SUPPLEMENTARY DATA

Grazoprevir and Elbasvir plus Ribavirin
For Chronic HCV Genotype-1 Infection
After Failure of Combination Therapy Containing a Direct-Acting Antiviral Agent

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EXPANDED ABSTRACT

Background: Further treatment options are needed for patients not achieving a sustained virologic response (SVR) on regimens containing directly-acting antiviral agents (DAA). The Phase-2 C-SALVAGE study evaluated an investigational interferon-free combination of grazoprevir (a NS3/4A protease inhibitor) and elbasvir (a NS5A inhibitor) with ribavirin for patients with chronic HCV genotype-1 infection who had failed licensed DAA-containing therapy.

Methods: C-SALVAGE was an open-label study of grazoprevir 100 mg and elbasvir 50 mg QD with weight-based ribavirin BID for 12 weeks in cirrhotic and non-cirrhotic patients with chronic HCV genotype-1 infection who had not attained SVR after ≥4 weeks of peginterferon and ribavirin plus either boceprevir, telaprevir, or simeprevir. Exclusion criteria included decompensated liver disease, hepatocellular carcinoma, HIV or HBV co-infection, thrombocytopenia <50 x 10^3/μL, or hypoalbuminemia <3.0 g/dL. Resistance-associated variants (RAVs) were identified at baseline by population sequencing. The primary efficacy outcome was a HCV RNA level below the assay limit of quantification (15 IU/mL) 12 weeks after the end of treatment (SVR12).

Results: Of the 79 patients treated with ≥1 dose of study drug, 34 (43.0%) had cirrhosis and 30 (38.0%) had genotype-1a infection. 66 (84%) patients had a history of virologic failure on a regimen containing a NS3/4A protease inhibitor; 12 of the other 13 patients discontinued prior treatment because of side-effects. At entry, 34 (43.6%) of 78 evaluable patients harbored NS3 RAVs. At the end of therapy, RNA levels were <15 IU/mL in all 79 (100%) patients. SVR12 rates were 76/79 (96.2%) overall, 28/30 (93.3%) patients with genotype 1a infection, 63/66 (95.5%) in patients with prior virologic failure, 33/36 (91.7%) in patients with identified NS3 RAVs, and 32/34 (94.1%) in cirrhotic patients. None of the 5 serious adverse events were considered drug-related.

Conclusions: In the C-SALVAGE trial, 79 patients with genotype-1 infection who had failed protease inhibitor-based regimens were treated with grazoprevir and elbasvir plus ribavirin, including 43% with compensated cirrhosis and 84% with prior virologic failure. Despite a high prevalence of RAVs at baseline, the only failures were 3 (3.8%) relapses. Grazoprevir and elbasvir plus ribavirin for 12 weeks provide a promising new and well-tolerated treatment option for patients after failure of triple therapy containing an earlier-generation protease inhibitor.


Reasons for Exclusion from the Per-Protocol Population

A total of 9 study participants were excluded from the per-protocol analysis for the following protocol violations:

- 1 participant had received prior therapy with a DAA not allowed by protocol
  - 1 patient had been previously treated with a course of faldaprevir + PR in addition to telaprevir + PR

- 4 participants had taken an unapproved DAA regimen prior to enrollment
  - 2 patients had received a short-duration regimen of simeprevir + PR in a clinical trial
  - 1 patient had received an additional 8 weeks of boceprevir beyond the 32-week maximum treatment duration as specified in the product label
  - 1 patient had received a 4-week lead-in of PR therapy alone before initiation of telaprevir

- 2 participants had taken an incorrect dose of study medication
  - both patients received 10 mg (instead of 50 mg) of elbasvir/day for the first 8 weeks of study treatment

- 1 participant was being evaluated for active malignancy at the time of entry
  - 1 patient was undergoing evaluation for an laryngeal neoplasm (but did not inform the site personnel until after randomization)

- 1 participant was not reasonably compliant with study medications
  - 1 patient with poor drug adherence throughout the treatment course

SVR_{12} was achieved in 68 (97.1%) of the 70 patients in the per-protocol population and in 8 (88.9%) of the 9 excluded patients. The sole excluded patient who did not attain SVR_{12} had previously received faldaprevir.
Table S1. Signature NS3 RAVs associated with early generation protease inhibitors detected by populations sequencing at baseline.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of patients</th>
<th>Number of patients with sequenced virus</th>
<th>Number of patients</th>
<th>Baseline NS3 RAVs (number of patients harboring the specified substitution)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Without detectable NS3 RAVs</td>
<td>With NS3 RAVs with ≤5X decreased GZP susceptibility*</td>
<td>With NS3 RAVs with &gt;5X decreased GZP susceptibility*</td>
</tr>
<tr>
<td>All</td>
<td>79</td>
<td>78</td>
<td>44 (56.4%)</td>
<td>30 (38.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With NS3 RAVs with ≤5X decreased GZP susceptibility*</td>
<td></td>
<td>With NS3 RAVs with &gt;5X decreased GZP susceptibility*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With NS3 RAVs with &gt;5X decreased GZP susceptibility*</td>
<td></td>
<td>With NS3 RAVs with &gt;5X decreased GZP susceptibility*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>V36M/L (8), T54S (4), Q80K (11), V107I (2), S122G (7), R155D/K/T (10), A156T (1), D168E/N (3), M175L (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sub-genotype</td>
<td></td>
<td>GT1a 30</td>
<td>30</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GT1b 49</td>
<td>48</td>
<td>37 (77.1%)</td>
</tr>
<tr>
<td>Cirrhosis Status</td>
<td></td>
<td>No 45</td>
<td>44</td>
<td>25 (56.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes 34</td>
<td>34</td>
<td>19 (55.9%)</td>
</tr>
<tr>
<td>Prior protease-inhibitor treatment</td>
<td></td>
<td>Boceprevir 28</td>
<td>27</td>
<td>17 (63.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Telaprevir 43</td>
<td>43</td>
<td>24 (55.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simeprevir 8</td>
<td>8</td>
<td>3 (37.5%)</td>
</tr>
</tbody>
</table>

EC<sub>50</sub>, effective concentration of drug necessary to inhibit replicon growth by 50% compared to the absence of drug; SVR<sub>12</sub>, sustained virologic response 12 weeks after cessation of study medications.
The following NS3A substitutions were considered as signature NS3 RAVs for the older protease inhibitors: V36A/G/L/M/I, T54A/C/G/S, V55A/I, Y56H, Q80K/R, V107I, 122A/G/R, 1132V, R155X, A156S/T/V/F/G, V158I, D168X, I/V170A/F/T/V, and M175L [2, 12].

*Fold-change in the EC₅₀ of grazoprevir to inhibit the variant replicon relative to a wild-type control referent [18].

*Based on GT1a NS3 RAVs: Y56H, R155G/T/W, A156G/T/V/L, and D168A/G/T/V/L/I/F/Y/E/H/K/. RAVs with >5-fold increased resistance to grazoprevir are in bold print.

*Includes only patients in the numerator with a past history of virologic failure.
Table S2a. Impact of signature NS3 RAVs associated with early generation protease inhibitors at baseline on SVR12 rates.

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Overall SVR12</th>
<th>SVR12 in patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Without detectable NS3 RAVs</td>
</tr>
<tr>
<td></td>
<td>75/78 (96.2%)</td>
<td>44/44 (100%)</td>
</tr>
<tr>
<td>Subtypes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GT1a</td>
<td>28/30 (93.3%)</td>
<td>7/7 (100%)</td>
</tr>
<tr>
<td>GT1a with Q80K</td>
<td>10/11 (90.9%)</td>
<td>----</td>
</tr>
<tr>
<td>GT1a without Q80K</td>
<td>18/19 (94.7%)</td>
<td>----</td>
</tr>
<tr>
<td>GT1b</td>
<td>47/48 (97.9%)</td>
<td>37/37 (100%)</td>
</tr>
<tr>
<td>Cirrhosis status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>43/44 (97.7%)</td>
<td>25/25 (100%)</td>
</tr>
<tr>
<td>Yes</td>
<td>32/34 (94.1%)</td>
<td>19/19 (100%)</td>
</tr>
<tr>
<td>Prior protease inhibitor treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boceprevir</td>
<td>26/27 (96.3%)</td>
<td>17/17 (100.0%)</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>41/43 (95.3%)</td>
<td>24/24 (100%)</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>8/8 (100%)</td>
<td>3/3 (100%)</td>
</tr>
</tbody>
</table>

EC₅₀, effective concentration of drug necessary to inhibit replicon growth by 50% compared to the absence of drug; SVR₁₂, sustained virologic response 12 weeks after cessation of study medications.

*The following NS3A substitutions were considered as signature NS3 RAVs for the older protease inhibitors: V36A/G/L/M/I, T54A/C/G/S, V55A/I, Y56H, Q80K/R, V107I, 122A/G/R, I132V, R155X, A156S/T/V/F/G, V158I, D168X, I/V170A/F/T/V, and M175L [2, 12].

**Fold-change in the EC₅₀ of grazoprevir to inhibit the variant replicon relative to a wild-type control referent [18].
Table S2b. Impact of specific protease inhibitors and signature RAVs at baseline on SVR_{12} rates.

<table>
<thead>
<tr>
<th>Prior DAA</th>
<th>Prior all-cause failures (N)</th>
<th>Baseline RAVs§, n/N (%)</th>
<th>SVR_{12} in patients with baseline RAVs, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NS3</td>
<td>NS5A</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>28</td>
<td>10/27 (37.0%)</td>
<td>3/28 (10.7%)</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>8</td>
<td>5/8 (62.5%)</td>
<td>0/8 (0.0%)</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>43</td>
<td>19/43 (44.2%)</td>
<td>5/43 (10.7%)</td>
</tr>
<tr>
<td>Any</td>
<td>79</td>
<td>34/78 (43.6%)</td>
<td>8/46 (17%)</td>
</tr>
</tbody>
</table>

§Patients may have harbored quasi-species with >1 mutation in the NS3 and/or NS5A genes.
Table S3. Subjects With Adverse Events (Incidence >0%) During the Treatment Phase and First 14 Follow-Up Days Regardless of Causality.

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With one or more adverse events</td>
<td>63</td>
<td>(79.7)</td>
</tr>
<tr>
<td>With no adverse events</td>
<td>16</td>
<td>(20.3)</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>6</td>
<td>(7.6)</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear discomfort</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3</td>
<td>(3.8)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>5</td>
<td>(6.3)</td>
</tr>
<tr>
<td>Anal fistula</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Aphthous stomatitis</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Change of bowel habit</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Cheilitis</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
<td>(6.3)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6</td>
<td>(7.6)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2</td>
<td>(2.5)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
<td>(11.4)</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Rectal haemorrhage</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>(5.1)</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>12</td>
<td>(15.2)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2</td>
<td>(2.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>22</td>
<td>(27.8)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2</td>
<td>(2.5)</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Category</td>
<td>Count</td>
<td>Percentage</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>-------</td>
<td>------------</td>
</tr>
<tr>
<td>Jaundice</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td>12</td>
<td>(15.2)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Erysipelas</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Genital herpes</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Hordeolum</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Influenza</td>
<td>3</td>
<td>(3.8)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Pharyngitis bacterial</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
<td>3</td>
<td>(3.8)</td>
</tr>
<tr>
<td>Accidental overdose</td>
<td>3</td>
<td>(3.8)</td>
</tr>
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<td><strong>Investigations</strong></td>
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<td>(5.1)</td>
</tr>
<tr>
<td>Haemoglobin decreased</td>
<td>4</td>
<td>(5.1)</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
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<td>(5.1)</td>
</tr>
<tr>
<td>Decreased appetite</td>
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<td>(2.5)</td>
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<tr>
<td>Dehydration</td>
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<td>(1.3)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>1</td>
<td>(1.3)</td>
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<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>9</td>
<td>(11.4)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3</td>
<td>(3.8)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>2</td>
<td>(2.5)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3</td>
<td>(3.8)</td>
</tr>
<tr>
<td><strong>Neoplasms benign, malignant and unspecified</strong></td>
<td>2</td>
<td>(2.5)</td>
</tr>
<tr>
<td>Laryngeal squamous cell carcinoma</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Seborrhoeic keratosis</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>17</td>
<td>(21.5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>(2.5)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>2</td>
<td>(2.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>(19.0)</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
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<td>(13.9)</td>
</tr>
<tr>
<td>Apathy</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Depression</td>
<td>2</td>
<td>(2.5)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7</td>
<td>(8.9)</td>
</tr>
<tr>
<td>Irritability</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Medical Condition</td>
<td>Count</td>
<td>Percentage</td>
</tr>
<tr>
<td>------------------------------------------------------</td>
<td>-------</td>
<td>------------</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Renal colic</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic, and mediastinal disorders</strong></td>
<td><strong>7</strong></td>
<td><strong>(8.9)</strong></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Cough</td>
<td>2</td>
<td>(2.5)</td>
</tr>
<tr>
<td>Dry throat</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>2</td>
<td>(2.5)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Oropharyngeal discomfort</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td><strong>12</strong></td>
<td><strong>(15.2)</strong></td>
</tr>
<tr>
<td>Alopecia</td>
<td>2</td>
<td>(2.5)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>2</td>
<td>(2.5)</td>
</tr>
<tr>
<td>Erythema</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3</td>
<td>(3.8)</td>
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<tr>
<td>Rash</td>
<td>3</td>
<td>(3.8)</td>
</tr>
<tr>
<td>Rash erythematous</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Rash macular</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Skin maceration</td>
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<td>(1.3)</td>
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<tr>
<td><strong>Vascular disorders</strong></td>
<td><strong>4</strong></td>
<td><strong>(5.1)</strong></td>
</tr>
<tr>
<td>Haematoma</td>
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<td>(1.3)</td>
</tr>
<tr>
<td>Hot flush</td>
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<td>(1.3)</td>
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<tr>
<td>Hypertension</td>
<td>1</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Pallor</td>
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<td>(1.3)</td>
</tr>
</tbody>
</table>

Percentages calculated by dividing the n patients with the specified adverse event divided by the 79 total patients. Terms adapted from MedDRA version 17.1. A subject is counted only once in each applicable row but can be included in multiple times under the same organ-system header.
Table S4. Subjects With Laboratory Findings That Met Predetermined Criteria During the Treatment Phase and First 14 Follow-Up Days.

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Grade 1:</th>
<th>Grade 2:</th>
<th>Grade 3:</th>
<th>Grade 4:</th>
</tr>
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<tbody>
<tr>
<td>Albumin (gm/dL)</td>
<td></td>
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<tr>
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<tr>
<td>Grade 2: 2.0 - 2.9</td>
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<td>(0.0)</td>
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<tr>
<td>Grade 3: &lt;2.0</td>
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<td>(0.0)</td>
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<td></td>
</tr>
<tr>
<td>Grade 4: Not Applicable</td>
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<td>Alkaline Phosphatase (IU/L)</td>
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</tr>
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<td>Grade 1: 1.25 - 2.5 x ULN</td>
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<td>(5.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2: 2.6 - 5.0 x ULN</td>
<td>0/79</td>
<td>(0.0)</td>
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<td></td>
</tr>
<tr>
<td>Grade 3: 5.1 - 10.0 x ULN</td>
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<td>(0.0)</td>
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<td>(0.0)</td>
<td></td>
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</tr>
<tr>
<td>1.1 - 2.5 x Baseline</td>
<td>1/79</td>
<td>(1.3)</td>
<td></td>
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<tr>
<td>&gt;2.5 - 5.0 x Baseline</td>
<td>0/79</td>
<td>(0.0)</td>
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<td></td>
</tr>
<tr>
<td>&gt;5.0 x Baseline</td>
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<td>(0.0)</td>
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<tr>
<td>Amylase (IU/L)</td>
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<td>10/79</td>
<td>(12.7)</td>
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<td>Grade 2: 1.6 - 2.0 x ULN</td>
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<td>(1.3)</td>
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<td>(0.0)</td>
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<tr>
<td>Creatine Kinase (IU/L)</td>
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<td>(0.0)</td>
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<tr>
<td>Creatinine (mg/dL)</td>
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<td></td>
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</tr>
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<td>&gt;2.5 x Baseline</td>
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<td>(0.0)</td>
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<tr>
<td>Direct Bilirubin (mg/dL)</td>
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<tr>
<td>Grade 1: 1.1 - 1.5 x ULN</td>
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<tr>
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</tr>
<tr>
<td>&gt;2.5 - 5.0 x Baseline</td>
<td>13/79</td>
<td>(16.5)</td>
<td></td>
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</tr>
<tr>
<td>&gt;5.0 - 10.0 x Baseline</td>
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<td>(0.0)</td>
<td></td>
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<tr>
<td>&gt;10.0 x Baseline</td>
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<td>Gamma Glutamyl Transferase (IU/L)</td>
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<tr>
<td>Test</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
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<td>---------</td>
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<tr>
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<td><strong>Alanine Aminotransferase (IU/L)</strong></td>
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<td>(0.0)</td>
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<tr>
<td>Grade 2: 2.6 - 5.0 x ULN</td>
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<td>(0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3: 5.1 - 10.0 x ULN</td>
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<tr>
<td>Grade 4: &gt;10.0 x ULN</td>
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<td>(0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1 - 2.5 x Baseline</td>
<td>0/79</td>
<td>(0.0)</td>
<td></td>
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<tr>
<td>&gt;2.5 - 5.0 x Baseline</td>
<td>0/79</td>
<td>(0.0)</td>
<td></td>
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<tr>
<td>&gt;5.0 x Baseline</td>
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<td>(0.0)</td>
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<td><strong>Aspartate Aminotransferase (IU/L)</strong></td>
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<td>(0.0)</td>
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</tr>
<tr>
<td>Grade 2: 2.6 - 5.0 x ULN</td>
<td>0/79</td>
<td>(0.0)</td>
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<tr>
<td>Grade 3: 5.1 - 10.0 x ULN</td>
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<td>(0.0)</td>
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</tr>
<tr>
<td>Grade 4: &gt;10.0 x ULN</td>
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<td>(0.0)</td>
<td></td>
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<tr>
<td>1.1 - 2.5 x Baseline</td>
<td>1/79</td>
<td>(1.3)</td>
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<tr>
<td>&gt;2.5 - 5.0 x Baseline</td>
<td>0/79</td>
<td>(0.0)</td>
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<td></td>
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<tr>
<td>&gt;5.0 x Baseline</td>
<td>0/79</td>
<td>(0.0)</td>
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<tr>
<td><strong>Bilirubin (mg/dL)</strong></td>
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<tr>
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<td>(5.1)</td>
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<tr>
<td>Grade 4: &gt;5.0 x ULN</td>
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<td>(1.3)</td>
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<tr>
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<td>(35.4)</td>
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<td>(2.5)</td>
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<tr>
<td>&gt;10.0 x Baseline</td>
<td>0/79</td>
<td>(0.0)</td>
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<td><strong>Prothrombin International Normalized Ratio</strong></td>
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<tr>
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<td>4/79</td>
<td>(5.1)</td>
<td></td>
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<tr>
<td>Grade 3: 2.1 - 3.0 x ULN</td>
<td>0/79</td>
<td>(0.0)</td>
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<td></td>
</tr>
<tr>
<td>Grade 4: &gt;3.0 x ULN</td>
<td>1/79</td>
<td>(1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1.5 x Baseline</td>
<td>4/79</td>
<td>(5.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Eosinophils/Leukocytes (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5% and Baseline &lt;5%</td>
<td>10/79</td>
<td>(41.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5% and Baseline ≥5%</td>
<td>2/79</td>
<td>(5.1)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Hemoglobin (gm/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocytes (x $10^3/\mu L$)</td>
<td>Grade 1: 2.0 - 2.5</td>
<td>1/79 (1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 2: 1.5 - 1.999</td>
<td>1/79 (1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3: 1.0 - 1.499</td>
<td>0/79 (0.0)</td>
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</tr>
<tr>
<td></td>
<td>Grade 4: &lt;1.0</td>
<td>1/79 (1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes (x $10^3/\mu L$)</td>
<td>Grade 1: 0.60 - 0.65</td>
<td>3/79 (3.8)</td>
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</tr>
<tr>
<td></td>
<td>Grade 2: 0.50 - 0.599</td>
<td>1/79 (1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3: 0.35 - 0.499</td>
<td>0/79 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 4: &lt;0.35</td>
<td>0/79 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils (x $10^3/\mu L$)</td>
<td>Grade 1: 1.00 - 1.3</td>
<td>4/79 (5.1)</td>
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</tr>
<tr>
<td></td>
<td>Grade 2: 0.75 - 0.999</td>
<td>0/79 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3: 0.50 - 0.749</td>
<td>0/79 (0.0)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Grade 4: &lt;0.50</td>
<td>0/79 (0.0)</td>
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<td></td>
</tr>
<tr>
<td>Platelet (x $10^3/\mu L$)</td>
<td>Grade 1: 100 - 124.999</td>
<td>3/79 (3.8)</td>
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<tr>
<td></td>
<td>Grade 2: 50 - 99.999</td>
<td>2/79 (2.5)</td>
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<tr>
<td></td>
<td>Grade 3: 25 - 49.999</td>
<td>1/79 (1.3)</td>
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<tr>
<td></td>
<td>Grade 4: &lt;25</td>
<td>0/79 (0.0)</td>
<td></td>
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</tr>
</tbody>
</table>

A patient was included in the highest applicable toxicity grade per test as determined by his/her worst post-baseline test result that was also worse than baseline. For tests with additional non-graded criterion categories, a patient was also included in the highest applicable non-graded category as determined by his/her worst post-baseline abnormal test result. The baseline test result is the result from the latest sample before the start of study therapy. LLN = lower limit of normal range; ULN, upper limit of normal range.
**C-SALVAGE:** GZR 100 mg + EBR 50 mg + weight-based RBV
x 12 weeks in treatment-experienced patients after failure of PI + PR
**Efficacy Endpoints Over Time (Full Analysis Set)**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Response Rate</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>EOT Response</td>
<td>100%</td>
<td>[95.4, 100]</td>
</tr>
<tr>
<td>SVR4</td>
<td>97.5%</td>
<td>[91.2, 99.7]</td>
</tr>
<tr>
<td>All Patients</td>
<td>96.2%</td>
<td>[89.3, 99.2]</td>
</tr>
<tr>
<td>Prior Virologic Failure</td>
<td>95.5%</td>
<td>[87.3, 99.1]</td>
</tr>
<tr>
<td>Prior Nonvirologic Failure</td>
<td>100%</td>
<td>[75.3, 100.0]</td>
</tr>
</tbody>
</table>

Grazoprevir (100 mg)
Elbasvir (50 mg)
Figure S1. Forest plot displaying SVR12 by subgroup.

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<tr>
<th>Category</th>
<th>n/m</th>
<th>SVR12 % (95% CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td>76/79</td>
<td>96.2% (89.3, 99.2)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>43/46</td>
<td>93.5% (82.1, 98.6)</td>
</tr>
<tr>
<td>Female</td>
<td>33/33</td>
<td>100% (89.4, 100.0)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>10/11</td>
<td>90.9% (58.7, 99.8)</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>66/68</td>
<td>97.1% (89.8, 99.6)</td>
</tr>
<tr>
<td><strong>HCV genotype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>28/30</td>
<td>93.3% (77.9, 99.2)</td>
</tr>
<tr>
<td>1b</td>
<td>48/49</td>
<td>98.0% (89.1, 99.0)</td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>44/45</td>
<td>97.8% (88.2, 99.9)</td>
</tr>
<tr>
<td>Yes</td>
<td>32/34</td>
<td>94.1% (80.3, 99.3)</td>
</tr>
<tr>
<td><strong>Screening HCV RNA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤800,000 IU/mL</td>
<td>27/29</td>
<td>93.1% (77.2, 99.2)</td>
</tr>
<tr>
<td>&gt;800,000 IU/mL</td>
<td>49/50</td>
<td>98.0% (89.4, 99.9)</td>
</tr>
<tr>
<td><strong>Signature NS3 RAVs at baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None detected</td>
<td>44/44</td>
<td>100% (92.0, 100)</td>
</tr>
<tr>
<td>≤5× fold elevation in GZR EC_{50}</td>
<td>28/30</td>
<td>93.3% (77.9, 99.2)</td>
</tr>
<tr>
<td>&gt;5× fold elevation in GZR EC_{50}</td>
<td>3/4</td>
<td>75.0% (19.4, 99.4)</td>
</tr>
<tr>
<td><strong>Time since prior DAA regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.1 years</td>
<td>26/29</td>
<td>89.7% (72.6, 97.8)</td>
</tr>
<tr>
<td>≥1.1 years</td>
<td>50/50</td>
<td>100% (92.9, 100)</td>
</tr>
<tr>
<td><strong>Prior PI therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boceprevir</td>
<td>27/28</td>
<td>96.4% (81.7, 99.9)</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>41/43</td>
<td>95.3% (84.2, 99.4)</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>8/8</td>
<td>100% (63.1, 100)</td>
</tr>
</tbody>
</table>

*One patient did not undergo sequencing of the NS3 gene.*