Sofosbuvir/Velpatasvir Fixed-Dose Combination for 12 Weeks Compared to Sofosbuvir with Ribavirin for 24 Weeks in Genotype 3 HCV-Infected Patients: The Randomized Controlled Phase 3 ASTRAL-3 Study

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Background

- **Sofosbuvir (SOF)**\(^1,2\)
  - Potent antiviral activity against HCV GT 1–6
  - Once-daily, oral, 400-mg tablet

- **Velpatasvir (VEL; GS-5816)**\(^3-5\)
  - Picomolar potency against GT 1–6
  - 2\(^{nd}\)-generation inhibitor with improved resistance profile

- **SOF/VEL FDC**
  - Once daily, oral, FDC (400/100 mg)

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Background and Aim
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- Phase 2 studies demonstrated that SOF + VEL administered as single agents resulted in high SVR12 rates in treatment-naïve and treatment-experienced patients with HCV GT 3 infection\(^1,2\)

- SOF and VEL have been coformulated as an FDC

- This Phase 3 study evaluated SOF/VEL for 12 weeks compared to SOF + RBV for 24 weeks in HCV GT 3 infected patients

Study Design
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- Open-label, active-comparator trial
- Broad inclusion criteria
- 1:1 randomization to SOF/VEL or SOF + RBV
  - Stratified by prior treatment (TN/TE) and cirrhosis (presence/absence)
- Conducted at 76 sites in US, Canada, UK, Germany, France, Italy, Australia, and New Zealand
Study Methods
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- HCV genotyping
  - Versant HCV genotype LiPA 2.0
  - TruGene
- HCV RNA
  - COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0 with LLOQ of 15 IU/mL
- HCV deep sequencing
  - Illumina MiSeq Platform (1% cut-off)
- Cirrhosis
  - Liver biopsy Metavir stage 4 or Ishak stage 5 or 6, or
  - Fibrotest >0.75 and APRI >2, or
  - Fibrosan >12.5 kPa
## Results: Demographics
### ASTRAL-3

<table>
<thead>
<tr>
<th></th>
<th>SOF/VEL 12 Weeks n=277</th>
<th>SOF + RBV 24 Weeks n=275</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (range)</td>
<td>49 (21–76)</td>
<td>50 (19–74)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>170 (61)</td>
<td>174 (63)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>250 (90)</td>
<td>239 (87)</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (range)</td>
<td>26 (17–48)</td>
<td>27 (17–56)</td>
</tr>
<tr>
<td>Cirrhosis, n (%)</td>
<td>80 (29)</td>
<td>83 (30)</td>
</tr>
<tr>
<td>Treatment experienced, n (%)</td>
<td>71 (26)</td>
<td>71 (26)</td>
</tr>
<tr>
<td>IL28B CC, n (%)</td>
<td>105 (38)</td>
<td>111 (40)</td>
</tr>
<tr>
<td>HCV RNA, log₁₀ IU/mL (range)</td>
<td>6.2 (3.7–7.5)</td>
<td>6.3 (3.6–7.5)</td>
</tr>
<tr>
<td>Patients, n (%)</td>
<td>SOF/VEL 12 Weeks n=277</td>
<td>SOF + RBV 24 Weeks n=275</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Completed drug</td>
<td>275 (99)</td>
<td>254 (92)</td>
</tr>
<tr>
<td>Discontinued</td>
<td>2 (&lt;1)</td>
<td>21 (8)</td>
</tr>
<tr>
<td>AE</td>
<td>0</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Noncompliance</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>0</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>
Results: SVR12
ASTRAL-3

*p-value for superiority of SOF/VEL compared with SOF + RBV.
Error bars represent 95% confidence intervals.
Results: SVR12 by Cirrhosis and Treatment History

ASTRAL-3

Error bars represent 95% confidence intervals.
Results: SVR12 by Cirrhosis and Treatment History

ASTRAL-3

Error bars represent 95% confidence intervals.
### Results: Safety

**ASTRAL-3**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>SOF/VEL 12 Weeks n=277</th>
<th>SOF + RBV 24 Weeks n=275</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td>245 (88)</td>
<td>260 (95)</td>
</tr>
<tr>
<td>Grade 3–4 AE</td>
<td>12 (4)</td>
<td>23 (8)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>6 (2)</td>
<td>15 (5)</td>
</tr>
<tr>
<td>D/C due to AE</td>
<td>0</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Laboratory Abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>20 (7)</td>
<td>47 (17)</td>
</tr>
<tr>
<td>Hb &lt;10 g/dL</td>
<td>0</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Hb &lt;8.5 g/dL</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Deaths
  - Gunshot wounds, 52-year-old white male (Treatment Day 74)
  - Unknown causes, 58-year-old white female (Treatment Day 141)
  - Unknown causes, 66-year-old white male (118 days after completing treatment)

- Each assessed by investigator as unrelated to study drug
## Results: AEs in >10% of Patients

### ASTRAL-3

<table>
<thead>
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<th>SOF/VEL 12 Weeks n=277</th>
<th>SOF + RBV 24 Weeks n=275</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>90 (32)</td>
<td>89 (32)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>71 (26)</td>
<td>105 (38)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>31 (11)</td>
<td>74 (27)</td>
</tr>
<tr>
<td>Nausea</td>
<td>46 (17)</td>
<td>58 (21)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>34 (12)</td>
<td>33 (12)</td>
</tr>
<tr>
<td>Irritability</td>
<td>23 (8)</td>
<td>40 (15)</td>
</tr>
<tr>
<td>Cough</td>
<td>14 (5)</td>
<td>35 (13)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8 (3)</td>
<td>35 (13)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>9 (3)</td>
<td>30 (11)</td>
</tr>
</tbody>
</table>
Conclusions
ASTRAL-3

- SOF/VEL for 12 weeks resulted in a 95% SVR12 rate in patients with HCV GT 3 infection
  - Statistically superior to SOF + RBV for 24 weeks (p <0.001)
  - 91% SVR12 rate in patients with cirrhosis

- SOF/VEL was well tolerated and, compared with SOF + RBV, lacked toxicities commonly associated with RBV

- SOF/VEL for 12 weeks provides a simple, safe, highly effective, RBV-free treatment for patients with HCV GT 3 infection
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Back Up
Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection

Study Endpoints
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- **Primary endpoint: SVR12**
  - HCV RNA <LLOQ at post-treatment Week 12

- **Efficacy analysis**
  - Non-inferiority of SOF/VEL to SOF + RBV with 10% margin
    - Lower bound of 95% CI for difference in SVR12 rates must be greater than –10%
  - If non-inferiority established, then superiority evaluated at significance level of 0.05

- **Safety**
  - AEs and discontinuations
  - Laboratory abnormalities
Results: SVR12 by Cirrhosis or Treatment History
ASTRAL-3

Error bars represent 95% confidence intervals.
Results: SVR12 by Cirrhosis or Treatment History
ASTRAL-3

Error bars represent 95% confidence intervals.
SVR12 was 84% (21/25) in patients with Y93H