New Research On Direct-acting Antivirals For The Treatment Of Hepatitis C
Highlights From EASL 2014, London, U.K.

This report contains highlights from a selection of abstracts and posters presented during the 2014 meeting of the European Association for the Study of the Liver (EASL) held in London, U.K. from April 9-15. These highlights were compiled by Drs. Alnoor Ramji and Eberhard L. Renner.

ABT Triple-therapy (3D) Regimens
Reviews of the SAPPHIRE I, SAPPHIRE II and TURQUOISE II studies, examining the efficacy and safety of ABT triple therapy in a range of patient types with HCV including treatment-naïve, treatment-experienced and compensated-cirrhosis populations.

Daclatasvir-containing Regimens
Efficacy and safety in the HALLMARK DUAL study in cirrhotic and non-cirrhotic patients, and a study of the effect of ribavirin on the safety of DCV + SOF in a broad range of patients.

MK-5172 + MK-8742 ± RBV
Examining results of the ongoing phase 2 C-WORTHY study among treatment-naïve patients with or without HIV co-infection, and among treatment-experienced non-responders.

Sofosbuvir-based Regimens
Reviews of several key reports including the ION-1, ION-2, ION-3 and COSMOS studies, examining the role of these regimens in various populations and the treatment duration required.

Consulting Authors:
Alnoor Ramji, MD
Clinical Assistant Professor of Medicine,
Division of Gastroenterology,
Providence Health Care,
University of British Columbia
Vancouver, BC

Eberhard L. Renner, MD, FRCPC
Professor of Medicine
Director, GI Transplantation
University Health Network/
University of Toronto
Toronto, ON

This report was made possible through the support of Bristol-Myers Squibb Canada.
ABT Triple Therapy (3D) in Treatment-naïve HCV Genotype 1 (SAPPHIRE I)


Objectives:
To evaluate the efficacy and safety of the combination of ABT-450/r, ombitasvir (formerly ABT-267) and dasabuvir (formerly ABT-333) (3D) + ribavirin (RBV) among treatment-naïve patients with chronic HCV, genotype 1.

Methods:
72-week study in which all patients received 12 weeks of therapy with 3D + RBV.
• The first 12 weeks of the study was the double-blind period, in which 473 patients received 3D + RBV and 158 received placebo. The initial placebo group then received treatment for the subsequent 12 weeks.
• At 24 weeks, SVR12, the primary endpoint, was analyzed for the initial treatment group. The results were compared (non-inferiority and superiority analyses) vs. a calculated historical rate for telaprevir + pegIFN/RBV (78%).

Study Population:
631 treatment-naïve patients with HCV, genotype 1. Patients with cirrhosis were not included in this study.
• Across treatment arms at baseline, 68.4-69.6% had a non-CC IL28B genotype, 66.5-68.1% were genotype 1a. Most patients (75.4-76.7%) were fibrosis stages F0 or F1.

Results:
• The overall SVR12 was 96.2% in the treatment group (Figure 1). This was both non-inferior and superior to the historical control rate.
  - SVR12 rates were also high in the GT1a and GT1b subgroups.
• Among patients who did not achieve SVR12, there was one virologic breakthrough, seven relapses, seven discontinuations and three lost to follow-up (Table 1).

Authors’ Conclusions:
The SVR12 rate was 96.2% for treatment-naïve GT1-infected patients receiving 12 weeks of co-formulated ABT-450/r, ombitasvir + dasabuvir + RBV. The SVR12 rates were high regardless of subtype (95.5% and 98.0% for GT1a and GT1b, respectively). The rate of virologic failure was low (0.2% breakthrough rate and 1.5% relapse rate). The regimen was generally well tolerated, with a low rate of study-drug discontinuation due to AEs.

This study has also been published: Feld JJ, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014; 370(17):1594-603
ABT Triple Therapy (3D) in Treatment-experienced HCV Genotype 1 (SAPPHIRE II)


Objectives:
To evaluate the efficacy and safety of the combination of ABT-450/r, ombitasvir (formerly ABT-267) and dasabuvir (formerly ABT-335) (3D) + ribavirin (RBV) among treatment-experienced patients with chronic HCV, genotype 1.

Methods:
72-week study in which all patients received 12 weeks of therapy with 3D + RBV.
- The first 12 weeks of the study was the double-blind period, in which 475 patients received 5D + RBV and 158 received placebo. The initial placebo group then received treatment for the subsequent 12 weeks.
- At 24 weeks, SVR12, the primary endpoint, was analyzed for the initial treatment group. The results were compared (non-inferiority and superiority analyses) vs. a calculated historical rate for telaprevir + pegIFN/RBV (65%) among patients previously treated with pegIFN/RBV.

Study population:
594 treatment-experienced patients with HCV, genotype 1. Patients with cirrhosis were not included in this study.
- Across treatment arms at baseline, 88.6-92.8% had a non-CC IL28B genotype, 58.2-58.8% were genotype 1a and 48.5-49.2% were prior null responders. Most patients (67.0-68.0%) were fibrosis stages F0 or F1.

Results:
- The overall SVR12 was 96.5% in the treatment group (Figure 1). This was both non-inferior and superior to the historical control rate.
  - SVR12 rates were also high in the GT1a and GT1b subgroups.
  - SVR12 rates were high among patients with prior null response (95.2%) (Figure 2)
- Among patients who did not achieve SVR12, there were no cases of virologic breakthrough, seven relapses (2.4%) and eight discontinuations.
  - Among the seven relapsers, five had at least one resistance-associated variant.

Authors’ Conclusions:
The SVR12 rate was 96.5% for treatment-experienced GT1-infected patients receiving 12 weeks of ABT-450/r/ombitasvir + dasabuvir + RBV. The SVR12 rates were high regardless of subtype (96.0% and 96.7% for GT1a and GT1b, respectively) and across all prior pegIFN/RBV response groups (95.5% in prior relapers, 100% in prior partial responders and 95.2% in prior null responders). The regimen was generally well tolerated, with a low rate of study-drug discontinuation due to AEs.

ABT Triple Therapy (3D) in HCV Patients with Compensated Cirrhosis (TURQUOISE II)


Objectives:
To evaluate the efficacy and safety of the combination of ABT-450/r, ombitasvir (formerly ABT-267) and dasabuvir (formerly ABT-555) (3D) + ribavirin (RBV) among patients with HCV and compensated cirrhosis.

Methods:
72-week study in which patients were randomized to receive 12 or 24 weeks of therapy with 3D + RBV.
- Primary endpoint was SVR12, compared for non-inferiority and superiority against a historical control (telaprevir + pegIFN/RBV).

Study Population:
580 patients with HCV and compensated cirrhosis, both treatment-naïve and treatment-experienced.
- Across treatment arms at baseline, 80.2-85.2% had a non-CC IL28B genotype, 67.5-70.3% were genotype 1a, and 57.0-58.7% were treatment-experienced (including 36.0-36.1% who were prior null responders). The proportion with a baseline Child-Pugh score > 5 was 18.3% to 18.6%, the proportion with serum albumin < 5.5 g/dL was 10.5-12.0% and the proportion with baseline platelets < 100 x10^9/L was 19.2-21.6%.

Results:
- The overall SVR12 rates were 91.8% and 95.9% for the 12-week and 24-week arms, respectively ($p = 0.089$ for the between-group comparison) (Figure 1).
  - Both groups were found to be significantly superior to the historical control.
  - SVR12 rates were also high in the GT1a (88.6% and 94.2% for 12- and 24-week groups, respectively and GT1b (98.5% and 100%).
  - Among prior null responders, the SVR12 was 80.0% for the 12-week regimen and 92.9% for the 24-week arm.
- Among patients who did not achieve SVR12, there were four cases of virologic breakthrough, thirteen relapses (2.4%) and seven discontinuations (Table 1).

Authors’ Conclusions:
This was the first dedicated trial of an IFN-free regimen in cirrhotic patients, including patients often ineligible for clinical trials (low platelets, low albumin, radiographic ascites). The SVR rates were 92% and 96% with 12 and 24 weeks of treatment, respectively, with high SVR rates in all subgroups analyzed. Twelve and 24 weeks of treatment were similarly well tolerated, with low rates of treatment discontinuation. Persons with genotype 1a with a prior null response and cirrhosis are a sub-group that appears to have a more favorable response with 24 weeks of therapy. Efficacy and safety in this large cirrhotic population was similar to non-cirrhotics treated with the same regimen.

CONSULTING AUTHORS’ COMMENTARY ON THE ABT 3D TRIALS: These three phase-3 studies have illustrated that the combination of ABT-450/r, ombitasvir and dasabuvir (3D) + ribavirin is highly efficacious for the treatment of patients with HCV. The patients enrolled in these three studies included those who were previously treatment-naïve, those who were treatment experienced and those with and without cirrhosis. The results from SAPHIRE I and II suggest that the regimen was approximately equally efficacious among those who were treatment-naïve and those who were treatment-experienced. In the TURQUOISE II study persons with cirrhosis, both treatment-naïve and experienced, achieved high SVR rates with 12 weeks of therapy. Though, in patients with genotype 1a, cirrhosis and previous null response, SVR12 with the 24-week regimen was higher than with the 12-week regimen. In all three studies, the regimen was found to be safe and well tolerated. These study reports did not provide much information on resistance-associated variants and their potential role in treatment failures, but given the low number of failures in the studies, it would be difficult to draw any conclusions in this regard.

Table 1. TURQUOISE II: Patients Not Achieving SVR12

<table>
<thead>
<tr>
<th>Event, n/N (%)</th>
<th>3D + RBV</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12-week arm</td>
<td>24-week arm</td>
<td></td>
</tr>
<tr>
<td>Patients not achieving SVR12</td>
<td>17/208 (8.2)</td>
<td>7/172 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Premature discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event, n</td>
<td>4/208 (1.9)</td>
<td>0/172 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Withdrew consent/other, n</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Virologic failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breakthrough Relapse through PTW12</td>
<td>1/208 (0.5)</td>
<td>0/172 (0.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12/203 (5.9)*</td>
<td>1/164 (0.6)**</td>
<td></td>
</tr>
</tbody>
</table>

*7/12 were GT1a null responders. **Significant difference.
- Virologic failure occurred in 17/380 patients (4.5%).
- 15 of these patients had at least 1 resistance-associated variant at the time of virologic failure.
- D168V (NS3) and Q30R (NS5A) seen most frequently in GT1a-infected patients.
- The significance and persistence of these variants are under investigation.

This study has also been published: Poordad F, et al. ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014 Apr 11 [Epub ahead of print].
Daclatasvir + Asunaprevir in HCV Genotype 1b
(HALLMARK DUAL)


Objectives:
To evaluate the efficacy and safety of the combination of daclatasvir (DCV) and asunaprevir (ASV) among patients with HCV genotype 1b.

Methods:
48-week study in which patients received 24 weeks of therapy with DCV + ASV, followed by 24 weeks of follow-up.
- Primary endpoint was SVR12

Study Population:
745 patients with HCV, including 305 treatment-naïve (205 of which are included in this analysis), 205 previous nonresponders and 255 interferon ineligible/intolerant.
- At baseline, 61-84% had a non-CC IL28B genotype and 16-47% had cirrhosis.

Results:
- The overall SVR12 rates were 90% for treatment-naïve patients, 82% for previous nonresponders and 82% for IFN ineligible/intolerant (Figure 1).
- Virologic response was similar among those with and without cirrhosis (Figure 2).
- Among patients who did not achieve SVR12, among treatment-naïve patients, 4% were due to virologic breakthrough and 3% due to relapse; among previous non-responders, 15% were due to breakthrough and 4% due to relapse; and among IFN ineligible/intolerant, 9% were due to breakthrough and 6% due to relapse.

Authors’ Conclusions:
All-oral DCV + ASV therapy achieved SVR12 rates up to 90% in treatment-naïve, 82% in non-responder and 82% in IFN ineligible/intolerant patients with genotype 1b. SVR12 rates were similar in non-cirrhotic (85%) and cirrhotic (84%) patients. No differences were observed by age, gender, race, IL28B genotype or prior IFN/RBV treatment experience. DCV + ASV was generally safe and well tolerated; only 2% of patients discontinued due to adverse events. DCV is being further evaluated in all-oral combinations in multiple patient populations of high unmet need.

CONSULTING AUTHORS’ COMMENTARY: The SVR12 rate showed that daclatasvir + asunaprevir is a very effective regimen in genotype 1b and is well tolerated. Cirrhosis does not appear to affect the regimen’s efficacy. Although the SVR12 rates appear lower than those reported with some other regimens at this meeting, one must caution against comparing non-head-to-head studies.
Daclatasvir + Sofosbuvir ± Ribavirin in HCV


**Objectives:**
To evaluate the efficacy and safety of the combination of daclatasvir (DCV) and sofosbuvir (SOF) among a population of patients with HCV and a broad range of baseline characteristics.*

**Methods:**
Open-label study in which patients received DCV + SOF ± ribavirin (RBV) for 12 or 24 weeks.

- Primary endpoint was SVR12.
- For the analysis presented at EASL, the focus of interest was the impact of RBV on the safety profile of the daclatasvir/sofosbuvir regimen.

**Study Population:**
211 patients with HCV, including 126 treatment-naïve, 85 with previous virologic failure with telaprevir or boceprevir plus peginterferon alfa-RBV.

- At baseline, across treatment arms, 50-95% had a non-CC IL28B genotype and 7-20% had a Metavir F4 score.

**Results:**
- With respect to efficacy, SVR12 rates were 98-100% in patients with genotype 1 (treatment-naïve and treatment-experienced) and 88-100% in treatment-naïve patients with genotypes 2 or 3 (results previously published [Table 1]*).
- With respect to overall safety, there was little difference between the arms that contained RBV and those that did not (Table 2).
  - There was one discontinuation due to adverse events (AEs) in each of the RBV arms, and none in the non-RBV arms.
- The most common AEs in all arms were fatigue, headache and nausea.
- AEs previously identified as being associated with RBV (e.g., anemia, cough, anxiety) were more common in the arms that included RBV.
- Psychiatric and cardiovascular AEs were also more common in the RBV arms.

**Authors’ Conclusions:**
DCV + SOF with or without RBV is generally well tolerated, with fatigue, headache and nausea being the most frequently reported AEs. Rates of serious AEs, grade 3/4 AEs and AEs leading to discontinuation were similar across treatment types. Ribavirin use was associated with an increased rate of AEs that included anemia, neuropsychiatric disorders and cardiac disorders. DCV + SOF is being further investigated in the ALLY phase 5 studies in patients who are cirrhotic or post-transplant (ALLY-1), HCV/HIV co-infected (ALLY-2) or GT3 infected (ALLY-3).

### Table 1. Efficacy Summary

<table>
<thead>
<tr>
<th>Patient group</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DCV + SOF</td>
</tr>
<tr>
<td>12 weeks</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Genotype 1, treatment-naïve</td>
<td>100% (41/41)</td>
</tr>
<tr>
<td>Genotype 1, previous PI failure</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Genotypes 2 or 3, treatment-naïve</td>
<td>Not evaluated</td>
</tr>
</tbody>
</table>

*Non-SVR12 patient was lost to follow-up.

### Table 2. Safety Summary

<table>
<thead>
<tr>
<th>Patient group</th>
<th>DCV + SOF</th>
<th>DCV + SOF + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 weeks</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>1 (2.4)</td>
<td>7 (8.8)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>0</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>AEs leading to dose interruption</td>
<td>0</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>AEs leading to dose reduction</td>
<td>NA*</td>
<td>NA*</td>
</tr>
<tr>
<td>Grade 3/4 AEs</td>
<td>1 (2.4)</td>
<td>2 (2.5)</td>
</tr>
</tbody>
</table>

*Lowest hemoglobin level on treatment; change from baseline calculated for lowest level on treatment.

**CONSULTING AUTHORS’ COMMENTARY:** Once-daily oral treatment with the NS5A inhibitor DCV + SOF has previously been shown to be associated with high SVR12 rates in untreated patients with genotypes 1, 2 or 3 and in patients with genotype 1 in whom previous treatment with protease inhibitors had failed. The safety observations from this poster echo those of other trials evaluating direct-acting antivirals (DAAs) with or without ribavirin for the treatment of HCV. Ribavirin use was associated with an increased rate of AEs which, as expected, included anemia.

**MK-5172 + MK-8742 ± RBV in Various Groups with HCV (C-WORTHY)**


**Objectives:**
To evaluate the efficacy and safety of the combination of MK-5172 + MK-8742 among a variety of different subgroups of patients with HCV (Figure 1):
- HIV/HCV co-infected, treatment-naïve, non-cirrhotic patients;
- HCV mono-infected, treatment-naïve, non-cirrhotic patients;
- HCV mono-infected, treatment-naïve, cirrhotic patients; and
- HCV mono-infected, treatment-experienced, null responders.

**Methods:**
Patients were treated with 12 or 18 weeks of MK-5172 + MK-8742 ± RBV.
- Those with cirrhosis received the 18-week regimen, while those without received 12 weeks.
- In each analysis, there was an arm with RBV and an arm without RBV.

**Results:**
- SVR rates have ranged from 90% to 98% across the treatment groups (Table 1).
- This trial is ongoing – many of the efficacy results are from early analyses (e.g., SVR4)

**Figure 1. C-WORTHY Study Design**
- MK-5172: once-daily NS3/4A second-generation protease inhibitor
- MK-8742: once-daily NS5A replication complex inhibitor
- MK-5172/MK-8742: high barrier to resistance, activity against common resistance-associated variants

**Table 1. C-WORTHY: Overall Efficacy For 12 Week Regimens (Intention to Treat)**

<table>
<thead>
<tr>
<th>Population</th>
<th>Cirrhosis</th>
<th>MK-5172/MK-8742 + RBV</th>
<th>MK-5172/MK-8742 (no RBV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV/HCV co-infected, treatment-naïve</td>
<td>Non-cirrhotic</td>
<td>28/29 (97%)</td>
<td>26/29 (90%)</td>
</tr>
<tr>
<td>HCV mono-infected, treatment-naïve</td>
<td>Non-cirrhotic</td>
<td>80/85 (94%)</td>
<td>43/44 (98%)</td>
</tr>
<tr>
<td>HCV mono-infected, treatment-naïve</td>
<td>Cirrhotic</td>
<td>28/31 (90%)</td>
<td>28/29 (97%)</td>
</tr>
<tr>
<td>HCV mono-infected, null</td>
<td>Cirrhotic and non-cirrhotic</td>
<td>30/32 (94%)</td>
<td>30/33 (91%)</td>
</tr>
</tbody>
</table>

These results support the ongoing phase-3 development of MK-5172 + MK-8742 ± RBV in various populations.

**CONSULTING AUTHORS’ COMMENTARY ON THE C-WORTHY STUDIES:** The combination of these two direct-acting antivirals results in high SVR rates across a diverse group of patient types, including prior treatment failures, those with cirrhosis and persons with HIV co-infection. Use of ribavirin does not appear to increase the overall SVR rate. However, these phase-2 studies involve only small numbers of patients and many of the analyses are, as yet, incomplete.
12 or 24 Weeks of Sofosbuvir/Ledipasvir in Treatment-naïve Genotype 1 HCV (ION-1)


**Objectives:**
To determine if the combination of sofosbuvir/ledipasvir (SOF/LDV) is effective in treatment-naïve, genotype-1, HCV-infected patients, to determine whether 12 weeks of treatment is sufficient and to determine the impact of including ribavirin in the regimen.

**Methods:**
HCV-infected patients were randomized to receive SOF/LDV ± RBV for 12 or 24 weeks (four treatment arms). Randomization was further stratified by HCV subtype and presence or absence of cirrhosis. The primary endpoint was SVR12 (superiority comparison vs. historical control rate of 60%).

**Study Population:**
865 patients were enrolled. Across treatment arms, 65-76% had a non-CC IL28B genotype and 15-17% had cirrhosis at baseline.

**Results:**
- **SVR 12 rates were 97% to 99% across treatment arms (Figure 1).**
  - No significant difference between arms.
  - Most non-SVR12 patients were lost to follow-up (Table 1).
  - The single patient with virologic breakthrough was deemed to be non-adherent to treatment.
  - The only true treatment failure observed was a relapse (not virologic failure).
  - No significant difference was seen among subgroups, including GT1a vs. 1b, cirrhotic vs. non-cirrhotic.
- **Presence of baseline NS5A mutations did not significantly impact SVR12 rates (96% SVR among these patients).**
  - However, both patients who relapsed had baseline NS5A mutation.

**Authors’ Conclusions:**
SOF/LDV for 12 weeks achieved an SVR12 rate of 99% in treatment-naïve GT1 patients. Adding RBV and/or extending SOF/LDV treatment duration to 24 weeks did not increase SVR12 rates. Patients with cirrhosis had similar high SVR rates. The presence of baseline NS5A mutations had no impact on SVR. SOF/LDV with or without RBV was safe and well tolerated. The addition of RBV contributed to a higher incidence of AEs and laboratory abnormalities.

---

**Figure 1. Results: SVR12 GT1 Treatment-naïve (ION-1)**

<table>
<thead>
<tr>
<th></th>
<th>LDV/SOF n = 214</th>
<th>LDV/SOF ± RBV n = 217</th>
<th>LDV/SOF n = 217</th>
<th>LDV/SOF + RBV n = 217</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12</td>
<td>211 (99)</td>
<td>211 (97)</td>
<td>212 (98)</td>
<td>215 (99)</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>0</td>
<td>0</td>
<td>1 (&lt; 1)</td>
<td>0</td>
</tr>
<tr>
<td>Relapse</td>
<td>1 (&lt; 1)</td>
<td>0</td>
<td>1 (&lt; 1)</td>
<td>0</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>2 (&lt; 1)</td>
<td>6 (3)</td>
<td>3 (1)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

- Single on-treatment breakthrough was due to non-compliance
  - patient had no detectable levels of LDV or SOF at the time of virologic failure

---

This study has also been published: Afifal N, et al. *Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection.* N Engl J Med 2014 Apr 11 [Epub ahead of print].
8 or 12 Weeks of Sofosbuvir/Ledipasvir in Treatment-naïve Genotype 1 HCV (ION-3)


Objectives:
To determine whether eight weeks of treatment with the combination of sofosbuvir/ledipasvir (SOF/LDV) is effective in treatment-naïve, genotype-1, HCV-infected patients, to determine whether there is a difference between 8 and 12 weeks of treatment and/or between the inclusion or exclusion of ribavirin in the regimen.

Methods:
HCV-infected patients were randomized to receive SOF/LDV ± RBV for eight weeks or SOF/LDV for 12 weeks (three treatment arms). Randomization was further stratified by HCV subtype and presence or absence of cirrhosis. The primary endpoint was SVR12 (non-inferiority comparison among the groups).

Study Population:
647 patients without cirrhosis were enrolled. Across treatment arms, 72-74% had a non-CC IL28B genotype.

Results:
- SVR 12 rates were 95% to 95% across treatment arms (Figure 1).
  - No significant difference between arms.
  - Most non-SVR12 patients were relapses (Table 1).

Authors’ Conclusions:
In patients without cirrhosis, SOF/LDV with or without RBV for eight weeks yielded high SVR rates, similar to treatment for 12 weeks. Host and viral factors traditionally associated with lower SVR rates did not affect SVR12 rates. An eight-week SOF/LDV treatment regimen is safe and effective for genotype-1 naïve persons without cirrhosis.

---

**Figure 1. Results: Non-inferiority Comparison**

GT1 Treatment-naïve (ION-3)

![Figure 1](image-url)

**Table 1. Results: Reasons For Not Achieving SVR**

GT1 Treatment-naïve (ION-3)

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>8 weeks</th>
<th>12 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDV/SOF</td>
<td>LDV/SOF + RBV</td>
</tr>
<tr>
<td>SVR12</td>
<td>202 (94)</td>
<td>201 (93)</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Relapse</td>
<td>11 (5)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>2 (&lt; 1)</td>
<td>6 (3)</td>
</tr>
</tbody>
</table>

---

*This study has also been published: Kowdley K, et al. Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis. N Engl J Med 2014-Apr 10 [Epub ahead of print].*
12 or 24 Weeks of Sofosbuvir/Ledipasvir in Treatment-experienced
Genotype 1 HCV (ION-2)

Afzal N, et al. All oral fixed-dose combination sofosbuvir/ledipasvir for 12 or 24 weeks in treatment-experienced

Objectives:
To determine if the combination of sofosbuvir/ledipasvir (SOF/LDV) is effective in treatment-experienced, genotype-1, HCV-infected patients, to determine whether 12 weeks of treatment is sufficient and to determine the impact of including ribavirin in the regimen.

Methods:
HCV-infected patients were randomized to receive SOF/LDV ± RBV for 12 or 24 weeks (four treatment arms). Randomization was further stratified by HCV subtype, presence or absence of cirrhosis and prior treatment response. The primary endpoint was SVR12 (superiority comparison vs. historical control null rate of 25%).

Study Population:
440 patients were enrolled. Across treatment arms, 85-91% had a non-CC II.28B genotype, 20% had cirrhosis at baseline, 41-46% were prior non-responders and 46-61% had previously failed protease inhibitor therapy.

Results:
- SVR 12 rates were 94% to 99% across treatment arms (Figure 1).
  - No significant difference between arms.
  - Most non-SVR12 patients were relapses, all of which were in the 12-week arms (Table 1).
  - The single patient with virologic breakthrough was deemed to be non-adherent to treatment.
  - The only true treatment failure observed was a relapse (not virologic failure).
  - Most of the patients who relapsed had cirrhosis.
- Presence of baseline NS5A mutations did not significantly impact SVR12 rates (89% SVR among these patients)
  - However, all 11 patients who relapsed had NS5A mutation at the time of relapse and 6 of these had the mutation at baseline.

Authors’ Conclusions:
SOF/LDV with or without RBV resulted in an SVR12 of 94-99% in treatment-experienced GT1 patients. Baseline NS5A mutations had no effect on SVR. RBV did not enhance SVR rates, alter viral kinetics or prevent relapse. The majority of patients who relapsed had cirrhosis. SOF/LDV ± RBV was safe and well tolerated. The addition of RBV contributed to a higher incidence of AEs and laboratory abnormalities.

CONSULTING AUTHORS’ COMMENTARY ON THE PHASE 3 ION STUDIES: These three phase-3 studies have illustrated that the combination of sofosbuvir and ledipasvir is highly efficacious for the treatment of patients with HCV genotype 1 infection. This includes patients who were previously treatment-naïve and those who were treatment experienced and those with and without cirrhosis and other factors previously associated with lower rates of sustained virologic response. Among the key findings are that there does not seem to be any additional benefit to including ribavirin in the treatment regimen. With respect to duration, the studies suggest that the optimal durations may be eight weeks for treatment-naïve patients without cirrhosis, 12 weeks for treatment-naïve patients with cirrhosis and treatment-experienced patients without cirrhosis. For treatment-experienced patients with cirrhosis, a 24-week regimen of SOF/LDV may be considered. Due to the low number of patients who relapsed in these studies, it is difficult to make any firm conclusions about the impact of resistance-associated variants on treatment success. With respect to safety, each of the studies showed that SOF/LDV was safe and well tolerated.

This study has also been published: Afzal N, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014 Apr 17; 370(16):1483-93.
Sofosbuvir-based Regimens in Treatment-experienced Genotypes 2 and 3


Objectives:
To test the effectiveness of retreatment with 24 weeks of sofosbuvir/ribavirin (SOF/RBV) or 12 weeks of SOF + PEG/RBV for patients who had previously relapsed following prior SOF-based therapies.

Methods and patients:
Interim report of an open-label study: retreatment with 24-week SOF/RBV or 12-week SOF + PEG/RBV for GT2 (n = 11) and GT3 (n = 96) patients who failed treatment in phase-2 and -3 studies.

Results:
SVR 12 rates (primary endpoint) were 92% for 12 weeks of SOF + PEG/RBV and 65% for 24 weeks SOF+RBV (Figure 1).
• The between-group difference was even more pronounced among patients with cirrhosis (88% vs. 47%).

CONSULTING AUTHORS’ COMMENTARY: Treatment for persons with HCV genotype 3 has become challenging, despite the new potent DAAAs. The optimal regimen is still being explored. The data in this study are not yet mature, with many persons still on therapy. However, this preliminary analysis suggests that the 12-week regimen of SOF + PEG/RBV may be the treatment of choice for retreatment in persons with genotype 3, particularly if cirrhosis is present. At present, the European and AASLD guidelines would suggest 24 weeks of SOF/RBV for retreatment of genotype 3 with/without cirrhosis.

Simeprevir + Sofosbuvir ± Ribavirin in HCV (COSMOS)


Objectives:
To determine the efficacy and safety of simeprevir + sofosbuvir (SMV/SOF) with or without ribavirin (RBV) among patients with hepatitis C, genotype 1 and advanced fibrosis (Metavir F3–4).

Methods:
Sub-analysis of the open-label COSMOS study; 87 patients with HCV GT1 and advanced fibrosis were randomized to receive SMV/SOF ± RBV for 12 or 24 weeks (four treatment arms).

Results:
Overall SVR 12 rate (primary endpoint) was 94%, with rates from 95% to 100% across treatment arms (Figure 2).
• The SVR12 rates were high across subgroups

CONSULTING AUTHORS’ COMMENTARY: The COSMOS study is a relatively small, phase-2 study. Results reveal that the simeprevir + sofosbuvir regimen results in a high SVR rate in treatment-naïve patients, as well as treatment-experienced (null) genotype 1 patients with or without cirrhosis. The 12-week regimen of SMV/SOF appears as efficacious as a 24-week course, and ribavirin does not appear to increase efficacy. This regimen is suggested in the AASLD 2014 guidelines, with both of these agents available in Canada. However, using them together would be considered an “off-label” use of each product.
Sofosbuvir Regimens for Patients with Negative Predictive Factors


Objectives:
To evaluate the influence of multiple, concomitant negative baseline host and viral factors on treatment outcome in patients receiving sofosbuvir (SOF)-based regimens.

Methods:
Retrospective analysis of data for 871 patients from six phase-2 and -3 studies of sofosbuvir-containing regimens.
- Investigators identified predictors of relapse and applied them to the pooled population of SOF-treated patients to determine their impact on SVR12 rates.

Results:
- Multivariate analysis identified six predictors of relapse: treatment experienced, male, weight ≥ 75 kg, IL28B non-CC genotype, cirrhosis and HCV RNA ≥ 800,000 IU/mL.
- SVR12 rates by number of these predictors are shown in Figure 1.

CONSULTING AUTHORS’ COMMENTARY: The risk-factor analysis suggests that sofosbuvir retains most of its efficacy even among patients with four negative predictive factors (88% SVR12 in such patients in this analysis). Although these are retrospective findings, they are nonetheless reassuring.

Sofosbuvir + Ribavirin in Patients with Portal Hypertension


Objectives:
To explore the safety and efficacy of sofosbuvir (SOF) + ribavirin (RBV) in HCV-infected patients with portal hypertension with or without decompensated liver disease.

Methods:
50 patients with compensated or decompensated cirrhosis, with esophageal or gastric varices, received with 48 weeks of therapy with SOF + RBV. This was an interim analysis conducted after 24 weeks of SOF + RBV in 25 patients.

Results:
- Over the first 24 weeks of the study, compensated and decompensated patients on treatment had high rates of virologic response (100% and 95%, respectively at week 24).
- Among treated patients, there were six patients with ascites at baseline and five patients with hepatic encephalopathy at baseline. At week 24, there were no cases of either complication (Table 1).

CONSULTING AUTHORS’ COMMENTARY: The results presented are preliminary findings of a SOF/RBV regimen in advanced cirrhosis and portal hypertension. The finding that clinical events (e.g., ascites, hepatic encephalopathy) can be resolved with SOF/RBV treatment among patients with cirrhosis and portal hypertension is an important one, potentially giving clinicians and their patients a tool to slow or even reverse the progression towards transplantation. It should be noted that persons are continuing on SOF/RBV at present.

Table 1. Results: Clinical Events

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Ascites</th>
<th>Hepatic encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SOF + RBV</td>
<td>Observation</td>
</tr>
<tr>
<td>Baseline</td>
<td>n = 25</td>
<td>n = 25</td>
</tr>
<tr>
<td>Week 12</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Week 24</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

No patients with spontaneous bacterial infection.
1 patient receiving SOF + RBV had an episode of bleeding varices.