chronic liver disease in the U.S.</li> </ul> | <p>If untreated, chronic HCV infection is a life-threatening condition, one that affects a large population. Patients can experience symptoms that are severe and debilitating. HCV infection is a significant and growing public health concern.</p>              |
| <a href="#">Current Treatment Options</a> | <ul style="list-style-type: none"> <li>• The current standard of care treatments for HCV GT 1 infection consist of interferon (IFN) sparing all oral direct-acting antivirals (DAAs), including ledipasvir/sofosbuvir, paritaprevir/ombitasvir/ritonavir + dasabuvir (+/- ribavirin [RBV]), and simeprevir in combination with sofosbuvir.</li> <li>• DAAs can result in sustained virologic response determined 12 weeks after the end of treatment (SVR12), considered a virologic cure, in up to 93-99% of GT 1 infected patients depending on the regimen.</li> </ul>   | <p>The treatment armamentarium would benefit from new therapeutic options that are well tolerated and equally or more efficacious than current DAA IFN-free options.</p> <p>There is a specific unmet medical need for IFN-free regimens for patients with CKD</p> |

| Dimension             | Evidence and Uncertainties   | Conclusions and Reasons        |   |                |             |                |  |       |       |      |             |             |              |        |        |         |     |     |                |                 |  |  |       |       |      |  |  |  |  |  |
|-----------------------|--|--------------------------------|---|----------------|-------------|----------------|--|-------|-------|------|-------------|-------------|--------------|--------|--------|---------|-----|-----|----------------|-----------------|--|--|-------|-------|------|--|--|--|--|--|
|                       | <ul style="list-style-type: none"> <li>During this NDA review cycle, two IFN-free regimens were approved for the treatment of HCV GT4 infected patients. These included 1) ombitasvir/paritaprevir/ritonavir with RBV for patients without cirrhosis based on an SVR12 rate of 100% and; 2) ledipasvir/sofosbuvir for treatment-naïve or treatment experienced patients (defined as those who have failed a PR-based regimen with or without an HCV protease inhibitor), with or without cirrhosis based on an overall SVR rate of 93%.</li> <li>During this NDA review cycle, ledipasvir/sofosbuvir was approved for the treatment of HCV GT6 infected patients including treatment-naïve or treatment experienced patients (defined as those who have failed a PR-based regimen with or without an HCV protease inhibitor), with or without cirrhosis based on an overall SVR rate of 96%.</li> <li>No IFN-free treatment options are available for HCV infected patients receiving hemodialysis.</li> </ul>   | <p>receiving hemodialysis.</p> |   |                |             |                |  |       |       |      |             |             |              |        |        |         |     |     |                |                 |  |  |       |       |      |  |  |  |  |  |
| <p><u>Benefit</u></p> | <ul style="list-style-type: none"> <li>The efficacy of EBR/GZR was established in five clinical trials (three Phase 3, one Phase 2/3, and one Phase 2), with a total of 1155 HCV patients across all trials. The trials varied in terms of the treatment regimen, treatment duration, HCV GT, and prior treatment experience.</li> <li>The primary efficacy endpoint was SVR12, or virologic cure. As displayed in the tables below, SVR12 rates varied depending on the regimen, HCV GT, and prior treatment history.</li> </ul> <table border="1" data-bbox="325 1068 1346 1292"> <thead> <tr> <th rowspan="2">Treatment-Naive</th> <th colspan="3">C-EDGE TN (060), C-EDGE COINFECTION (061)</th> <th colspan="2">C-SURFER (052)</th> </tr> <tr> <th>GT 1a</th> <th>GT 1b</th> <th>GT 4</th> <th>GT1a CKD/HD</th> <th>GT1b CKD/HD</th> </tr> </thead> <tbody> <tr> <td>EBR/GZR, 12w</td> <td>92-94%</td> <td>96-99%</td> <td>96-100%</td> <td>97%</td> <td>92%</td> </tr> </tbody> </table><br><table border="1" data-bbox="325 1365 1205 1443"> <thead> <tr> <th rowspan="2">PR-Experienced</th> <th colspan="3">C-EDGE TE (068)</th> </tr> <tr> <th>GT 1a</th> <th>GT 1b</th> <th>GT 4</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table> | Treatment-Naive                | C-EDGE TN (060), C-EDGE COINFECTION (061) |                |             | C-SURFER (052) |  | GT 1a | GT 1b | GT 4 | GT1a CKD/HD | GT1b CKD/HD | EBR/GZR, 12w | 92-94% | 96-99% | 96-100% | 97% | 92% | PR-Experienced | C-EDGE TE (068) |  |  | GT 1a | GT 1b | GT 4 |  |  |  |  | <p>Five clinical trials provide substantial evidence of effectiveness of EBR/GZR in the following populations:</p> <ol style="list-style-type: none"> <li>(1) TN and PR-experienced GT 1a infected patients without baseline NS5A polymorphisms (12 weeks duration)</li> <li>(2) TN and PR-experienced GT 1b infected patients (12 weeks duration)</li> <li>(3) PI/PR-experienced GT 1 infected patients (12 weeks duration with RBV)</li> <li>(4) TN GT 4 infected patients (12 weeks duration)</li> <li>(5) PR-experienced GT 4 infected patients (16 weeks duration with RBV)</li> <li>(6) Advanced CKD patients including those on hemodialysis (same</li> </ol> |
| Treatment-Naive       | C-EDGE TN (060), C-EDGE COINFECTION (061)  |                                |   | C-SURFER (052) |             |                |  |       |       |      |             |             |              |        |        |         |     |     |                |                 |  |  |       |       |      |  |  |  |  |  |
|                       | GT 1a  | GT 1b                          | GT 4                                      | GT1a CKD/HD    | GT1b CKD/HD |                |  |       |       |      |             |             |              |        |        |         |     |     |                |                 |  |  |       |       |      |  |  |  |  |  |
| EBR/GZR, 12w          | 92-94%   | 96-99%                         | 96-100%                                   | 97%            | 92%         |                |  |       |       |      |             |             |              |        |        |         |     |     |                |                 |  |  |       |       |      |  |  |  |  |  |
| PR-Experienced        | C-EDGE TE (068)  |                                |   |                |             |                |  |       |       |      |             |             |              |        |        |         |     |     |                |                 |  |  |       |       |      |  |  |  |  |  |
|                       | GT 1a  | GT 1b                          | GT 4                                      |                |             |                |  |       |       |      |             |             |              |        |        |         |     |     |                |                 |  |  |       |       |      |  |  |  |  |  |
|                       |  |                                |   |                |             |                |  |       |       |      |             |             |              |        |        |         |     |     |                |                 |  |  |       |       |      |  |  |  |  |  |

| Dimension | Evidence and Uncertainties   |                 |       |         | Conclusions and Reasons   |  |
|-----------|--|-----------------|-------|---------|---|--|
|           | EBR/GZR, 12w   | 90%             | 100%  | 78%     | regimens as above, with appropriate modifications for RBV dosing) |  |
|           | EBR/GZR + RBV, 12w   | 93%             | 97%   | 93%     |   |  |
|           | EBR/GZR, 16w   | 94%             | 96%   | 60%     |   |  |
|           | EBR/GZR + RBV, 16w   | 95%             | 100%  | 100%    |   |  |
|           | PI/PR Experienced*   | C-SALVAGE (048) |       |         | (b) (4)   |  |
|           |  | GT 1a           | GT 1b | (b) (4) |   |  |
|           | EBR/GZR + RBV, 12w   | 93%             | 98%   |         |   |  |
|           | *PI = boceprevir, simeprevir, or telaprevir  |                 |       |         |   |  |
|           | <ul style="list-style-type: none"> <li>SVR12 rates were comparable in subjects with or without cirrhosis, with or without HIV coinfection, and with or without CKD.</li> <li>TN and TE clinical trials included GT 6 but contained few (n=15 and n=6, respectively) subjects.</li> <li>Post-hoc analyses of pooled Phase 2 and Phase 3 trials showed that exclusion of GT 1a infected subjects with baseline NS5A polymorphisms decreased the virologic failure rate from 5% to 1% (TN subjects) and from 8% to 2% (TE subjects).</li> <li>Overall, 96-97% of GT1a infected subjects with baseline NS5A polymorphisms who failed treatment developed additional resistance-associated substitutions, and 58% developed resistance to both NS5A inhibitors and NS3/4A PIs, substantially limiting future treatment options.</li> <li>Although there were fewer GT 1b failures, all six GT 1b infected subjects with baseline NS5A polymorphisms who failed treatment developed additional resistance, potentially limiting future treatment options.</li> </ul> |                 |       |         |   | <p>Baseline NS5A resistance testing should be considered for all TN and TE GT 1a infected patients to increase the likelihood of virologic cure and to decrease the risk of development of additional resistance-associated substitutions. In PR-experienced GT 1a infected subjects, screening for baseline NS5A polymorphisms allows for administration of a well-tolerated and convenient regimen (i.e., EBR/GZR for 12 weeks without RBV) for patients in whom NS5A polymorphisms are not present.</p> |
|           |  |                 |       |         |   | <p>The presence of baseline NS5A polymorphisms did not appear to impact efficacy in TN GT 1b subjects. Although baseline NS5A polymorphisms did appear to impact efficacy in some TE GT1b patients, NS5A resistance testing is not deemed necessary for this patient population due to the high overall SVR rates achieved with EBR/GZR in TE GT1b subjects in the clinical trials.</p>  |

| Dimension          | Evidence and Uncertainties  | Conclusions and Reasons  |
|--------------------|---|--|
|                    |   | <p>EBR/GZR fills an important unmet medical need for CKD patients receiving hemodialysis. EBR/GZR is also another highly effective RBV-free single tablet once daily treatment option for TN and PR-experienced GT 1 and TN GT 4 infected patients. EBR/GZR with RBV is a highly effective option for PI/PR-experienced patients with GT 1 infection and PR-experienced patients with GT 4 infection.</p>  |
| <p><u>Risk</u></p> | <ul style="list-style-type: none"> <li>The safety database for EBR/GZR includes the five aforementioned clinical trials and is considered adequate. C-EDGE TN (060) and C-SURFER (052) included a placebo-controlled comparison for safety with deferred treatment in subjects who were randomized to placebo. The hepatic safety pool included additional subjects who received GZR 100 mg and EBR 50 mg for at least 12 weeks in other clinical trials.</li> <li>Late ALT elevation was the major safety issue identified in this review. This event was previously identified and associated with higher doses of GZR. In the hepatic safety pool, 12/1558 (0.8%) subjects experienced this event, which consisted of a swift ALT elevation &gt;5x the upper limit of normal (ULN) generally at or after treatment week 8 and usually without symptoms. All events completely resolved following cessation of treatment. Higher rates of ALT elevations occurred in the following subpopulations: female sex (2%), Asian race (3%), and age &gt; 65 years (2%). None were associated with clinical AEs.</li> <li>Fatigue, headache, nausea, and asthenia were the most common adverse events (AEs) reported across trials and occurred at a similar rate as placebo.</li> <li>Subjects treated with EBR/GZR and RBV had notably higher rates of AEs compared to EBR/GZR without RBV. All were common and well-known RBV-related adverse reactions. Additionally, RBV-treated subjects had a higher rate of discontinuation due to psychiatric AEs.</li> <li>Drug-drug interactions (DDI) may increase or decrease systemic exposures of GZR and/or EBR, which may increase the risk of adverse reactions or</li> </ul> | <p>Hepatic safety issues with EBR/GZR at the proposed to-be-marketed dosages were well characterized during this review. The major safety issue identified, late ALT elevation, occurred infrequently. Late ALT elevation was a laboratory event rather than a clinical event.</p> <p>The safety issues with RBV are well known and are not exacerbated by EBR/GZR.</p> <p>EBR/GZR with or without RBV demonstrated an overall favorable safety profile.</p> |

Cross Discipline Team Leader Review

| Dimension                       | Evidence and Uncertainties  | Conclusions and Reasons  |
|---------------------------------|---|--|
|                                 | decrease efficacy, respectively.  |  |
| <a href="#">Risk Management</a> | <ul style="list-style-type: none"> <li>Late ALT elevation is included as a Warning and Precaution in the EBR/GZR product label. Currently approved HCV NS3/4 protease inhibitors (PIs) are associated with similar hepatic events, which are also labeled as a Warning and Precaution.</li> <li>The Applicant conducted numerous DDI studies to characterize the impact of EBR/GZR on concomitant drugs, and vice versa.</li> </ul> | The risk of late ALT elevation is appropriately highlighted in the label. Risk factors and specific guidance for conducting hepatic laboratory testing were added. Instructions for discontinuation of EBR/GZR are adequate and consistent with other NS3/4 PIs. Labeling adequately addresses DDIs by designation of drugs as contraindicated or not recommended, as appropriate. |

## 2. Background

The U.S. Centers for Disease Control and Prevention estimates that there are 2.7 million persons in the U.S. with chronic hepatitis C virus (HCV) infection. The majority (approximately 75%) of these persons are infected with genotype 1 virus, predominately genotype 1a. Approximately 20% of these persons are infected with genotypes 2 or 3, approximately 5% with genotype 4, and less than 1% with genotypes 5 or 6.

The treatment of chronic HCV infection has been in rapid evolution since the approval of the first direct acting agents (DAAs) for HCV in 2011, the NS3/4A protease inhibitors boceprevir and telaprevir. These were followed by the approval of sofosbuvir (an NS5B RNA-dependent RNA polymerase inhibitor) and simeprevir (an NS3/4A protease inhibitor) in 2013. These in turn were followed by the approval of a number of interferon-free HCV treatment regimens including simeprevir plus sofosbuvir; ledipasvir/sofosbuvir; ombitasvir/paritaprevir/ritonavir plus dasabuvir; ombitasvir/paritaprevir/ritonavir; and daclatasvir plus sofosbuvir. There are currently FDA approved, interferon-free HCV treatment regimens for genotypes 1 through 6, many of which offer treatment success rates well in excess of 90%.

This New Drug Application (NDA), submitted by Merck Sharp & Dohme Corp., contains information to support the approval of Zepatier, an interferon-free, complete regimen proposed for the treatment of chronic HCV infection genotypes 1, 4, or 6 in adults. Zepatier is comprised of grazoprevir (GZR), an HCV NS3/4 protease inhibitor, and elbasvir (EBR), an HCV NS5A inhibitor, coformulated as a fixed dose combination (FDC) tablet and administered with or without ribavirin. If approved, GZR would represent the 5<sup>th</sup> approved HCV NS3/4 protease inhibitor and EBR would represent the 4<sup>th</sup> approved HCV NS5A inhibitor to date.

IND 110261 for GZR was opened in November 2010 and initial development involved studying GZR in combination with pegylated interferon alfa-2b and ribavirin (PR). In March 2012, a partial clinical hold was placed on IND 110261 secondary to dose related increases in hepatic transaminases which were observed in clinical trial PN003 in which GZR was studied in combination with PR. The partial clinical hold was released in August 2012 with the proviso that the Applicant would not exceed a GZR dose of 100 mg per day in clinical trials. A 200 mg daily dose was allowed in studies involving healthy (non-HCV infected) subjects, as exposure was comparable to a 100 mg dose in HCV-infected patients.

The regulatory history was also notable for granting breakthrough designation in August 2013 for EBR/GZR for the treatment of chronic HCV infection (subsequently specified as HCV genotype 1 infection). In April 2015, the Agency rescinded this breakthrough designation based on the approval of treatment regimens demonstrating high sustained virologic response (SVR) rates and favorable safety profiles in HCV genotype 1 (GT1) infection. Breakthrough therapy designation was granted in April 2015 for EBR/GZR for both the treatment of chronic HCV genotype 4 (GT4) infection and the treatment of chronic HCV GT1 infection in patients with end stage renal disease on hemodialysis.

This cross-discipline team leader review will present the major findings from the NDA review of the Zepatier fixed dose combination (FDC) tablet. For a more comprehensive assessment, the reader is referred to the specific discipline reviews for the Zepatier NDA.

### **3. Product Quality**

NDA 208261 was recommended for approval from the Product Quality perspective by the review team headed by Dr. Stephen Miller. There are no unresolved product quality issues that would preclude approval at this time.

#### General product quality considerations

According to the Quality Assessment review, the data presented in the NDA and amendments are adequate to assure that the composition, manufacturing processes, and specifications for EBR/GZR FDC are appropriate. The expiration dating period of 24 months when stored below at USP controlled room temperature is supported by adequate data. No product quality microbiology issues were identified. The dissolution method and dissolution acceptance criterion were acceptable for both GZR and EBR. Adequate data were provided to support the discriminating ability of the dissolution method. The specified impurities were reviewed by Dr. Mark Powley and deemed acceptable from a pharmacology/toxicology perspective. The proposed labeling is adequate from the product quality perspective pending minor revisions.

#### Facilities review/inspection

All facilities inspections have been completed and the Office of Pharmaceutical Quality and Office of Compliance have determined these facilities to be acceptable.

### **4. Nonclinical Pharmacology/Toxicology**

The nonclinical safety profile of EBR and GZR has been evaluated in safety pharmacology studies in rats and dogs; repeat-dose toxicology studies in mice, rats and dogs for up to 3, 6 and 9 months duration, respectively; phototoxicity studies in rats; fertility and pre- and post-natal developmental studies in rats; embryo-fetal developmental studies in rats and rabbits; and genetic toxicology studies. Dr. Christopher Ellis recommended approval of this NDA based on his review of the nonclinical safety information provided in the submission. Please refer to the Pharmacology/Toxicology review by Dr. Christopher Ellis for additional details.

#### General nonclinical pharmacology/toxicology considerations

For EBR, no target organs of toxicity were identified following oral administration of up to 1000 mg/kg/day, in toxicology studies in mice, rats and dogs for up to 1, 6 and 9 months, respectively, at area under the curve (AUC) exposures  $\geq 55$  (mice), 9 (rats) and 8 (dogs) times higher than clinical exposure at the recommended dose. There were no significant neurological, cardiovascular, or pulmonary findings in the safety pharmacology studies of EBR.

For GZR, the main target organs of toxicity identified following oral GZR administration were the liver and gallbladder (mice and dogs), manifested primarily as elevated bilirubin and liver enzymes and histologic changes in the liver and gallbladder. Hepatobiliary toxicity occurred at AUC exposures  $\geq 74$  times higher than anticipated clinical exposure. The other identified target organs of toxicity with GZR were of questionable clinical relevance, given the high human exposure multiples where toxicity was observed, and included the testes (dogs), gastrointestinal tract (mice and rats), red blood cells (mice and dogs) and kidney (mice). Apart from a finding of increased heart rate in telemeterized dogs, there were no significant neurological, cardiovascular, or pulmonary findings in the safety pharmacology studies of GZR.

### Reproductive toxicology

#### Male fertility:

Following EBR administration for one month in the rat fertility study, a slight decrease (~15%) in sperm count, without effects on testicular weight, sperm motility and morphology or male fertility parameters, was observed at an estimated AUC exposure 9 times higher than clinical exposure at the recommended dose, with no effects on sperm count seen at exposure 5 times higher than clinical exposure. No testicular toxicity was observed in rats administered EBR for up to 6 months at AUC exposure 11 times higher than clinical exposure at the recommended dose.

Following GZR administration, testicular findings in dogs included seminiferous tubule degeneration, reduced testicular weights and decreased amount of sperm in epididymis. No testicular effects were seen at AUC exposures 231 and 37 times higher than clinical exposure at the recommended dose in the 1 and 9 month studies, respectively. In addition, testicular toxicity was not observed in mice and rats following oral GZR administration for up to 3 and 6 months, respectively, at AUC exposures 747 (mice) and 282 (rats) times higher than clinical exposure at the recommended dose.

#### Female Fertility:

No drug-related effects were observed on female fertility at EBR AUC exposure 7 times higher than clinical exposure and GZR exposure 84 times the clinical exposure.

#### Embryo-Fetal Development:

There were no significant developmental or maternal effects in rats or rabbits administered GZR, thus providing approximately a 117-fold and 41-fold exposure multiple (EM) respectively, based on AUC. There were no significant developmental effects in rats administered EBR, providing a 10-fold EM based on AUC; maternal effects consisted of decreased body weight gain. No significant developmental or maternal effects were noted in rabbits administered EBR, providing an approximately 18-fold EM based on AUC.

#### Pre- and Post-Natal Development:

No significant developmental effects were identified in rats administered GZR resulting in an approximately 78-fold EM based on maternal AUC. No significant developmental effects were identified in rats administered EBR, resulting in a 10-fold EM based on maternal AUC.

#### Genetic toxicology and carcinogenicity

EBR and GZR were not mutagenic or clastogenic as tested in the Ames assay, the in vitro chromosomal aberration assay in CHO cells and an in vivo rat micronucleus assay. Carcinogenicity studies with EBR and GZR are not being conducted, given the intended treatment duration (<6 months) and lack of a specific cause for concern.

## 5. Clinical Pharmacology

The Office of Clinical Pharmacology found sufficient clinical pharmacology information for NDA approval pending labeling agreement with the applicant. Please refer to the clinical pharmacology review by Dr. Su-Young Choi, Dr. Luning (Ada) Zhuang, and Dr. Stanley Au for additional details.

#### General clinical pharmacology/biopharmaceutics considerations, including absorption, food effects, metabolism, half-life, and excretion

Following oral administration of GZR and EBR,  $C_{max}$  was reached at 2 hours and 3 hours post-dose, respectively. EBR/GZR may be administered without regard to food as changes in drug exposure were not deemed clinically relevant after a high-calorie, high fat meal in healthy subjects.

GZR and EBR are metabolized by cytochrome P450 (CYP) 3A4 *in vitro*. The primary route of excretion of both drugs is feces, with < 1% elimination in urine. GZR and EBR have mean apparent elimination half-lives of 31 hours and 24 hours, respectively, in HCV-infected patients. GZR PK is linear up to 100 mg but exhibits non-linear PK above 100 mg (more than dose-proportional increases); EBR PK is linear up to 100 mg but exhibits non-linear PK above 100 mg (less than dose proportional increases).

#### Critical intrinsic factors potentially affecting elimination: hepatic impairment, renal impairment, gender, race, and age

##### Hepatic impairment:

GZR exposures ( $AUC_{24hr}$ ) were increased by 1.7-fold, 4.8-fold and 11.7-fold, in non-HCV-infected subjects with mild, moderate, and severe hepatic impairment, respectively, as compared to matched healthy volunteers. The magnitude of the increased GZR exposure in patients with mild hepatic impairment is not considered clinically relevant. The exposure increases noted in subjects with moderate or severe hepatic impairment are considered clinically relevant as GZR-associated hepatotoxicity is exposure dependent (see Section 8, Safety).

No clinically significant difference in EBR exposures was noted between subjects with mild hepatic impairment and subjects with normal hepatic function in population pharmacokinetic analyses.

#### Renal impairment:

HCV uninfected and HCV infected patients with severe renal impairment, including those receiving hemodialysis, showed no clinically significant differences in GZR or EBR exposures compared to matched healthy volunteers. Furthermore, GZR and EBR were minimally eliminated by a 4-hour hemodialysis session.

#### Gender, Race, and Age:

Based on population PK analyses, GZR exposures are estimated to be 30% higher in females compared to males, 50% higher in Asians compared to Whites, and 20% higher in elderly ( $\geq 65$  years of age) compared to younger ( $< 65$  years of age) patients. See Section 8 for a discussion of these factors in regard to GZR-associated hepatotoxicity.

Based on population PK analyses, EBR exposures are estimated to be 50% higher in females compared to males, 15% higher in Asians compared to Whites, and 16% higher in elderly ( $\geq 65$  years of age) compared to younger ( $< 65$  years of age) patients. These differences are not clinically relevant.

#### Drug-drug interactions

EBR and GZR are substrates of CYP3A4. EBR and GZR are substrates of P-gp *in vitro*, but the role of intestinal P-gp in the absorption of EBR and GZR appears to be minimal. GZR is a substrate and inhibitor of OATP1B1/3, and a weak inhibitor of CYP3A4.

As discussed at length in Section 8, GZR has a well characterized, exposure-related, hepatotoxicity profile. Based on the known toxicity profile of GZR, the review team determined that drug-drug interactions (DDIs) leading to a  $(b)(4)$  increase in GZR exposures warranted a “not recommended” designation in the label; DDIs due to OATP1B1/3 inhibition or leading to a  $(b)(4)$  increase in GZR exposures warranted a contraindication in the label.

The following labelling recommendations were made by the clinical pharmacology team with respect to DDIs:

**Co-administration is contraindicated due to significant increases in GZR exposure, which may increase the risk of late  $(b)(4)$  ALT elevation: atazanavir, darunavir, lopinavir, saquinavir, tipranavir, cyclosporine,  $(b)(4)$  or other OATP1B inhibitors that may significantly increase GZR exposure.**

**Co-administration is not recommended due to significant increases in GZR exposure: ketoconazole**

**Co-administration is contraindicated due to significant decreases in GZR or EBR exposures: efavirenz, phenytoin, carbamazepine, St. John's Wort (Hypericum perforatum) or other strong CYP3A4 inducers**

**Dose adjustment of co-administrated drugs or close clinical monitoring is recommended: atorvastatin, rosuvastatin, lovastatin, fluvastatin, simvastatin and tacrolimus**

No clinically relevant drug interactions were observed with acid reducing agents (proton pump inhibitors, H2 blockers, antacids), buprenorphine/naloxone, digoxin, dolutegravir, methadone, mycophenolate mofetil, oral contraceptive pills, phosphate binders, pitavastatin, pravastatin, prednisone, raltegravir, ribavirin, rilpivirine, tenofovir disoproxil fumarate, and sofosbuvir

QT assessment:

A thorough QT study was conducted for GZR and EBR as individual products and the results were reviewed by FDA's Interdisciplinary Review Team for QT Studies. No significant QTc prolongation effect was detected with GZR administered at a dose of 1600 mg or EBR administered at a dose of 700 mg. The largest upper bounds of the 2-sided 90% CI for the mean differences between GZR and placebo and between EBR and placebo were below 10 ms, the threshold for regulatory concern. Both of the largest lower bounds of the two sided 90% CI in the GZR study and EBR study for the  $\Delta\Delta\text{QTcF}$  for moxifloxacin were greater than 5 ms, and the moxifloxacin profiles over time were adequately demonstrated, indicating that assay sensitivity was established.

Formulation

The pivotal clinical trials were performed with the to-be-marketed fixed-dose formulation; therefore bridging information between formulations is not required.

## 6. Clinical Microbiology

Please refer to the joint virology review by Dr. Takashi Komatsu and Dr. Patrick Harrington for a detailed assessment of the non-clinical virology data. The following summary of the HCV replicon data related to the impact of NS3 or NS5A substitutions is provided to support the discussion of the clinical virology data in Section 7, Clinical/Statistical Efficacy.

Selection of HCV genotype 1a replicons with GZR resulted in single NS3 substitutions D168A/E/G/S/V which reduced cell culture antiviral activity by 2- to 81-fold. Selection of HCV genotype 1b replicons resulted in single NS3 substitutions F43S, A156S/T/V, and D168A/G/V which reduced cell culture antiviral activity by 3- to 375-fold. Selection of HCV genotype 4 replicons resulted in single NS3 substitutions D168A/V which reduced cell culture antiviral activity by 110- to 320-fold.

Selection of HCV genotype 1a replicons with EBR resulted in single NS5A substitutions Q30D/E/H/R, L31M/V and Y93C/H/N which reduced cell culture antiviral activity by 6- to

2,000-fold. Selection of HCV genotype 1b replicons resulted in single NS5A substitutions L31F and Y93H which reduced cell culture antiviral activity by 17- to 67-fold. Selection of HCV genotype 4 replicons resulted in single NS5A substitutions L30S, M31V, and Y93H which reduced cell culture antiviral activity by 3- to 23-fold. Additionally, EBR demonstrated cross-resistance to key resistance-associated substitutions for other NS5A inhibitors at positions M/L28, Q/R30, L31, H58, or Y93.

## **7. Clinical/Statistical- Efficacy**

This section summarizes the efficacy analyses conducted by the review team for the key trials supporting the Applicant's proposed indication, namely, the treatment of chronic HCV GT 1, 4 or 6 in adults to include subjects with and without cirrhosis, end-stage renal disease, HIV co-infection, and prior PR and PR/protease inhibitor (PI) failures. The section will primarily focus on Clinical Trials 048, 052, 060, 061, and 068. Additionally, this section will discuss the impact of baseline NS5A polymorphisms on clinical efficacy. Please refer to the Clinical Review by Dr. Sarita Boyd and Dr. Prabha Viswanathan, the Virology Review by Dr. Takashi Komatsu, and the Statistical Review by Dr. LaRee Tracy for complete details. Overall, the FDA reviewers' independent analyses confirmed the Applicant's primary and secondary efficacy findings for the pivotal trials. However, the interpretation of the importance of the impact of baseline NS5A polymorphisms on efficacy varied considerably between the Agency and the Applicant.

Of the five trials that will be reviewed in this section, two trials (048 and 061) were open-label, uncontrolled trials; two trials (052 and 060) utilized a double-blind design (through the first 12 weeks of treatment) comparing immediate versus delayed treatment; and one trial (068) compared two durations of EBR/GZR with and without RBV. Please refer to Table 1 below for a summary of the clinical trial designs. Subjects in the delayed treatment group (DTG) received placebo for the first 12 weeks concurrent with subjects receiving EBR/GZR in the immediate treatment group (ITG). The purpose of the DTG was only to provide comparative safety data for Trials 052 and 060. The primary endpoint for the five trials under discussion was sustained virologic response or SVR (defined as proportion of subjects achieving a HCV RNA level below the lower limit of quantification) measured 12 weeks following the end of treatment, henceforth referred to as SVR12. SVR12 represents the Agency's preferred primary endpoint for HCV treatment trials. The Phase 2/3 and 3 trials were designed to demonstrate that the proportion of subjects achieving SVR12 in the EBR/GZR arm was superior to a pre-specified historical rate; a rate that varied according to the HCV sub-population and genotype studied. Please refer to the statistical review for the justification of the historical control rates selected for these trials and the inherent limitations of historically controlled trials.

**Table 1: Key Efficacy Trials**

| Study                             | Population                                 | GT     | Treatment  | # of Subjects   | Control                  | Historical Rate* |
|-----------------------------------|--|--------|--|---|--------------------------|------------------|
| <b>Phase 2 Trials</b>             |  |        |  |   |                          |                  |
| 048<br>C-<br>SALVAGE              | Prior<br>DAA/P/R<br>failures (+/-C)        | 1      | EBR/GZR + R<br>x 12 weeks                              | 79  | None                     | None             |
| <b>Phase 2/3 or Phase 3</b>       |  |        |  |   |                          |                  |
| 052<br>C-SURFER                   | CKD stages<br>4-5, including<br>dialysis   | 1      | EBR/GZR x<br>12 weeks,<br>(ITG v. DTG)<br>(randomized) | ITG/PK: 122<br>DTG: 133   | <b>Placebo<br/>(DTG)</b> | <b>45%</b>       |
| 060<br>C-EDGE TN                  | TN (+/-C)                                  | 1,4, 6 | EBR/GZR x<br>12 weeks,<br>(ITG v. DTG)<br>(randomized) | ITG: 316<br>DTG: 105  | <b>Placebo<br/>(DTG)</b> | <b>73%</b>       |
| 061<br>C-EDGE<br>CO-<br>INFECTION | HIV co-<br>infected<br>(TN+/- C)           | 1,4, 6 | EBR/GZR x<br>12 weeks                                  | 218   | <b>None</b>              | <b>70%</b>       |
| 068<br>C-EDGE TE                  | P/R PTF, +/-<br>C, +/- HIV<br>co-infection | 1,4, 6 | EBR/GZR +/-<br>R x 12 or 16<br>weeks<br>(randomized)   | EBR/GZR 12 w: 105<br>EBR/GZR/RBV 12w: 104<br>EBR/GZR 16w: 105<br>EBR/GZR/RBV 16w: 106 | <b>None</b>              | <b>58%</b>       |

GT=Genotype; DAA=Direct-acting Antivirals; TN=Treatment-Naïve; CKD=Chronic Kidney Disease; ITG=Immediate Treatment Group; DTG=Deferred Treatment Group; PK=Intensive PK Group;

P/R=Pegylated Interferon/Ribavirin; PTF=Prior Treatment Failure; R=Ribavirin; NC=non-cirrhotic

\*Historical rate used to assess SVR12 in the EBR/GZR treatment group for test of superiority; trials with no historical rate were hypothesis generating only

Source: NDA 208261, Statistical Review, L. Tracy, adapted

The study designs, key demographics, and key efficacy results from each of the trials outlined above will be reviewed. This will be followed by a discussion of sub-group analyses of interest and by conclusions on effectiveness based on the totality of evidence from the clinical trials.

### Study designs, key demographics, and key efficacy results

#### Trial 060 (C-EDGE TN)

Trial 060 was a Phase 3 randomized, parallel-group, placebo-controlled, double-blind trial. The patient population consisted of TN cirrhotic and non-cirrhotic subjects with chronic HCV GT 1, 4, or 6 viral infection. The regimen was EBR/GZR for 12 weeks (immediate treatment group [ITG]) vs. placebo (deferred treatment group [DTG]). The DTG received EBR/GZR for 12 weeks following unblinding. Subjects were randomized 3:1 to the ITG versus the DTG respectively. Randomization was stratified by fibrosis stage (cirrhotic vs. non-cirrhotic) and HCV subtype (GT 1a vs. GT 1 non-a vs. GT 4/6). Twenty-two percent of subjects in the ITG were classified as cirrhotic. Please refer to the Clinical Review for a description of the protocol-defined methods to determine the presence or absence of cirrhosis. The key efficacy findings from Trial 060 are outlined in Table 2 below.

**Table 2: Trial 060: Key Efficacy Results (ITG)**

| Treatment Regimen | SVR12 (FAS; n=316) |
|-------------------|--------------------|
|                   | EBR/GZR x 12 weeks |

|                                    |                       |
|------------------------------------|-----------------------|
| <b>SVR Achieved (%)</b>            | <b>299 (94.6)</b>     |
| 95% CI <sup>^</sup> , p-value*     | 91.5, 96.8<br><0.0001 |
| <b>SVR Not Achieved</b>            | <b>17 (5.4)</b>       |
| <b>Non-virologic failure</b>       | <b>4 (1.3)</b>        |
| Death                              | 2 (0.6)               |
| LTF/Missing Value                  | 1 (0.3)               |
| Adverse Event Discontinuation      | 1 (0.3)               |
| <b>Virologic failure</b>           | <b>13 (4.1)</b>       |
| Breakthrough                       | 1 (0.3)               |
| Relapse                            | 12 (3.8)              |
| 1a (N=157)                         | 9 (6.0)               |
| 1b (N=131)                         | 1 (1.0)               |
| 4 (N=10)                           | (b) (4)               |
| <b>% SVR by Genotypes (95% CI)</b> |                       |
| 1a (n=157)                         | 91.7 (86.3, 95.5)     |
| 1b (n=131)                         | 98.5 (94.6, 99.8)     |
| 4 (n=18)                           | 100.0 (81.5, 100.0)   |
|                                    | (b) (4)               |

<sup>^</sup>Clopper-Pearson exact method

\*One-sided Exact test, alpha=0.025 based on test for true proportion=0.73.

Source: NDA 208261, Statistical Review, L. Tracy, adapted

### Trial 061 (C-EDGE CO-INFECTION)

Trial 061 was a Phase 3 non-randomized, uncontrolled, multi-center clinical trial that assessed the efficacy and safety of EBR/GZR for 12 weeks in TN cirrhotic and non-cirrhotic subjects with HCV GT 1, 4, or 6 infection and HIV coinfection. Sixteen percent of the enrolled subjects were classified as cirrhotic. Notably, no GT6 subjects were enrolled in this trial. The key efficacy findings from Trial 061 are outlined in Table 3 below.

**Table 3: Trial 061: Key Efficacy Results**

| <b>Treatment Regimen</b>              | <b>SVR12 (FAS; n=218)</b> |
|---------------------------------------|---------------------------|
|                                       | <b>EBR/GZR 12 weeks</b>   |
| <b>SVR Achieved (%)</b>               | <b>207 (95.0)</b>         |
| 95% CI <sup>^</sup> , p-value*        | 91.2, 97.5, <0.0001       |
| <b>SVR Not Achieved</b>               | <b>11 (5)</b>             |
| <b>Non-virologic failure</b>          | <b>4 (1.8)</b>            |
| LTF/Missing Value                     | 3                         |
| Early Discontinuation <sup>^</sup>    | 1                         |
| <b>Virologic failure</b>              | <b>7 (3.2)</b>            |
| Relapse                               | 7 (3.2)                   |
| 1a (N=144)                            | 5 (3)                     |
| 1b (N= 44)                            | 1(2)                      |
| 4 (N=28)                              | 1(4)                      |
| <b>SVR by HCV genotype (95% CI)**</b> |                           |
| 1a (n=144)                            | 94.4 (89.4, 97.6)         |
| 1b (n=44)                             | 95.5 (84.5, 99.4)         |
| 4 (n=28)                              | 96.4 (81.7, 99.9)         |

<sup>^</sup>Clopper-Pearson exact method

\*One-sided exact test, true p=0.70 based on historical estimate  
 \*\*One subject with GT 1 other and one with GT6-both achieved SVR4 and SVR12  
 Source: NDA 208261, Statistical Review, L. Tracy, adapted

Trial 068 (C-EDGE TE)

Trial 068 was a Phase 3 randomized (1:1:1:1), parallel-group, open-label clinical trial. Each of the four trial arms received a different treatment regimen that included EBR/GZR +/- RBV for 12 weeks and EBR/GZR +/- RBV for 16 weeks. The patient population consisted of TE cirrhotic and non-cirrhotic subjects with HCV GT 1, 4, or 6 infection who failed prior treatment with PR. Of note, only six HCV GT6 infected subjects were enrolled in this trial; four subjects in the arm receiving EBR/GZR for 16 weeks and 2 subjects in the arm receiving EBR/GZR + RBV for 16 weeks. A total of 37 GT4 infected subjects were enrolled in the trial (range of 5-15 subjects across trial arms). Prior PR relapsers, partial responders, and null responders accounted for 33-38%, 20-22%, and 41-47% of enrolled subjects across arms respectively. HIV coinfecting subjects were eligible for enrollment and comprised 5-6% of subjects across trial arms. Thirty-four to thirty-six percent of the enrolled subjects across arms were classified as cirrhotic. The key efficacy findings from Trial 068 are outlined in Table 4 below.

**Table 4: Trial 068: Key Efficacy Results**

|  | <b>EBR/GZR<br/>(N=105)</b>           | <b>EBR/GZR + RBV<br/>(N=104)</b>   | <b>EBR/GZR<br/>(N=105)</b>         | <b>EBR/GZR + RBV<br/>(N=106)</b>     |
|--|--------------------------------------|------------------------------------|------------------------------------|--------------------------------------|
| <b>Treatment Duration</b>                | <b>12 Weeks</b>                      |                                    | <b>16 Weeks</b>                    |                                      |
| <b>SVR Achieved (%)</b>                  | <b>97 (92.4)</b>                     | <b>98 (94.2)</b>                   | <b>97 (92.4)</b>                   | <b>103 (97.2)</b>                    |
| 95% CI <sup>^</sup>                      | 85.5, 96.7                           | 87.9, 97.9                         | 85.5, 96.7                         | 92.0, 99.4                           |
| p-value*                                 | <0.0001                              | <0.0001                            | <0.0001                            | <0.0001                              |
| <b>SVR Not Achieved</b>                  | <b>8 (7.6)</b>                       | <b>6 (5.8)</b>                     | <b>8 (7.6)</b>                     | <b>3 (2.8)</b>                       |
| <b>Non-virologic failure</b>             | <b>2 (1.9)</b>                       | <b>0 (0.0)</b>                     | <b>1 (1.0)</b>                     | <b>3 (2.8)</b>                       |
| LTF/Missing Value                        | 0                                    | 0                                  | 1                                  | 2                                    |
| AE Discontinuation <sup>^</sup>          | 1 (1.0)                              | 0                                  | 0                                  | 1 (0.9)                              |
| Early Termination**                      | 1 (1.0)                              | 0                                  | 0                                  | 0                                    |
| <b>Virologic failure</b>                 | <b>6 (5.7)</b>                       | <b>6 (5.8)</b>                     | <b>7 (6.7)</b>                     | <b>0 (0.0)</b>                       |
| Relapse                                  | 6                                    | 6                                  | 4                                  | 0                                    |
| 1a                                       | 5                                    | 4                                  | 3                                  | 0                                    |
| 1b                                       | 0                                    | 1                                  | 1                                  | 0                                    |
| 4  | 1                                    | 1                                  | 0                                  | 0                                    |
| Breakthrough                             | 0                                    | 0                                  | 1                                  | 0                                    |
| Rebound                                  | 0                                    | 0                                  | 2                                  | 0                                    |
| <b>%SVR12 By Genotype (95% CI; n/N)#</b> |                                      |                                    |                                    |                                      |
| 1a                                       | <b>90.2</b> (79.8, 96.3;<br>55/61)   | <b>93.3</b> (83.8, 98.2;<br>56/60) | <b>93.8</b> (82.8, 98.7;<br>45/48) | <b>94.8</b> (85.6, 98.9;<br>55/58)   |
| 1b                                       | <b>100.0</b> (89.7, 100.0;<br>34/34) | <b>96.6</b> (82.2, 99.9;<br>20/29) | <b>95.8</b> (85.8, 99.5;<br>46/48) | <b>100.0</b> (90.3, 100.0;<br>36/36) |
| 4  | <b>77.8</b> (40.0, 97.2; 7/9)        | <b>93.3</b> (68.1, 99.8;<br>14/15) | <b>60.0</b> (14.7, 94.7;<br>3/5)   | <b>100.0</b> (63.1, 100.0;<br>8/8)   |

(b) (4)

<sup>^</sup>Clopper-Pearson exact method  
 \*One-sided Exact test, alpha=0.025 (two-sided) based on test for true proportion=0.58.  
 \*\*Physician decision to remove subject from treatment

#GT 1 other omitted due to small counts

Source: NDA 208261, Statistical Review, L. Tracy, adapted

Trial 048 (C-Salvage)

Trial 048 was a Phase 2, open-label, single-arm study of GZR 100 mg/EBR 50 mg + RBV for 12 weeks for treatment of HCV GT1 infected subjects who had failed a prior approved DAA regimen of boceprevir, telaprevir, simeprevir or sofosbuvir taken with PR. Subjects must have received at least 4 weeks of prior DAA treatment, and approximately 80% must have met virologic failure criteria with or without resistance-associated substitutions potentially attributable to failure with the prior regimen.

Notably, ninety-eight percent of enrolled subjects were white and 43% were classified as cirrhotic. All enrolled subjects failed prior therapy with HCV protease inhibitors including boceprevir, telaprevir or simeprevir and none failed prior therapy with sofosbuvir (an NS5B inhibitor). The key efficacy findings from Trial 048 are outlined in Table 5 below.

**Table 5: Trial 048: Key Efficacy Results**

| GZR 100 mg/EBR 50 mg + RBV for 12 weeks | SVR12          |             |
|---|----------------|-------------|
|   | % (n/N)        | 95% CI*     |
| <b>Full Analyses Set</b>                | 96.2 (76/79) ^ | 89.3, 99.2  |
| <b>By Genotype (FAS)</b>                |                |             |
| 1a                                      | 93.3 (28/30)   | 77.9, 99.2  |
| 1b                                      | 98.0 (48/49)   | 89.2, 100.0 |

^ Three subjects failed to achieve SVR12 due to relapse

\* Clopper Pearson exact method

Source: NDA 208261, Statistical Review, L. Tracy

Trial 052 (C-SURFER)

Protocol 052 is a randomized, parallel-group, multi-site, multi-national, placebo-controlled trial in Stage 4 or 5 CKD subjects infected with GT 1 HCV, with or without prior treatment experience and with or without cirrhosis. Definitions of CKD and ESRD were based on the National Kidney Foundation (United States): Stage 4 is defined as estimated glomerular filtration rate (eGFR) of 15-29 mL/min/1.73 m<sup>2</sup>; Stage 5 (ESRD) is defined as eGFR < 15 ml/min/1.73m<sup>2</sup> or need for renal replacement therapy. Subjects co-infected with HIV, subjects receiving peritoneal dialysis and subjects with new or worsening cardiovascular or cerebrovascular disease in the 3 months prior to study enrollment were excluded. Eligible subjects were randomized 1:1 to either the ITG or DTG. Subjects in the ITG received GZR 100 mg/ EBR 50 mg once daily for 12 weeks. Subjects in the DTG received placebo during the initial 12 week treatment period; after a 4 week unblinding period, these subjects received GZR 100 mg/EBR 50mg once daily for 12 weeks. Randomization was stratified according to baseline dialysis and diabetes status.

Total enrollment included 111 subjects in the ITG and 113 subjects in the DTG. An additional 11 subjects were enrolled into an intensive PK subgroup and these subjects were included in the ITG efficacy analyses. Ninety-four percent of subjects in the ITG were classified as non-

cirrhotic, 82% were treatment-naïve, 34% were diabetic, and 78% were receiving hemodialysis. The key efficacy findings from Trial 052 are outlined in Table 6 below.

**Table 6: Trial 052: Key Efficacy Results**

| GZR 100 mg QD/EBR 50 mg QD for<br>12 weeks |                     | <b>SVR12<br/>(FAS; n=122)</b> |
|--|---------------------|-------------------------------|
| <b>SVR Achieved (%)</b>                    |                     | <b>115 (94.3)</b>             |
|  | 95% CI <sup>^</sup> | 88.5, 97.7                    |
|  | p-value*            | <0.0001                       |
| <b>SVR Not Achieved</b>                    |                     | <b>7 (5.7)</b>                |
| Relapse                                    |                     | 1 (0.8)                       |
| Missing unrelated to treatment             |                     | 6 (4.9)                       |
| <b>SVR by HCV genotype</b>                 |                     |                               |
| 1a   |                     | 61/63 (96.8)                  |
|  | 95% CI <sup>^</sup> | 89.0, 99.6                    |
| 1b   |                     | 54/59 (91.5)                  |
|  | 95% CI <sup>^</sup> | 81.3, 97.2                    |

<sup>^</sup>Clopper-Pearson exact method

\*One-sided exact test, true p=0.53 based on historical estimate

Source: NDA 208261, Statistical Review, L. Tracy

#### Sub-group analyses of interest across all key efficacy trials

Based on the totality of the available data across the key efficacy trials, no significant differences in efficacy were noted with respect to the following factors: age, gender, race, geographical region, prior PR treatment history, cirrhosis status, or HIV co-infection. There was a trend toward improvement in SVR12 rates in the key trials in subjects with baseline HCV RNA  $\leq$  800,000 IU/mL compared to those with baseline HCV RNA  $>$  800,000 IU/mL; however, statistical significance was only reached in Trial 060 with respect to differences in this parameter. Please refer to the Statistical Review for detailed analyses.

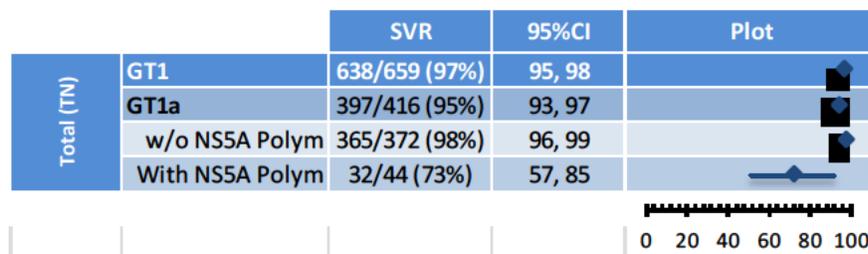
The remainder of this section will focus on the impact of key NS5A baseline viral polymorphisms on efficacy. For the primary resistance analyses, the Applicant conducted Sanger population nucleotide sequencing on all subjects, which typically detects highly prevalent variants that comprise at least 15-25% of the viral population. Subsequent analyses (which were not independently reviewed) were conducted on a subset of subjects using a next generation sequencing assay with a 1% sensitivity cutoff.

For this discussion, a polymorphism will be defined as an amino acid variant that (a) differs from the “wild-type” consensus for the HCV subtype, and (b) predominates in the viral population of an individual; thus, only the population sequencing data are considered. A key NS5A resistance-associated polymorphism will be defined as a polymorphism occurring at any one of the following five NS5A amino acid positions: 28, 30, 31, 58, and 93. The prevalence of key NS5A baseline polymorphisms was approximately 20% in GT1a subjects enrolled in clinical trials of EBR/GZR in the U.S. This rate is consistent with rates reported in other HCV development programs. The prevalence of polymorphisms in the EBR/GZR development program appears to be similar regardless of the gender, race, or ethnicity of HCV infected patients.

The Agency’s analyses demonstrated that both treatment-naïve and PR-treatment experienced patients who were infected with HCV genotype 1a virus with one or more key NS5A polymorphism(s) at baseline were significantly less likely to benefit from a 12 week course of EBR/GZR than subjects infected with HCV genotype 1a virus without key NS5A polymorphisms. Although a similar pattern was noted for PR treatment-experienced subjects infected with HCV genotype 1b virus, the magnitude of the impact was substantially smaller. Please note that in addition to utilizing data from the Phase 2/3 and Phase 3 trials discussed above, the NS5A analyses presented below also include relevant data from Trial 035, a large, Phase 2, multicenter, randomized, parallel-group, exploratory trial. Of note, the presence of baseline NS3 polymorphisms did not substantively impact efficacy.

Figure 1 below demonstrates both clinically and statistically significantly (based on the lack of overlap of 95% CIs) lower SVR rates in TN subjects with baseline NS5A resistance-associated polymorphisms than those without polymorphisms (73% vs 98% respectively).

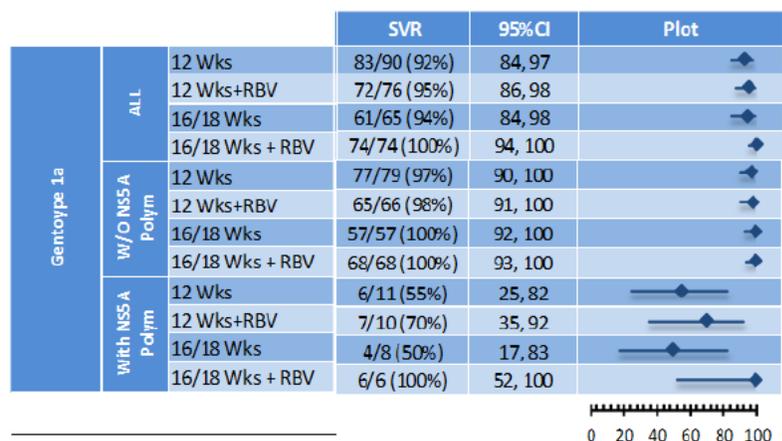
**Figure 1: SVR12 Rates in Treatment-Naïve Subjects (GT1a)**



Source: NDA 208261, Virology Review, T. Komatsu

Similarly, Figure 2 below demonstrates substantially lower SVR rates in TE subjects with baseline NS5A resistance-associated polymorphisms. Exclusion of subjects with baseline polymorphisms yields an SVR rate of 97% in the 12 week EBR/GZR arm. It appears that extending treatment duration to 16 or 18 weeks together with the addition of RBV may overcome the impact of baseline NS5A polymorphisms in HCV GT1a infected subjects; however the data are insufficient (N=6 subjects across two different treatment durations) to draw any definitive conclusions.

**Figure 2: SVR12 Rates in PR Treatment-Experienced Subjects (GT1a)**



Source: NDA 208261, Virology Review, T. Komatsu

It should be noted that there are clinically significant consequences of virologic failure for patients with NS5A polymorphisms in genotype 1a. Amongst patients with genotype 1a virus with NS5A polymorphisms who failed treatment, 96% of subjects gained an NS3/4A resistance substitution OR an additional NS5A substitution(s); approximately 75% of subjects gained an additional NS5A resistance substitution(s); and approximately 60% of subjects gained an additional NS3/4A AND NS5A resistance substitution(s). Based on these outcomes, treatment failure may substantially impact retreatment options for patients.

Conclusions on effectiveness

The Applicant has requested a treatment indication to include patients infected with HCV GT1, HCV GT4, and HCV GT6 virus. Conclusions related to each of these genotypes will be discussed separately.

HCV GT1

The Applicant has provided substantial evidence of effectiveness as required by law [see 21 CFR 314.126(a)(b)] to support approval for HCV GT1a and HCV GT1b infected patients. EBR/GZR has demonstrated efficacy for the treatment of GT1 infection in treatment naïve and PR (and PR + PI) treatment experienced subjects including subjects with cirrhosis, subjects co-infected with HIV, and subjects with ESRD receiving hemodialysis. Overall, SVR12 rates ranged from 90-97% in GT1a and 92-100% in GT1b subjects in the key trials supporting efficacy. However, as previously noted, efficacy in HCV GT1a infected patients was significantly impacted by the presence of key NS5A baseline polymorphisms. This issue will be addressed through labeling (see Section 12, Labeling). (b) (4)

Of interest, exposure-response analyses conducted by the Clinical Pharmacology review team indicated that EBR exposures were significant predictors of SVR12. In subjects with baseline NS5A resistance, the predicted SVR12 rate with 20 mg and 50 mg EBR was 60% and 80%, respectively. This raises the question of whether higher EBR doses may have been able to

overcome the impact of baseline NS5A polymorphisms; however, dosages in excess of 50 mg were not evaluated by the Applicant.

### HCV GT4

The Applicant has provided substantial evidence of effectiveness as required by law [see 21 CFR 314.126(a)(b)] to support approval for HCV GT4 infected patients. EBR/GZR for 12 weeks has demonstrated efficacy for the treatment of HCV GT4 infection in treatment naïve subjects with SVR12 rates ranging from 96-100% in the Phase 3 trials 060 and 061. In Trial 060, 18/18 subjects achieved SVR12; in Trial 061, 27/28 subjects achieved SVR12. Additional supportive data are available from Trial 047, a Phase 2, multi-site, multi-national, open-label exploratory trial performed in non-cirrhotic TN subjects with HCV GT 2, 4, 5 or 6 infection. SVR12 was achieved in 9/10 GT4 infected subjects randomized to receive 12 weeks of EBR/GZR (the Applicant's proposed regimen in product labeling for this population).

Limited direct data are available in HCV GT4 PR-experienced subjects to support the Applicant's proposed regimen of EBR/GZR + RBV for 16 weeks in this population. In Trial 068, a total of 37 GT4 infected, PR-experienced subjects were enrolled. The overall SVR12 rate in this group was 86%, and ranged from 60% to 100% across trial arms. Eight GT4 subjects were enrolled in the arm receiving EBR/GZR + RBV for 16 weeks; all eight subjects achieved SVR12. The review team recognized the limitations of these data, but concluded that the totality of evidence supports the Applicant's proposed regimen for this population. HCV GT4 is rare in the U.S. and patients who are DAA-naïve and PR-experienced represent a small and ever shrinking sub-population. Further complicating these analyses, there are many subtypes of HCV GT4, and therefore it is not feasible to conduct well-powered clinical trials evaluating efficacy across all HCV GT4 subtypes (and subgroups therein). The Division has precedent for leveraging data from a sub-population (e.g., HIV co-infected subjects) in one genotype (e.g., GT1) to support efficacy in a far less prevalent genotype (e.g., GT4) when data from the sub-population of interest are limited or not directly available, and when differences in efficacy are not anticipated. Furthermore, within a particular HCV genotype, poor response to PR is often driven host factors that seem to have less of an impact on treatment efficacy with IFN-free regimens. Given (1) the high efficacy of EBR/GZR ± RBV for 12 or 16 weeks in HCV GT1 TN and TE subjects, (2) the high efficacy of EBR/GZR for 12 weeks in HCV GT4 TN subjects, and (3) the 8/8 (100%) SVR12 rate for HCV GT4 PR-experienced subjects who received EBR/GZR + RBV for 16 weeks in Trial 068, approval of EBR/GZR for HCV GT4 PR-experienced patients appears to be well supported. The recommended 16-week EBR/GZR + RBV regimen for this population takes into consideration the limitations of available data and represents a conservative regimen intended to maximize treatment efficacy.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

## 8. Safety

This section will provide a focused summary of the safety data from the Phase 3 clinical trials 060, 061, and 068. A separate discussion of safety in the Phase 2/3 clinical trial 052 will also be provided. For a complete description of these data and the Agency's independent safety analyses, please refer to the joint Clinical Review performed by Dr. Sarita Boyd and Dr. Prabha Viswanathan.

### *Adequacy of the safety database, Applicant's safety assessments, and submission quality*

The safety database for EBR/GZR was adequate to assess safety for the proposed indication, dosage regimen, duration of treatment and patient populations. It was consistent with the safety considerations as outlined in the Draft Guidance for Industry: *Chronic Hepatitis C Virus Infection: Developing Direct Acting Antiviral Agents for Treatment*. The safety database at the time of NDA submission included 1747 subjects who received GZR 100 mg and EBR 50 mg for at least 12 weeks, and 360 subjects who received GZR 100 mg and EBR 50 mg for 16-18 weeks.

The Applicant performed a comprehensive assessment of safety, including but not limited to a detailed analysis of hepatotoxicity. The Applicant responded in a timely fashion to our requests for additional safety related information and analyses. The submission quality was adequate to perform a thorough safety review and there were no substantive issues with data integrity.

Key safety results, including deaths, serious adverse events (SAEs), discontinuations due to AEs, results of laboratory tests, and immunogenicity

Overall, the safety profile of EBR/GZR was acceptable. Fatigue, headache, and nausea were the most common AEs reported across trials of EBR/GZR (without RBV), but these events occurred at similar rates in the delayed treatment arm (i.e., placebo arm) of trial 060. The majority of AEs were mild to moderate in severity. Extending the duration of EBR/GZR administration from 12 weeks to 16 weeks in the clinical trials did not appear to negatively impact the safety profile in a substantive manner. However, the addition of RBV to the EBR/GZR regimen had a clinically significant impact on tolerability and safety. The impact of RBV can be clearly seen in Table 7 which compares the treatment emergent AEs in the pooled arms of Trial 068 in subjects receiving or not receiving RBV as a component of their treatment regimen. Additionally, the rate of discontinuation of study drug(s) due to AEs in Study 068 was higher in subjects who received RBV as a component of their treatment regimen (see below for additional detail).

**Table 7: C-EDGE TE: Treatment-Emergent Adverse Events in Pooled Arms +/- RBV, Regardless of Relatedness and Severity ( $\geq 5\%$  difference between arms)**

| Preferred Term         | EBR/GZR<br>x 12w or 16w (n=210) | EBR/GZR+RBV<br>x 12w or 16w (n=210) |
|------------------------|---------------------------------|-------------------------------------|
|                        | N (%)                           | N (%)                               |
| Fatigue                | 37 (18)                         | 60 (29)                             |
| Nausea                 | 13 (6)                          | 33 (16)                             |
| Anemia                 | 0                               | 29 (14)                             |
| Accidental overdose    | 4 (2)                           | 29 (14)                             |
| Dyspnea (includes DOE) | 3 (1)                           | 30 (14)                             |
| Pruritus               | 6 (3)                           | 22 (10)                             |
| Insomnia               | 11 (5)                          | 21 (10)                             |
| Vomiting               | 2 (1)                           | 16 (8)                              |
| Dyspnea exertional     | 1 (<1)                          | 11 (5)                              |

Source: NDA 208261, Clinical Review, S. Boyd and P. Viswanathan

Two treatment-emergent deaths occurred in Phase 3 clinical trials 060, 061, and 068 cumulatively. The treatment-emergent deaths were due to a strangulated hiatal hernia in one subject and previously undiagnosed lymphoma with abdominal and pericardial involvement in another subject. Both cases were confirmed by autopsy and both were judged unlikely to be related to study drug(s) by the clinical reviewer. One additional death occurred two weeks after completion of treatment. The cause of death was reported as ventricular arrhythmia presumably secondary to atherosclerosis of the coronary vessels, a finding documented at autopsy. This case was also judged as unlikely to be related to study drug(s) by the clinical reviewer as there was no evidence of cardiac toxicity during treatment (based on reported AEs, laboratory results, vital signs, and ECG results), and at the time of death, systemic exposure of EBR/GZR was unlikely given the half-life of both drugs. I concur with Dr. Boyd's assessment of causality in all of these cases.

The rates of serious AEs (SAEs) in clinical trials 060, 061, and 068 were low, ranging from 1-4% across trials. This was consistent with the rate of 3% reported for SAEs in the placebo group of trial 060. No specific SAE was reported in more than one subject. I concur with the clinical reviewer that the SAEs in the Phase 3 trials do not raise significant safety concerns. There was a

lack of concerning trends and the vast majority of subjects either had an alternate explanation for the SAE, experienced resolution of SAE with continued study treatment, or experienced negative dechallenge.

Overall, 1% (10/954) of subjects in the Phase 3 trials who received EBR/GZR with or without RBV and regardless of treatment duration discontinued study drug due to an AE. However, in Trial 068, discontinuations due to AEs occurred at a substantially higher rate in the arm receiving 16 weeks of EBR/GZR with RBV (5%, 5/106) compared to the other three treatment arms (0-1%). The majority of AEs leading to discontinuation in the 16 week EBR/GZR + RBV arm appeared to be related to RBV. These included depression +/- suicidal ideation in two subjects and decreased hemoglobin, dyspnea, palpitations, and pre-syncope in one subject. Another subject in the 16 week EBR/GZR + RBV arm developed a constellation of symptoms including dysphagia, confusional state, dyspnea, and anxiety approximately two weeks after treatment initiation, but the narrative included insufficient information to reliably assess causality. It is notable that no subjects in the arm receiving 16 weeks of EBR/GZR without RBV discontinued study drug(s) due to an AE. One subject in the 12 week EBR/GZR + RBV arm discontinued RBV only on Day 3 due to related affect lability, which quickly resolved despite completion of treatment with EBR/GZR alone.

Overall, laboratory analyses did not reveal any significant safety concerns that were not already well characterized prior to the NDA submission. Creatinine kinase (CK) elevations (all grades) occurred in slightly more subjects treated with EBR/GZR (9%) compared to placebo (6%); the majority of CK elevations in EBR/GZR-treated subjects were grade 1 (6%) or grade 2 (2%). The primary safety signal of interest, hepatotoxicity manifested by elevation of transaminase levels, is described in detail below under the sub-section entitled "Submission-Specific Safety Issues."

As EBR/GZR is comprised of well-characterized small molecules with no biologic components, there are no concerns regarding immunogenicity.

#### Specific safety studies/clinical trials

This sub-section will summarize the results of clinical trial 052, an ongoing Phase 2/3 trial in subjects with HCV infection and chronic kidney disease (CKD), including subjects receiving hemodialysis (HD).

Similar to the Phase 3 trials previously discussed, the most common AEs reported in the immediate treatment group (ITG) of Trial 052 were fatigue, headache, and nausea. These events occurred at similar rates in the placebo phase of the delayed treatment group.

As anticipated, due to the higher overall rates of morbidity and mortality in this population, SAEs (including deaths) occurred at a substantially greater frequency in this trial compared to the Phase 3 trials (060, 061, and 068) previously discussed. Deaths occurred in 1% of subjects in the ITG and 4% of subjects in the DTG. All of these deaths were judged by the clinical reviewer to be more likely related to co-morbidities and complications associated with CKD/HD than study drug(s); I concur with the clinical reviewer's assessment. SAEs occurred in 23% of subjects in the ITG and 20% of subjects in the DTG. However, SAEs judged related to study

drug(s) by investigators occurred in only 1% of subjects in both treatment groups. One notable SAE involved a subject in the active drug phase of the DTG who developed rising creatinine one week after beginning open-label EBR/GZR. A biopsy was performed which revealed interstitial nephritis. This SAE was judged as drug-related by the investigator and prompted discontinuation of treatment. Interstitial nephritis and other types of renal injury will continue to be assessed during post-marketing pharmacovigilance. No discontinuations of study drug(s) due to AEs occurred in subjects in the ITG, while discontinuations of study drug(s) due to AEs occurred in 4% of subjects in the placebo phase of the DTG.

Certain laboratory abnormalities are common among advanced CKD patients, such as low hemoglobin and elevated creatinine, amylase and alkaline phosphatase. A similar distribution of laboratory abnormalities reflecting this pattern was noted in the ITG and DTG of Trial 052. There was no evidence of a greater frequency or severity of hepatotoxicity as manifested by transaminitis or hyperbilirubinemia in Trial 052 as compared to the other Phase 3 trials.

#### Submission-specific safety issues

As discussed in Section 2 (Background), it was demonstrated early in clinical development (in PN003) that the use of GZR in conjunction with PR was associated with dose-related, late-occurring increases in transaminases. Late transaminase elevations > 2-fold the upper limit of normal (ULN) occurred in 4%, 3%, 21%, and 24% of subjects in the 100, 200, 400, and 800 mg dose groups in PN003, respectively, and were generally of larger magnitude in the 400 and 800 mg dose groups. There was one clear case of liver injury in a patient who received 800 mg of GZR, but symptoms and laboratory abnormalities resolved after stopping the drug. A characteristic pattern for these events was appreciated consisting of improvement and/or normalization of transaminases with initiation of GZR + PR treatment followed by a rapid elevation in transaminase levels generally occurring at or after Week 8 of treatment. The Applicant and the Agency agreed upon pre-specified definitions for “late ALT/AST elevations” and “hepatic events of clinical interest” as well as management strategies for hepatotoxicity in all future clinical trials involving GZR. Please refer to the Clinical Review for additional details on these definitions and management strategies. A similar pattern of late ALT/AST elevation was subsequently documented with the use of EBR/GZR (with or without RBV) in later drug development as described below.

In order to have the greatest ability to discern and describe hepatic events, the clinical reviewer pooled a number of clinical trials to form the hepatic safety population. The hepatic safety population consisted of 1558 subjects who received GZR 100 mg and EBR 50 mg with or without RBV for at least 12 weeks in six clinical trials including three Phase 2 and three Phase 3 trials (Trials 060, 061, and 068). Subjects in the DTG/placebo arm of Trial 060 served as a comparator.

As displayed in Table 8, treatment with EBR/GZR for at least 12 weeks resulted in a low but increased incidence of pre-specified hepatic abnormalities, including late ALT or AST elevations > 5x ULN, compared to placebo. Importantly, no placebo-treated subjects experienced an increase in liver enzymes >5x ULN, supporting the supposition that late ALT/AST elevations of this degree are likely drug-related rather than disease-related.

**Table 8: Liver Abnormalities and Events in the Hepatic Safety Population: EBR/GZR vs. Placebo**

| Event   | EBR/GZR +/- RBV x 12-18w<br>(n=1558) | Placebo x 12w<br>(n=105) |
|---|--------------------------------------|--------------------------|
|   | N (%)                                | N (%)                    |
| Pre-specified Hepatic Lab Abnormality or Event <sup>1</sup> | 18 (1.2)                             | 0                        |
| Pre-specified Late ALT/AST Elevation <sup>2</sup>           | 12 (0.8)                             | 0                        |

<sup>1</sup> Late ALT/AST elevation<sup>2</sup> or Hepatic ECI or Discontinuation due to Pre-specified Liver Event

<sup>2</sup> ALT or AST elevation >5 x ULN after TW4 with a normal ALT or AST between TW2 and TW4

Source: NDA 208261, Clinical Review, S. Boyd and P. Viswanathan, adapted

Table 9 summarizes mean ALT and AST values from baseline through the follow-up visit four weeks after end of treatment (FU4) for the 12 subjects who experienced a pre-specified late ALT/AST elevation event. All late ALT/AST events completely resolved, defined as ALT, AST, and total bilirubin levels within normal limits. Most events resolved by FU4, some as early as end of treatment, and all by FU12.

**Table 9: Mean Liver Enzyme Results in Subjects with a Pre-specified Late ALT/AST Elevation Event**

| N=12      | Baseline | Nadir | Peak | EOT <sup>1</sup> | FU4 |
|-----------|----------|-------|------|------------------|-----|
| ALT (U/L) | 68       | 19    | 396  | 249              | 24  |
| AST (U/L) | 65       | 24    | 221  | 151              | 28  |

<sup>1</sup>Three subjects discontinued at the time of peak ALT/AST, and therefore, the EOT values for these subjects are the same as the peak values. If these three subjects are removed from the EOT, the mean EOT ALT and AST falls to 89 U/L and 63 U/L, respectively.

EOT = end of treatment, FU4 = Follow-up visit four weeks after end of treatment

Normal range (Central lab): ALT [10-33 U/L], AST [10-36 U/L]

Source: NDA 208261, Clinical Review, S. Boyd and P. Viswanathan

Grade 1 total bilirubin elevations were noted in half of subjects with late ALT/AST elevation while no grade 3 or 4 bilirubin elevations were reported. An elevated absolute eosinophil count in conjunction with late ALT/AST elevation was rarely reported. Symptoms potentially related to hepatic injury were noted in only 1 of the 12 subjects in question and consisted of abdominal pain two days after onset of the late ALT/AST elevation event.

Higher late ALT/AST event rates were demonstrated in female, Asian, or older subjects as compared to male, White, or younger subjects, respectively (see Table 10 below). In population pharmacokinetic analyses using data from subjects who received the to-be marketed dose of 100 mg of GZR, GZR AUCs were estimated to be 30% higher in female subjects as compared to male subjects, 50% higher in Asian subjects as compared to White subjects, and 20% higher in older subjects (≥ 65 years old) as compared to younger subjects (< 65 years old). It is unclear to what extent the higher exposures contributed to the higher adverse event rates. Of note, cirrhotic subjects were not demonstrated to be at a higher risk of late ALT/AST elevations than non-cirrhotic subjects despite higher GZR exposures in cirrhotic subjects.

**Table 10: Observed rates of late AST/ALT elevation following 100 mg GZR administration in CHC patients**

| Population comparison   | Observed AST/ALT elevation event rates |
|-------------------------|--|
| Female vs. Male         | 1.4% (11/791) vs. 0.23% (3/1296)       |
| Asian vs. White         | 2.3% (4/175) vs. 0.8% (8/1579)         |
| Older (65+) vs. Younger | 1.4% (3/224) vs. 0.6% (11/1863)        |

<sup>†</sup>The observed rates were calculated using data from any subject who received 100 mg GZR (±EBR, ±Peg-IFN/ribavirin, ±sofosbuvir) at least 8 weeks (PN003, PN035, PN038, PN039, PN047, PN048, PN052, PN058, PN059, PN060, PN061, PN068, and PN074).

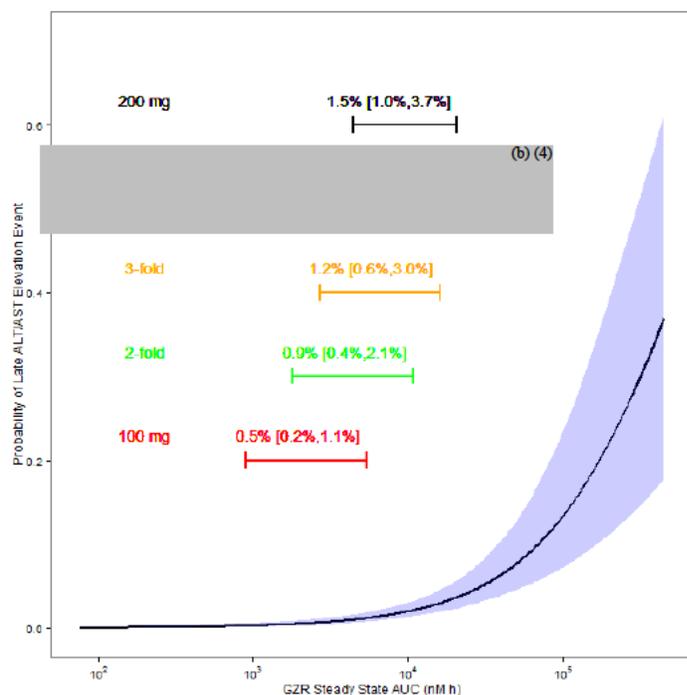
Source: Clinical Pharmacology Review Drs. Choi and Zhuang

The clinical pharmacology review team conducted exposure-safety analyses focusing on incidents of late ALT/AST elevations. For this assessment, they used data from thirteen Phase 2 and Phase 3 trials in which subjects received daily GZR doses ranging from 25 to 800 mg. As expected, the exposure-response analyses demonstrated that occurrence of late ALT/AST elevation was correlated with GZR exposures.

The Applicant analyzed the relationship between the predicted rate of late ALT/AST elevation events compared to the fold change in GZR exposure with 100 mg in a reference population. The reference population included non-cirrhotic, non-severe CKD, non-Asian HCV-infected subjects (i.e., subjects not expected to have higher GZR exposures) receiving GZR 100 mg in Phase 2 or Phase 3 studies. The predicted rate of late ALT/AST elevation events in the reference population was 0.5% with GZR 100 mg. The predicted rates with increased GZR exposures of 5-fold (corresponding to GZR 200 mg) and 14-fold (corresponding to GZR 200 – 400 mg) were approximately 2% and 5%, respectively. (b) (4)

The clinical pharmacology review team conducted an independent assessment of the exposure-response relationship between late ALT/AST elevations and GZR exposure (see Figure 3 below). They concluded that a 3-fold upper bound would be a more appropriate exposure threshold from a safety perspective (b) (4). A 3-fold increase in GZR exposure would be expected to result in a median late ALT/AST elevation event rate of 1.2% with an upper bound of 3% (90% CI). I concur with the clinical pharmacology review team’s recommendation for a 3-fold upper bound for GZR exposures. As noted in Section 5 of the CDTL review, this upper bound was used to guide labeling decisions with respect to intrinsic and extrinsic factors.

**Figure 3: Exposure-Safety Evaluation for GZR**



The red line represents the 90% prediction interval of GZR exposure covered by a dose of 100 mg and the number above the line shows the median (90%) predicted safety event rate for those exposures. The green and yellow bars represent a 2- and 3-fold increase in GZR exposure, respectively, compared to that of 100 mg.

Source: Clinical Pharmacology reviewers Drs. Choi and Zhuang

Prior to NDA submission, we requested that the Applicant assemble an independent committee of drug induced liver injury experts and practicing HCV clinicians to formally assess the hepatic safety profile of EBR/GZR. The committee concluded the following: 1) A late ALT/AST elevation event, and more specifically late ALT elevation events, is an appropriate marker for assessing hepatic safety of GZR; 2) No cases clearly fulfilled the accepted criteria for Hy's Law that would indicate significant hepatic injury, although some patients met the numerical criteria [please refer to the FDA Clinical Review for the complete details of the single subject receiving GZR/EBR who met numerical criteria for Hy's Law]; 3) At the recommended dose of EBR/GZR 100mg/50mg, the overall benefit: risk ratio is positive; 4) The overall level of concern regarding hepatic safety findings with EBR/GZR, administered at doses of 100mg/50mg is low; and 5) More specific recommendations for ALT monitoring should be provided in the label.

The primary clinical reviewer and I were in general agreement with the overall conclusions of the hepatic safety committee and agree that the benefit of treatment with EBR/GZR at the to-be-marketed dose outweighs the risk and implications of hepatic events. Of note, there were no liver-related deaths or SAEs and no discontinuations due to hepatic events that were not pre-specified. The late ALT/AST elevations that occurred in clinical trials with the to-be-marketed dose of EBR/GZR were predictable in frequency and severity and manageable with appropriate monitoring.

The Clinical Review also describes the results of focused safety analyses for cardiopulmonary events, musculoskeletal events, skin and soft tissue events, gastrointestinal events, neurological events, and renal events (in subjects with normal baseline renal function). No significant safety signals related to EBR/GZR were identified in these safety explorations.

## **9. Advisory Committee Meeting**

An advisory committee was not convened to discuss this application. EBR/GZR was granted breakthrough designation for both the treatment of HCV GT4 infection and the treatment of HCV GT1 infection in patients with end stage renal disease receiving hemodialysis.

## **10. Pediatrics**

To date, no trials in subjects < 18 years of age were conducted or are ongoing. The Applicant submitted an initial Pediatric Study Plan (iPSP) for EBR/GZR in advance of the NDA submission. The document was reviewed and found to be generally satisfactory by both the review division and the Pediatric Review Committee (PeRC). The Agency's recommendations for revisions were conveyed to the Applicant. The Applicant accepted the Division's recommendations, and both the Division and the PeRC approved of the Applicant's Agreed PSP. The Division issued a formal notice of Agreed PSP on February 10, 2015.

The Applicant requested a waiver for studying children < 3 years of age. The Division and PeRC granted this waiver based on the high rate of spontaneous viral clearance and lack of significant disease progression in this age group. The Applicant requested a deferral of pediatric studies until data from Phase 3 studies are complete and have been reviewed by the Agency. The Division and PeRC granted the deferral request based on the need for a thorough analysis of the adult safety data, particularly exposure-related hepatic events, to inform dose selection for pediatric studies.

The proposed pediatric development plan includes a (b) (4) study to evaluate the safety and efficacy of EBR/GZR in children ages 3 to < 18 years of age. (b) (4)

(b) (4)

(b) (4)

## 11. Other Relevant Regulatory Issues

- Financial disclosures

Financial disclosures were provided and reviewed for investigators involved in the key Phase 2/3 and Phase 3 trials, namely Trials 052, 060, 061, and 068. There were no financial disclosures of significant concern, individually or collectively. The financial disclosures do not impact the approvability of EBR/GZR. Please refer to the Clinical Review for additional details.

- Other Good Clinical Practice (GCP) issues

The clinical trials were conducted in accordance with ICH Good Clinical Practice (GCP) Guidelines.

- Office of Scientific Investigations (OSI) audits

Inspection sites were selected from two pivotal Phase 3 trials, Trial 060 and Trial 068, which encompassed the majority of the patient population reflected in the proposed indication. Six total sites were selected from the large number of sites per study primarily based on enrollment volume and protocol deviation frequency. Both domestic and foreign sites were selected (4 domestic sites and 2 sites located in France) because Clinical Trials 060 and 068 were conducted as global trials with substantial foreign enrollment. The clinical data submitted were deemed acceptable based on the inspection findings. Please refer to the OSI Consult Review for further details.

## 12. Labeling

### Prescribing Information

(N.B. Table numbers have not been finalized in labeling; therefore they are represented by letters in this section)

- **INDICATIONS AND USAGE section:**

The Applicant's proposed indication for Zepatier was for the treatment of chronic HCV genotypes 1, 4, <sup>(b) (4)</sup> infection in adults. <sup>(b) (4)</sup>

- **DOSAGE AND ADMINISTRATION section:**

Substantial revisions were made to this section including:

The addition of Section 2.1 entitled, Testing Prior to the Initiation of Therapy. This includes a subsection entitled, NS5A Resistance Testing in HCV Genotype 1a Infected Patients. The Agency's proposed language for this subsection is as follows: *Testing patients with HCV genotype 1a infection for the presence of virus with NS5A resistance-associated polymorphisms <sup>(b) (4)</sup> prior to initiation of treatment with Zepatier. In subjects receiving Zepatier for 12 weeks, sustained virologic response (SVR) rates were lower in genotype 1a-infected patients with one or more baseline NS5A resistance-associated polymorphisms at positions 28, 30, 31 or 93 at baseline [see Microbiology (12.4)], Table Y.* <sup>(b) (4)</sup>

However, the potential impact of the specific H58D polymorphism will be duly noted in Section 12.4 (Microbiology) of the USPI.

The Agency is also recommending substantial revisions to the Applicant's proposed dosage regimens and durations for EBR/GZR based on GT and prior treatment experience. Table X displays the Agency's current dosing recommendations which cover GT1 and GT4 patients.

**Table X: Agency's Current Dosing Recommendations for EBR/GZR**

| Patient Population   | Treatment                   | Duration |
|--|-----------------------------|----------|
| Genotype 1a* or 1b <sup>†</sup> : Treatment-naïve or PegIFN/RBV-experienced <sup>‡</sup> | ZEPATIER                    | 12 weeks |
| Genotype 1a* or 1b: PegIFN/RBV/PI-experienced <sup>§</sup>                               | ZEPATIER + RBV <sup>#</sup> | 12 weeks |

|   |                             |          |
|---|-----------------------------|----------|
| Genotype 4: Treatment-Naïve                     | ZEPATIER                    | 12 weeks |
| Genotype 4: PegIFN/RBV-experienced <sup>‡</sup> | ZEPATIER + RBV <sup>#</sup> | 16 weeks |

\*See section 2.1 Testing prior to the initiation of therapy in genotype 1a-infected patients.

<sup>‡</sup>Patients who have failed treatment with peginterferon alfa (PegIFN) + ribavirin (RBV).

<sup>#</sup>Patients who have failed treatment with peginterferon alfa + ribavirin + HCV protease inhibitor (PI) boceprevir, simeprevir, or telaprevir.

# For patients with CrCl less than or equal to 50 mL per minute, including patients receiving hemodialysis, refer to the ribavirin tablet prescribing information for the correct ribavirin dosage.

The Applicant's initial proposal for GT1a patients included EBR/GZR for 12 weeks for treatment naïve or treatment experienced relapsers (as consistently defined by the Applicant to include patients who relapsed after treatment with PR or PR + boceprevir, simeprevir, or telaprevir) and EBR/GZR for 16 weeks + RBV for prior treatment experienced patients (b) (4)

However, the Applicant's labeling did not address the impact of baseline NS5A polymorphisms, particularly with respect to treatment naïve patients. The Agency determined that a 12 week regimen of EBR/GZR without RBV is appropriate for GT1a infected patients without baseline NS5A polymorphisms regardless of prior PR-treatment experience. (b) (4)

(b) (4)

(b) (4)

(b) (4)

n regard to GT1a patients with prior PR + PI (boceprevir, simeprevir, or telaprevir) treatment experience, the Agency has determined that the recommended regimen should be EBR/GZR + RBV for 12 weeks as this was the only regimen studied in this population. (b) (4)

The Applicant's initial proposal for GT1b patients included a recommendation for EBR/GZR for 12 weeks without RBV in all GT1b patients regardless of prior treatment experience. The Agency agrees with this approach for DAA-naïve patients, but recommends a regimen of EBR/GZR + RBV for 12 weeks in GT1b patients with prior PR + PI (boceprevir, simeprevir, or telaprevir) treatment experience for the reasons outlined above for GT1a patients. (b) (4)

(b) (4)

The Applicant's initial proposal for GT4 patients included EBR/GZR for 12 weeks for treatment naïve or treatment experienced PR-relapsers and EBR/GZR for 16 weeks + RBV for prior PR-treatment experienced patients (b) (4) The Agency generally agrees with this approach but recommends the following:

- 1) EBR/GZR for 12 weeks in treatment naïve GT4 infected patients
- 2) EBR/GZR + RBV for 16 weeks in all PR-treatment experienced patients, including relapsers. The Agency is concerned that the reason for prior treatment failure may not be readily available to the HCV care provider and therefore suboptimal dosing may result.

Additionally, the data from Trial 068 supporting the Applicant's proposal included only two GT4 prior relapsers who received EBR/GZR for 12 weeks without RBV.

[Redacted] (b) (4)

The Applicant's initial proposal [Redacted] (b) (4)

[Redacted]

However, based on the Agency's current dosing recommendations for EBR/GZR [Redacted] (b) (4)

[Redacted] herefore, the Agency recommends that regimens for patients with severe renal impairment or ESRD, including patients on dialysis, should be consistent with the recommended regimens for all patients and should include the use of RBV if appropriate. The Rebetol USPI provides guidance on appropriate dosing of RBV in ESRD, including hemodialysis.

- **CONTRAINDICATIONS section:**

The following contraindications (CIs) are recommended by the Agency:

- If ZEPATIER is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. Refer to the ribavirin prescribing information for a list of contraindications for ribavirin.
- ZEPATIER is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) due to the expected significantly increased grazoprevir plasma concentration and the increased risk of alanine aminotransferase (ALT) elevations
- ZEPATIER is contraindicated with organic anion transporting polypeptide 1B (OATP1B) inhibitors, strong inducers of cytochrome P450 3A (CYP3A), or efavirenz

A complete list of drugs contraindicated with EBR/GZR is provided in tabular form in the product label. Please refer to Section 5 (Clinical Pharmacology) of this review as well as the Clinical Pharmacology Review for additional rationale supporting these CIs.

It is notable that the Applicant's initial labelling proposal for Child-Pugh B patients [Redacted] (b) (4) in this population. [Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4) The Division believes a contraindication in this patient population may be more effective in deterring potential off-label use of EBR/GZR in Child-Pugh B patients [Redacted] (b) (4)

- **WARNINGS AND PRECAUTIONS section:**

The Applicant proposed a Warning for increased risk of ALT elevations in the initial labeling. The language was found generally acceptable, however the Agency advocated for the following revisions which were subsequently accepted by the Applicant:

- The addition of the following statement defining populations with increased risk: *Higher rates of late ALT elevations occurred in the following subpopulations: female sex (2% [3/16 (b) (4)]), Asian race (2% [4/16 (b) (4)]), and age 65 years or older (2% [3/16 (b) (4)])*
- The addition of hepatic laboratory monitoring on treatment as follows: *Hepatic laboratory testing should be performed prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, additional hepatic laboratory testing should be performed at treatment week 12.*

- **MICROBIOLOGY section:**

(b) (4)  
(b) (4). Section 2.1 (NS5A Resistance Testing in HCV Genotype 1a Infected Patients) in Dosage and Administration directs the reader to this table.

- **CLINICAL STUDIES section:**

- The Agency worked closely with the Applicant to ensure that the clinical trials of primary importance were displayed in as clear, concise, and clinically meaningful a manner as possible given the complexity of the data. This included the removal of data that were not directly relevant to dosing recommendations.

## 13. Postmarketing Recommendations

### Risk Evaluation and Management Strategies (REMS)

Based on the overall safety profile of EBR/GZR, a REMS is not recommended.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The following is the Agency's listing of recommended PMR/PMCs to date.

The approval of EBR/GZR will trigger required pediatric studies under PREA. These PREA post-marketing requirements incorporate the studies outlined in the iPSP (see Section 10, Pediatrics) as follows:

1. Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of elbasvir and grazoprevir in pediatric subjects 3 to 17 years of age with chronic hepatitis C infection
2. Collect and analyze long-term safety data for subjects enrolled in the pediatric elbasvir and grazoprevir safety, pharmacokinetic and efficacy study. Data should be collected for at least 3 years following the end of treatment in order to characterize the long-term safety of elbasvir and grazoprevir including growth assessment, sexual maturation and characterization of elbasvir and grazoprevir resistance associated substitutions in viral isolates from subjects failing therapy.

In order to further characterize resistance to EBR/GZR and cross-resistance with other DAAs, the Agency has recommended the following virology-related postmarketing studies. As resistance in HCV is considered a significant safety issue, our recommendation will be a PMR under FDAAA.

1. Please conduct site-directed mutant phenotype analyses of grazoprevir against HCV replicons carrying the following NS3 substitutions: I48A/V (GT1a), T185S (GT1a/GT1b), E357G/K (GT1a). Please include cross-resistance analyses with approved NS3/4A inhibitors.
2. Please conduct site-directed mutant phenotype analyses of elbasvir against HCV replicons carrying the following NS5A substitutions: K24R (GT1a), H54Y (GT4d), E62D (GT1a), D427N (GT1a). Please include cross-resistance analyses with approved NS5A inhibitors

In order to assess durability of SVR, the Division will issue PMCs to provide SVR24 data from the key efficacy trials of EBR/GZR. The PMC language has not been finalized at the time of this writing.

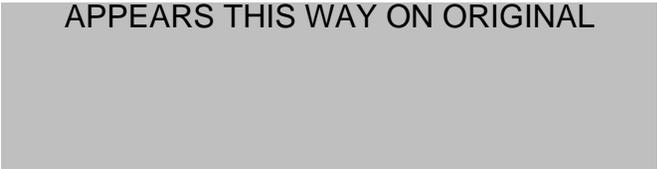
In the hope of establishing an optimal EBR/GZR-based treatment regimen for patients with baseline NS5A polymorphisms, the Division will issue a PMC to conduct a trial in HCV GT1a infected subjects with baseline NS5A resistance-associated polymorphism to evaluate if a longer duration of treatment with EBR/GZR and the addition of ribavirin reduces the rate of virologic

failure and the rate of treatment-emergent drug resistant viral populations. The PMC language has not been finalized at the time of this writing.

## **14. Recommended Comments to the Applicant**

There are no additional comments to be conveyed to the Applicant at this time.

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12/21/2015