Future Therapies for HCV infection

SAVINO BRUNO, MD
Director
Internal Medicine and Hepatology Unit
AO Fatebenefratelli e Oftalmico, Milano
How has the HCV treatment landscape evolved in the last few years?

1998
- IFN 24 weeks
- IFN 48 weeks
- IFN + RBV 48 weeks
- Peg-IFNα + RBV 48 weeks
- SVR (%): 6, 13, 41
- TVR/BOC + Peg-IFNα + RBV 48 weeks
- SVR (%): 56, 75

2012

What next?

Goal of HCV therapy

IFN
24 weeks
IFN
48 weeks
IFN + RBV
48 weeks
Peg-IFNα + RBV
48 weeks
TVR/BOC + Peg-IFNα + RBV

SVR (%)

0 20 40 60 80 100

1998 2012 2014?

IFN
24 weeks
1
IFN
48 weeks
1
IFN + RBV
48 weeks
1,2
Peg-IFNα + RBV
48 weeks
3
TVR/BOC + Peg-IFNα + RBV
4-8

6 13 41 56 75

Targets for current DAAs in development

- Receptor binding and endocytosis
- Fusion and uncoating
- Transport and release
- (+) RNA
- Translation and polyprotein processing
- RNA replication
- Virion assembly
- Membranous web
- ER lumen

2nd generation NS3/4 protease inhibitors

2nd generation NS5A* inhibitors
* Role in HCV lifecycle not well defined

NS5B polymerase inhibitors
- Nucleoside/nucleotide
- Non-nucleoside

## Characteristics of HCV DAA classes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NS3/4A Protease inhibitors</th>
<th>NS5B Nucleos(t)ide polymerase inhibitors NUC</th>
<th>NS5B Non-nucleos(t)ide polymerase inhibitors NNPI</th>
<th>NS5A Replication complex inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potency</td>
<td>High, variable among HCV geno/subtypes</td>
<td>Moderate-high, consistent across geno/subtypes (broad genotype coverage)</td>
<td>Variable, variable across geno/subtypes (most are genotype/subtype specific)</td>
<td>High, multiple HCV genotypes</td>
</tr>
<tr>
<td>Barrier to resistance</td>
<td>Low 1a &lt; 1b</td>
<td>High 1a = 1b</td>
<td>Very low 1a &lt; 1b</td>
<td>Low 1a &lt; 1b</td>
</tr>
<tr>
<td>DDI potential</td>
<td>High</td>
<td>Low</td>
<td>Variable</td>
<td>Low-moderate</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Rash Anemia ↑ Bilirubin</td>
<td>Mitochondrial nucleos(t)ide interactions (ART, RBV)</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Variable: QD to TID</td>
<td>QD</td>
<td>Variable: QD to TID</td>
<td>QD</td>
</tr>
<tr>
<td>Comments</td>
<td>2nd generation Pis: better barrier, pangenotypic</td>
<td>Single target active site</td>
<td>Allosteric inhibition, many targets</td>
<td>Multiple mode of action</td>
</tr>
</tbody>
</table>

- **NS3/4A Protease inhibitors**: Better barrier, pangenotypic
- **NS5B Nucleos(t)ide polymerase inhibitors NUC**: Single target active site
- **NS5B Non-nucleos(t)ide polymerase inhibitors NNPI**: Allosteric inhibition, many targets
- **NS5A Replication complex inhibitors**: Multiple mode of action
Features of an ideal treatment regimen for HCV?

- All oral
- Pan-genotypic activity
- Potent efficacy across all patient populations including ESLD
- High barrier to resistance
- Optimal safety/tolerability profile
- >90% SVR
- Few drug-drug interactions
- Simple stopping rules & treatment algorithm
- Favourable pill burden
- Short treatment duration
- Price sustainable
No cross resistance between classes: a combination of DAAs can eliminate RAVs

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>HCV Target</th>
<th>NS3 Linear</th>
<th>NS3 Macrocyclic</th>
<th>NS5A inhibitor</th>
<th>NS5B nucleoside</th>
<th>NS5B Palm</th>
<th>NS5B Thumb</th>
<th>IFN</th>
<th>RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>V36</td>
<td>NS3 Protease</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>T54</td>
<td></td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>V55</td>
<td></td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>V170</td>
<td></td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>R155</td>
<td></td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>A156</td>
<td></td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Q80</td>
<td></td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>D168</td>
<td></td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>M28</td>
<td>NS5A</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Q30</td>
<td></td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>L31</td>
<td></td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Y93</td>
<td></td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>S282</td>
<td>NS5B</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>C316</td>
<td></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>M414</td>
<td></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Y448</td>
<td></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>R422</td>
<td></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>M423</td>
<td></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>P495</td>
<td></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

R: resistant (>4-fold increase in EC$_{50}$)  
S: susceptible (<4-fold change in EC$_{50}$)

What are the potential advantages of combination regimens containing multiple DAAs?

- Maximise potency, barrier to resistance and genotypic coverage
- Improved tolerability
  - Fewer or easily manageable adverse events
- Increased eligibility
  - E.g. patients with advanced disease, or IFN-intolerant patients
- Shortened treatment duration
- Easier dosing regimens
  - Reduced pill burden, once-daily drugs
  - Fixed-dose combinations

Two parallel paths in development

Efficacy and safety assessment ongoing

- Peg-IFN/RBV + add-ons:
  2nd wave-1\textsuperscript{st} generation PI, 2\textsuperscript{nd} generation PI, NS5A, Nuc, NNPI

  - Interferon backbone: difficult/intolerable for some patients

- Interferon-free combination therapy:

  - Multiple strategies: PI + Nuc, PI + NS5A ± NNPI, Nuc + NS5A ± NNPI

  - ± RBV
Two parallel paths in development

- Peg-IFN/RBV + add-ons:
  - 2nd wave-1st generation PI
    - Danoprevir RTV boosted (China only?)
    - Vaniprevir (Japan only)
    - Simeprevir
    - Faldaprevir
  - 2nd generation PI
    - MK 5172
    - NUC
    - Sofosbuvir
Two parallel paths in development

- FDA unanimously recommended approval

**Simeprevir**, in G1 both treatment naïve and experienced

**Sofosbuvir**, in treatment naïve (G1-4) and experienced (G2-3) with (G1-4) and without (G2-3) P/R
**QUEST-1: Simeprevir + P/R RGT in Treatment-Naive GT 1 HCV**

- **Randomized, double-blind, placebo-controlled phase III trial**
  - 12% to 13% had cirrhosis, 56% to 57% had GT 1a HCV

**Treatment-naive pts with GT 1 HCV (N = 394)**

- **Stratified by GT 1 subtype, IL28B genotype**

### Wk 12
- **Simeprevir 150 mg QD + P/R**
  - (n = 264)
- **Placebo + P/R**
  - (n = 130)

### Wk 24
- **P/R**

### Wk 48
- **P/R**

*Response-guided therapy: Patients with HCV RNA < 25 IU/mL at Wk 4 and HCV RNA undetectable at Wk 12 received a total of 24 wks of therapy. Those not achieving this on-treatment response received 48 wks of therapy.*

*P/R, peginterferon alfa-2a 180 µg/wk + ribavirin 1000-1200 mg/day.*
QUEST-1: Virologic Response to Simeprevir + P/R Treatment

Virologic Outcomes

<table>
<thead>
<tr>
<th>Week 4</th>
<th>SMV + P/R</th>
<th>P/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV RNA Undetectable (%)</td>
<td>80</td>
<td>12</td>
</tr>
<tr>
<td>n/N = 202/254</td>
<td>210/264</td>
<td>65/130</td>
</tr>
</tbody>
</table>

SVR12 by RGT Group

<table>
<thead>
<tr>
<th>SVR12 (%)</th>
<th>SMV Arm: Total Duration of RGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>85%</td>
<td>24 Wks: 203/224</td>
</tr>
<tr>
<td>91%</td>
<td>48 Wks: 6/28</td>
</tr>
</tbody>
</table>

85% of pts in SMV arm met RGT criteria

Jacobson I, et al. EASL 2013
QUEST-1: SVR12 by Fibrosis Level, Subtype, and Baseline Resistance

Jacobson I, et al. EASL 2013
QUEST-2: Virologic Response to Simeprevir + P/R Treatment

Manns M, et al. EASL 2013

91% of pts in SMV arm met RGT criteria

SVR12 (%)

n/N = 209/257

Overall

SMV Arm: Total Duration of RGT

202/235

7/22

24 wks

48 wks
Higher rates of SVR12 with SMV, irrespective of HCV genotype or cirrhosis.

Baseline Q80K mutation not a predictor of response (unlike in QUEST-1).

Simeprevir + PR for HCV genotype 1 in treatment-naïve patients: efficacy in difficult-to-treat patient sub-populations in the QUEST 1 and 2 phase III trials

<table>
<thead>
<tr>
<th></th>
<th>SVR12, n/N (%)</th>
<th>RVR, n/N (%)</th>
<th>SVR12, n/N (%) in those who achieved RVR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SMV/PR</td>
<td>PBO/PR</td>
<td>SMV/PR</td>
</tr>
<tr>
<td>All patients</td>
<td>419/521 (80.4)</td>
<td>132/264 (50.0)</td>
<td>404/521 (77.5)</td>
</tr>
<tr>
<td>METAVIR F4</td>
<td>29/48 (60.4)*</td>
<td>11/32 (34.4)</td>
<td>32/48 (66.7)</td>
</tr>
<tr>
<td>IL28B TT</td>
<td>47/77 (61.0)*</td>
<td>8/38 (21.1)</td>
<td>53/77 (68.8)</td>
</tr>
<tr>
<td>HCV GT 1a overall</td>
<td>191/254 (75.2)*</td>
<td>62/131 (47.3)</td>
<td>184/254 (72.4)</td>
</tr>
<tr>
<td>With Q80K</td>
<td>49/84 (58.3)*</td>
<td>62/131 (47.3)†</td>
<td>53/84 (63.1)</td>
</tr>
</tbody>
</table>

*p<0.05 for all comparisons SMV vs PBO; †Pooled placebo, includes all GT 1a patients

Jacobson IM, et al. AASLD 2013
Simeprevir plus PegIFN and Ribavirin in GT-1 patients partial and null responders

Zeuzem S, et al. 012
Simeprevir + PR in HCV genotype 1 patients who relapsed after previous interferon-based therapy: the PROMISE phase III trial

<table>
<thead>
<tr>
<th></th>
<th>RVR, % (n/N)</th>
<th>SVR12 % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SMV/PR (N=260)</td>
<td>PBO/PR (N=133)</td>
</tr>
<tr>
<td>All patients</td>
<td>77.2 (200/259)*</td>
<td>3.1 (4/129)</td>
</tr>
<tr>
<td>METAVIR F4</td>
<td>76.9 (30/39)</td>
<td>0.0 (0/19)</td>
</tr>
<tr>
<td>IL28B TT</td>
<td>90.3 (28/31)</td>
<td>0.0 (0/15)</td>
</tr>
<tr>
<td>HCV GT 1a</td>
<td>68.2 (75/110)</td>
<td>3.9 (2/51)</td>
</tr>
<tr>
<td>With Q80K</td>
<td>44.8 (13/29)</td>
<td>5.9 (1/17)</td>
</tr>
</tbody>
</table>

* p<0.001 vs PBO/PR
† pooled PBO 1a/other

Forns X, et al. AASLD 2013
Simeprevir + PR for HCV genotype 1

Summary

~80% SVR in treatment naive and relapser patients and most (85%) will need only 24 weeks of treatment

No adjustment for cirrhosis

Reduced SVR for G1a, advanced fibrosis and cirrhosis, prior partial (75%)/null responders (50%) and IL28 non CC

Pre-testing of G1a patients for Q80K polymorphisms

Resistance in those without SVR (NS3 PI mutations in 98% of SMV-treated non-SVR patients)
Two parallel paths in development

- Peg-IFN/RBV + add-ons:
  - Nuc
  - Sofosbuvir
NEUTRINO: 12 Wks’ Sofosbuvir + P/R in Treatment-Naive GT 1/4/5/6 HCV Patients

- Open-label, single-arm study of sofosbuvir 400 mg QD + P/R for 12 wks in treatment-naive patients with GT 1/4/5/6 HCV
  - 17% had cirrhosis; 89% had GT 1, 9% had GT 4, < 1% had GT 5, 2% had GT 6 HCV

P/R: pegIFN alfa-2a 180 µg/wk + RBV 1000-1200 mg/day

Lawitz E, et al. NEJM 2013
NEUTRINO: SVR12 With Sofosbuvir + P/R According to Genotype and Fibrosis Level

SVR12 According to Genotype

- GT 1: 89%
- GT 4: 96%
- GT 5,6: 100%

n/N = 261/292, 27/28, 7/7

SVR12 According to Fibrosis Level

- No Cirrhosis: 92%
- Cirrhosis: 80%

252/273, 43/54

Lawitz E, et al. NEJM 2013
Sofosbuvir + P/R for HCV genotype 1 naive

Summary

SVR rates >90% with 12 weeks of treatment

More than 80% in Cirrhotics

Safety and tolerability concerns, potentially limited by short Peg IFN course
Two parallel paths in development

- Interferon-free combination therapy: Nuc ± RBV

Sofosbuvir
FISSION: Sofosbuvir/RBV vs PegIFN/RBV in Treatment-Naive GT 2/3 HCV Patients

- Randomized, controlled, open-label phase III noninferiority trial
  - 20% to 21% had cirrhosis; 72% had GT 3 HCV

Stratified by HCV GT (2 vs 3), HCV RNA (< vs ≥ 10^6 IU/mL), cirrhosis (yes vs no)

Wk 12

Wk 24

Sofosbuvir 400 mg QD + RBV 1000-1200 mg/day (n = 256)

PegIFN alfa-2a 180 µg/wk + RBV 800 mg/day (n = 243)

Gane E, et al. EASL 2013
FISSION: Sofosbuvir/RBV Noninferior to P/R in Tx-Naive GT 2/3 HCV Patients

- **Sofosbuvir/RBV**
- **Noninferior**
- **to**
- **P/R**
- **in**
- **Tx-Naive GT 2/3 HCV Patients**

**SVR12**

On Treatment

<table>
<thead>
<tr>
<th></th>
<th>Wk 4</th>
<th>Wk 12</th>
<th>Wk 24</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + RBV</td>
<td>99/249/250</td>
<td>99/242/244</td>
<td>99/207/224</td>
<td>99/188/190</td>
</tr>
<tr>
<td>PegIFN + RBV</td>
<td>67/158/236</td>
<td>67/242/244</td>
<td>67/207/224</td>
<td>67/170/253</td>
</tr>
</tbody>
</table>

**P < .001**

Gane E, et al. EASL 2013
FISSION: SVR12 According to Genotype and Fibrosis Level

Genotype 2

<table>
<thead>
<tr>
<th>No Cirrhosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 2</td>
<td>Genotype 2</td>
</tr>
<tr>
<td>Sofosbuvir + RBV</td>
<td>PegIFN + RBV</td>
</tr>
<tr>
<td>58/59</td>
<td>10/11</td>
</tr>
<tr>
<td>44/54</td>
<td>8/13</td>
</tr>
<tr>
<td>98</td>
<td>91</td>
</tr>
<tr>
<td>82</td>
<td>62</td>
</tr>
</tbody>
</table>

Genotype 3

<table>
<thead>
<tr>
<th>No Cirrhosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 3</td>
<td>Genotype 3</td>
</tr>
<tr>
<td>Sofosbuvir + RBV</td>
<td>PegIFN + RBV</td>
</tr>
<tr>
<td>89/145</td>
<td>99/139</td>
</tr>
<tr>
<td>61</td>
<td>71</td>
</tr>
<tr>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>13/38</td>
<td>11/37</td>
</tr>
</tbody>
</table>

Gane E, et al. EASL 2013
FUSION: Sofosbuvir + RBV for 12 or 16 Wks in Tx-Experienced including cirrhosis GT 2/3 HCV Pts

- Randomized, double-blind, placebo-controlled phase III trial
  - 62% to 64% had GT 3 HCV, 33% to 35% had cirrhosis, 75% to 76% were previous relapsers

Nelson D, et al. EASL 2013
FUSION: Overall Efficacy Outcomes of Sofosbuvir + RBV in GT 2/3

Nelson D, et al. EASL 2013
FUSION: SVR12 With Sofosbuvir + RBV by Genotype and Fibrosis Level

Nelson D, et al. EASL 2013
POSITRON: Sofosbuvir + RBV for 12 Wks in GT 2/3 IFN-Unwilling/Intolerant/Ineligible

- Randomized, double-blind, placebo-controlled phase III trial

<table>
<thead>
<tr>
<th>Baseline Factor</th>
<th>Sofosbuvir + RBV (n = 207)</th>
<th>Placebo (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 2</td>
<td>109 (53)</td>
<td>34 (48)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>31 (15)</td>
<td>13 (18)</td>
</tr>
<tr>
<td>Interferon unwilling</td>
<td>102 (49)</td>
<td>30 (42)</td>
</tr>
<tr>
<td>Interferon ineligible</td>
<td>88 (43)</td>
<td>33 (47)</td>
</tr>
<tr>
<td>Interferon intolerant</td>
<td>17 (8)</td>
<td>8 (11)</td>
</tr>
</tbody>
</table>

Sofosbuvir 400 mg QD + RBV 1000-1200 mg/day (n = 207)

Stratified by cirrhosis (yes vs no)

**Wk 12**

Baseline Factor, n (%)
POSITRON: Virologic Response in GT 2/3 IFN-Unwilling/Intolerant/Ineligible

Overall Outcomes

- **HCV RNA < LLOQ (%):**
  - Wk 4: 99/204
  - EOT: 100/202
  - SVR12: 78/161

- **SVR12 (%):**
  - No cirrhosis: 92/85
  - Cirrhosis: 94/16

- SVR12 0% for placebo

*Jacobson I, et al. NEJM 2013*
Extended (24 weeks) treatment duration of Sofosbuvir plus Ribavirin in genotype 3 patients naïve or previous treatment failure: The VALENCE trial

SVR 12 (%)

<table>
<thead>
<tr>
<th></th>
<th>Non cirrhotics</th>
<th>Cirrhotics</th>
<th>Non cirrhotics</th>
<th>Cirrhotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve</td>
<td>86/92</td>
<td>12/13</td>
<td>85/100</td>
<td>60/45</td>
</tr>
<tr>
<td>Treatment-experienced</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

250 genotype 3 patients (both naïve and previous treatment failure) all treated with Sofosbuvir+Ribavirin for 24 weeks

Zeuzem S, et al. AASLD 2013,
Virologic Response Rates to Sofosbuvir-Containing Regimens Are Similar in Patients With and Without Traditional Negative Predictive Factors: A Retrospective Analysis of Phase 3 Data

<table>
<thead>
<tr>
<th>FISSION</th>
<th>POSITRON</th>
<th>FUSION</th>
<th>NEUTRINO</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF+RBV x 12 wks</td>
<td>SOF+RBV x 12 wks</td>
<td>SOF+RBV x 16 wks</td>
<td>SOF+PEG+RBV x 12 wks</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>47 (23/49)</td>
<td>61 (19/31)</td>
<td>31 (11/36)</td>
</tr>
<tr>
<td>No cirrhosis</td>
<td>72 (147/204)</td>
<td>81 (142/176)</td>
<td>61 (39/64)</td>
</tr>
<tr>
<td>Male</td>
<td>61 (103/168)</td>
<td>73 (85/117)</td>
<td>42 (30/71)</td>
</tr>
<tr>
<td>Female</td>
<td>79 (67/85)</td>
<td>84 (76/90)</td>
<td>69 (20/29)</td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>100 (7/7)</td>
<td>73 (11/15)</td>
<td>50 (2/4)</td>
</tr>
<tr>
<td>Age &gt;65</td>
<td>66 (163/246)</td>
<td>78 (150/192)</td>
<td>55 (39/71)</td>
</tr>
<tr>
<td>IL28B TT</td>
<td>56 (14/25)</td>
<td>65 (17/26)</td>
<td>79 (15/19)</td>
</tr>
<tr>
<td>IL28B non-TT</td>
<td>69 (156/226)</td>
<td>80 (144/181)</td>
<td>43 (35/81)</td>
</tr>
<tr>
<td>BMI &lt;30</td>
<td>65 (50/77)</td>
<td>82 (58/71)</td>
<td>38 (11/29)</td>
</tr>
<tr>
<td>BMI ≥30</td>
<td>68 (120/176)</td>
<td>76 (103/136)</td>
<td>52 (46/88)</td>
</tr>
<tr>
<td>HbA1c ≥6.5</td>
<td>42 (5/12)</td>
<td>92 (11/12)</td>
<td>46 (5/11)</td>
</tr>
<tr>
<td>HbA1c &lt;6.5</td>
<td>69 (165/240)</td>
<td>77 (150/195)</td>
<td>51 (45/89)</td>
</tr>
<tr>
<td>Black</td>
<td>75 (9/12)</td>
<td>89 (8/9)</td>
<td>100 (5/5)</td>
</tr>
<tr>
<td>Non-black</td>
<td>67 (161/241)</td>
<td>77 (153/198)</td>
<td>47 (45/95)</td>
</tr>
<tr>
<td>HCV RNA ≥10^7</td>
<td>61 (11/18)</td>
<td>93 (26/28)</td>
<td>56 (15/27)</td>
</tr>
<tr>
<td>HCV RNA &lt;10^7</td>
<td>68 (159/235)</td>
<td>75 (135/179)</td>
<td>48 (35/73)</td>
</tr>
<tr>
<td>Opiate replacement</td>
<td>50 (12/24)</td>
<td>88 (15/17)</td>
<td>0 (0/3)</td>
</tr>
<tr>
<td>No opiate replacement</td>
<td>69 (158/229)</td>
<td>77 (146/190)</td>
<td>52 (50/97)</td>
</tr>
</tbody>
</table>

In this large cohort of patients participating in SOF-containing Phase 3 studies with or without PEG-IFN and across genotypes 1-6, traditional negative predictive factors did not have a consistent influence on response rates with the exception of cirrhosis and sex.

Mangia A, et al. AASLD 2013
Sofosbuvir + RBV for HCV genotype 2/3

Summary

G2= SVR rates >90% with 12 weeks of treatment
Cirrhotics and prior partial/null responders may benefit from 16 weeks

G3= want more
24 weeks better than 12, especially for prior experienced, and IL28 non CC
SVR rates in cirrhotics suboptimal also with longer treatment duration
Summary of Safety Findings From Phase III Trials

- **Sofosbuvir**[1-4]
  - Generally well tolerated; low rates of grade 3/4 AEs, serious AEs, and treatment discontinuation due to AEs; improved profile with SOF/RBV vs pegIFN/RBV
  - Greatly improved Hb profile with simeprevir and faldaprevir vs boceprevir/telaprevir with no significant increase over pegIFN/RBV[5-7]

- **Simeprevir**[5,6]
  - Generally well tolerated; no added safety signals with triple therapy

Summary of Resistance Findings From Phase III Trials

- **Sofosbuvir**\(^{[1-4]}\)
  - No S282T mutations identified; other NS5B genetic variants not associated with change in phenotypic susceptibility
- **Simeprevir**\(^{[5,6]}\)
  - Baseline Q80K polymorphism present in 41% of patients with GT 1a HCV and associated with lower SVR12 rate in QUEST-1\(^{[5]}\)
  - Emergent NS3 protease mutations in > 90% of patients without SVR (GT 1a: R155K alone, with mutations at positions 80 and/or 168; GT 1b: most common mutation D168V, Q80R + D168E)\(^{[5,6]}\)

FDA Approval Timeline

2013

**Geno-2,3:**
Sofosbuvir + RBV

**Geno-1:**
Sofosbuvir + PEG/RBV
Simeprevir + PEG/RBV

2014

**Geno-1b:**
Faldaprevir + PEG/RBV

**Geno-1:**
Sofosbuvir + Ledipasvir
ABT450/r+ABT267+ABT333

2015

**Geno-1:**
Daclatasvir + Asunaprevir
+ BMS791325
Faldaprevir + Deleobuvir + PI-668?
MK5172 + MK 8742?
Final results of phase III STARTVerso1 trial

- 78% were white, 81% Europe, 19% Japan; 66% had GT 1b HCV; 39% had IL28B CC; 6% were cirrhotic

*RGT: At Wk 12, patients with ETS continued P/R to Wk 24; patients without ETS continued triple therapy to Wk 24 followed by P/R to Wk 48.
†RGT: At Wk 24, patients with ETS stopped treatment; patients without ETS continued P/R to Wk 48.
ETS defined as HCV RNA < 25 IU/mL at Wk 4 and HCV RNA < 25 IU/mL, target not detected at Wk 8.
According to ETS, Genotype, and Fibrosis Level

<table>
<thead>
<tr>
<th>Genotype</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 1a</td>
<td>69/45</td>
</tr>
<tr>
<td>GT 1b</td>
<td>84/60</td>
</tr>
<tr>
<td>&lt; F3</td>
<td>81/45</td>
</tr>
<tr>
<td>≥ F3</td>
<td>67/16</td>
</tr>
<tr>
<td>F4</td>
<td>56/16</td>
</tr>
</tbody>
</table>

ETF defined as HCV RNA < 25 IU/mL at Wk 4 and HCV RNA < 25 IU/mL, target not detected at Wk 8.

- 23% of pts with GT 1a HCV had Q80K at baseline; not predictive of SVR12

Ferenci P, et al. EASL 2013
A pooled analysis of two randomized, double-blind placebo-controlled Phase III trials (STARTVerso1&2) of faldaprevir + PR in genotype-1 treatment-naïve patients with chronic hepatitis C

<table>
<thead>
<tr>
<th></th>
<th>Placebo + PR (N=264)</th>
<th>FDV 120mg + PR (N=521)</th>
<th>FDV 240mg + PR (N=524)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12</td>
<td>131 (50)</td>
<td>382 (73)</td>
<td>378 (72)</td>
</tr>
<tr>
<td>n/N (%) North America Europe Asia</td>
<td>49/109 (45) 53/108 (49) 29/47 (62)</td>
<td>135/215 (63) 160/207 (77) 87/99 (88)</td>
<td>129/216 (60) 164/211 (78) 85/97 (88)</td>
</tr>
<tr>
<td>GT1 subtype 1a 11b</td>
<td>53/125 (42)</td>
<td>77/138 (56)</td>
<td>158/247 (64)</td>
</tr>
<tr>
<td>IL28B genotype CC 1 non-CC</td>
<td>63/94 (67)</td>
<td>67/169 (40)</td>
<td>191/213 (90)</td>
</tr>
<tr>
<td>Liver fibrosis Less than F3 / F3 or greater</td>
<td>108/205 (53)</td>
<td>22/57 (39)</td>
<td>316/408 (77)</td>
</tr>
<tr>
<td>ETS</td>
<td>50 (19)</td>
<td>436 (84)</td>
<td>441 (84)</td>
</tr>
<tr>
<td>SVR12 in patients with ETS, n/N (%)</td>
<td>41/50 (82)</td>
<td>362/436 (83)</td>
<td>368/441 (83)</td>
</tr>
</tbody>
</table>

Jensen DM, et al. AASLD 2013
Two parallel paths in development

Interferon-free combination therapy:

1 Nuc + 1\textsuperscript{st} generation NS5A

\textbf{Sofosbuvir} + Daclatasvir ± RBV (Development combination program discontinued)

2 Nuc + 2\textsuperscript{nd} wave-1\textsuperscript{st} generation PI

\textbf{Sofosbuvir} + \textbf{Simeprevir} ± RBV

3 Nuc + 2\textsuperscript{nd} generation NS5A

\textbf{Sofosbuvir} + \textbf{Ledipasvir}± \textbf{NNPI} ± RBV
Daclatasvir+Sofosbuvir±Ribavirin in chronic HCV genotype 1-infected patients who previously failed Telaprevir or Boceprevir

41 GT1 non cirrhotic patients with previous breakthrough (n=15), relapse (n=13), or non response (n=14) to pegIFN/RBV+TVR (n=33) or BOC (n=9)

Sułkowski MS, et al. EASL 2013
COSMOS Study

Sofosbuvir + Simeprevir + RBV

Genotype 1, treatment naïve and null responder with and without cirrhosis

High SVR12 rates (79-96%) in null responder Metavir F0-F2

High SVR4 rates (96-100%) in naïve and null responders with Metavir F3-F4

Addition of RBV may not be needed to achieve high SVR rates

12 weeks of treatment may confer similar SVR rate compared to 24 weeks treatment

SOF + SMV + RBV was generally well tolerated

Jacobson IM, AASLD 2013
Once daily Sofosbuvir/Ledipasvir fixed dose combination with or without ribavirin: the ELECTRON trial

Study design

Week 0  Week 6  Week 12

SOF/LDV FDC (n =10)

SOF/LDV FDC + RBV (n =10)

SOF/LDV FDC + RBV (n =25)

SOF/LDV FDC + RBV + GS-9669 (n =25)

SOF/LDV FDC + RBV (n =25)

SVR 12

Gt 1 Experienced

Gt 1 Naïve

F4

F3/F4

F0/F1/F2

Gane EJ, et al. AASLD 2013, 73
The ELECTRON trial: SVR12 according to treatment duration
Genotype 1, Treatment naïve, non cirrhotics

SVR 12 (%)

- SOF+LDV+RBV 12 weeks: 100/25/25
- SOF/LDV+RBV 8 weeks: 100/21/21
- SOF/LDV+RBV 6 weeks: 68/21/21

Gane EJ, et al. AASLD 2013, 73
The ELECTRON trial: SVR12 results in Genotype 1 Treatment-experienced patients with advanced fibrosis/cirrhosis

- SOF/LDV 12 weeks: 70%
- SOF/LDV+RBV 12 weeks: 99%
- SOF/LDV+RBV 12 weeks: 25%
- SOF/LDV+GS-9669 12 weeks: 100%

Gane EJ, et al. AASLD 2013, 73
Once daily Sofosbuvir/Ledipasvir fixed dose combination with or without Ribavirin resulted in >95% SVR in patients with HCV genotype 1, including patients with cirrhosis: The LONESTAR trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR 12 (%)</th>
<th>Naïve (no cirrhosis)</th>
<th>PI failures (50% cirrhosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/LDV 8 weeks</td>
<td>95/20</td>
<td>19/20</td>
<td>18/19</td>
</tr>
<tr>
<td>SOF/LDV+RBV 8 weeks</td>
<td>100/21</td>
<td>21/21</td>
<td>18/19</td>
</tr>
<tr>
<td>SOF/LDV 12 weeks</td>
<td>95/19</td>
<td>18/19</td>
<td>18/19</td>
</tr>
<tr>
<td>SOF/LDV 12 weeks</td>
<td>95/19</td>
<td>18/19</td>
<td>21/21</td>
</tr>
<tr>
<td>SOF/LDV+RBV 12 weeks</td>
<td>100/21</td>
<td>21/21</td>
<td>21/21</td>
</tr>
</tbody>
</table>

Lawitz E, et al. AASLD 2013
Two parallel paths in development

Efficacy and safety assessment ongoing

- Interferon-free combination therapy without Nuc:

**BMS**) 2\textsuperscript{nd} wave-1\textsuperscript{st} generation PI + NS5A ± RBV ± NNPI

**Abbvie**) 2\textsuperscript{nd} wave-1\textsuperscript{st} generation PI + NS5A + NNPI ± RBV

**Merck**) 2\textsuperscript{nd} generation PI and NS5A

**BI**) 2\textsuperscript{nd} wave-1\textsuperscript{st} generation PI + NNPI + NS5A ± RBV
Two parallel paths in development
Efficacy and safety assessment ongoing

- Interferon-free combination therapy without Nuc:
  - (capsules from 2013 AASLD)

High SVR12 (>90%) Rates With All-Oral Regimen of Daclatasvir, Asunaprevir, and BMS-791325 for 12 Weeks in Treatment-Naive Patients With Genotype 1 HCV
High SVR12 Rates With All-Oral Regimen of ABT-450/ RTV, ABT-267, ABT-333 and RBV 12 Weeks in Treatment-Naive and Null responders Patients With Genotype 1 HCV
High Virologic Efficacy and Favorable Safety of 12-Week, All-Oral Regimens of MK-5172/ MK-8742 with and without Ribavirin in Previously Untreated Genotype 1 HCV
In a small, ongoing phase II study, 81% of patients treated by Faldaprevir + Deleobuvir + BI PPI-668 achieved undetectable HCV RNA by Week 4, and 100% of evaluable patients had SVR4
Phase 2b study of the interferon-free and ribavirin-free combination of daclatasvir, asunaprevir and BMS-791325 for 12 weeks in treatment-naïve patients with chronic HCV genotype 1 infection

- All treatment-naïve genotype 1 patients treated with Daclatasvir (DCV) 30 mg BID + Asunaprevir (ASV) 200 mg BID + BMS-791325 (‘325) 75 mg BID (N=80 pts) or 150 mg BID (N=86 pts)
- Cirrhotics = 10% each group

Everson GT, et al. AASLD 2013 LB-1
Interferon- and ribavirin-free regimen of ABT-450/r + ABT-267 + ABT-333 in HCV genotype 1b-infected treatment-naïve patients and prior null responders

Genotype 1b non cirrhotic patients, both naive and null responders, were treated for 12 weeks

*2 patients did not achieve SVR12 due to loss to follow-up
**1 patient experienced breakthrough and 3 patients relapsed

Lawitz E, et al. AASLD 2013, 75
High efficacy and safety of the all-oral combination regimen, MK-5172/MK-8742 ± Ribavirin for 12 weeks in HCV genotype 1 non cirrhotic treatment-naïve patients: The C-WORTHY Study

Lawitz E, et al. AASLD 2013, 76
Sofosbuvir in combination with PegIFN and Ribavirin for 24 weeks provides high SVR rates in HCV-infected Genotype 2 or 3 Treatment-experienced patients with and without compensated cirrhosis: Results from the LONESTAR-2 Study

Study population:
• HCV genotype 2 or 3 patients (50% with compensated cirrhosis) treated with:
  SOF 400 mg once daily+PEG 180 mcg once weekly+RBV 1000-1200 mg daily
• All patients had achieved previous treatment failure with peginterferon and ribavirin

Lawitz E, et al. AASLD 2013, LB-4
The LONESTAR-2 Trial: SVR12 by cirrhosis status

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No cirrhosis</th>
<th>Cirrhosis</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 2</td>
<td>9/9</td>
<td>13/14</td>
<td>100</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>83</td>
<td>10/12</td>
<td>83</td>
</tr>
</tbody>
</table>

Lawitz E, et al. AASLD 2013, LB-4
Summary of phase 2 studies

Excellent SVR rates in genotype 1 with all oral tx with short treatment duration across any fibrosis stage and prior treatment history including patients with both PI’s failure and cirrhosis

Good results in G3 with cirrhosis treated by P/R + Nuc

Number of included patients still low, geno-4,5,6 and HIV-coinfected poorly studied

Post-OLT and decompensated patients studied only by compassionate way
Open questions regarding the future of HCV treatment

• How do we determine the best regimen (duration, combination of drugs) for genotype 1 going forward?
• What aspect of cirrhosis impairs response?
• Can these effects be overcome with higher or longer drug exposure?
• Why does genotype 3 cirrhotic do so poorly and how can we do better?
• Is one-size-fits-all treatment a possibility?
• What are the remaining needs for high-risk patients with new HCV therapies going forward?
• How will we manage patients who fail DAA therapies?
Conclusion

- What we still need to know....
  - How can we combine the best agents of different classes across industry lines?
  - *Will the next generation DAA be sustainable by Health Care Systems worldwide?*
Thank you for your attention!

The opinions expressed here represent the opinion of the author. All products mentioned in the presentation should be applied according to the Product Labels.
- BACK UP
Once Daily Sofosbuvir/Ledipasvir Fixed Dose Combination ± Ribavirin Resulted in ≥95% SVR In Patients with HCV Genotype 1, Including Patients with Cirrhosis: the LONESTAR trial

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Treatment-naïve</th>
<th>Protease-Inhibitor Experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SOF/LDV FDC 8 Weeks (n=20)</td>
<td>SOF/LDV FDC+RBV 8 Weeks (n=21)</td>
</tr>
<tr>
<td>RVR</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>EOTR</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>SVR4</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>SVR12</td>
<td>95%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*One patient has not yet returned for post-treatment follow up.

60 non-cirrhotic treatment-naïve patients with HCV genotype 1 were randomized 1:1:1 to receive: 1) FDC for 8 weeks, 2) FDC + RBV for 8 weeks, or 3) FDC for 12 weeks. In parallel, 40 patients who had not achieved SVR after previous treatment with a protease inhibitor regimen (50% of whom also had compensated cirrhosis) were randomized to receive 12 weeks of: 1) FDC or 2) FDC + RBV.

Lawitz E, et al. AASLD 2013
SVR by fibrosis stage in G1 naïve patients treated with Faldaprevir, BI207127 and Ribavirin (The SOUND-C2 Study)

Zeuzem S, et al. EASL 2013

* BI207127 600 mg BID or TID
AVIATOR: SVR12 Rates With ABT-450/RTV, ABT-267, ABT-333, and RBV

Treatment-Naive Patients

Null Responders

Observed data (above bar)

ITT (within bar)

<table>
<thead>
<tr>
<th></th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-450</td>
<td>88</td>
<td>83</td>
<td>96</td>
</tr>
<tr>
<td>ABT-267</td>
<td>86</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td>ABT-333</td>
<td>100</td>
<td>87</td>
<td>100</td>
</tr>
<tr>
<td>RBV</td>
<td>84</td>
<td>96</td>
<td>89</td>
</tr>
</tbody>
</table>

8 weeks: 56/24
12 weeks: 29/12

88 83 89 87 96 89 93

ABT-450: Protease/RTV QD
ABT-267: NS5A QD
ABT-333: NNPI BID

High Efficacy and Safety of the All-Oral Combination Regimen, MK-5172/MK-8742 +/- RBV for 12 Weeks in HCV Genotype 1 treatment-naïve non cirrhotic patients: The CWORTHY Study

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>Regimen</th>
<th>TW1</th>
<th>TW2</th>
<th>TW4</th>
<th>TW8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>MK-5172/MK-8742 (both doses) + RBV (N = 38)</td>
<td>19/37 (51%)</td>
<td>33/37 (89%)</td>
<td>36/36 (100%)</td>
<td>32/32 (100%)</td>
</tr>
<tr>
<td>1b</td>
<td>MK-5172/MK-8742 (both doses) + RBV (N = 14)</td>
<td>10/13 (77%)</td>
<td>14/14 (100%)</td>
<td>14/14 (100%)</td>
<td>8/8 (100%)</td>
</tr>
<tr>
<td></td>
<td>MK-5172/MK-8742 50 mg (N = 12*)</td>
<td>5/12 (42%)</td>
<td>10/11 (91%)</td>
<td>11/11 (100%)</td>
<td>5/5 (100%)</td>
</tr>
</tbody>
</table>

*Excludes one patient who received RBV due to a dosing error. TW, treatment week.

Lawitz E, et al. AASLD 2013
Efficacy and Safety of Sofosbuvir in Patients According to Fibrosis Stage: An Analysis of Phase 3 Data

<table>
<thead>
<tr>
<th></th>
<th>SOF+RBV 12 wks</th>
<th>SOF+RBV 16 wks</th>
<th>SOF+P/R 12 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FISSION</td>
<td>POSITRON</td>
<td>FUSION</td>
</tr>
<tr>
<td>GT2/3 TN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>67 (170/253)</td>
<td>78 (161/207)</td>
<td>50 (50/100)</td>
</tr>
<tr>
<td>F0-F2</td>
<td>69 (62/90)</td>
<td>81 (107/132)</td>
<td>70 (26/37)</td>
</tr>
<tr>
<td>F3</td>
<td>55 (12/22)</td>
<td>76 (19/25)</td>
<td>40 (10/25)</td>
</tr>
<tr>
<td>F4</td>
<td>48 (10/21)</td>
<td>70 (35/50)</td>
<td>37 (14/38)</td>
</tr>
<tr>
<td>Platelets ≤125</td>
<td>53 (17/32)</td>
<td>60 (15/25)</td>
<td>29 (7/24)</td>
</tr>
<tr>
<td>Platelets ≤100</td>
<td>33 (4/12)</td>
<td>67 (10/15)</td>
<td>33 (4/12)</td>
</tr>
</tbody>
</table>

Patel K, et al. AASLD 2013
Next step for CUPIC’s PI’s treatment failure

SOFOSBUVIR + LEDIPASVIR + RBV

0 W12 W24

SOFOSBUVIR + LEDIPASVIR

Courtesy of Bronowicky JP
Baseline characteristics which influence treatment outcomes deeply changed in the era of all oral therapy.

### Characteristic:
- **HCV genotype**
  - Easy to treat: 2
  - Difficult to treat: 4, 1b, 1a, 3
- **Fibrosis stage**
  - Easy to treat: F0–F2
  - Difficult to treat: F3, F4, Decompensated
- **Treatment history**
  - Easy to treat: Naive
  - Difficult to treat: Peg-IFN/RBV failure, DAA failure?
## Summary

### Genotype 1 Treatment Naive

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>94%</td>
<td>ABT450/r+ABT333+ RBV (#33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>88%</td>
<td>ABT450/r+ABT333+ RBV (#41)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>85%</td>
<td>ABT450/r+ABT333+ RBV (#79)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90%</td>
<td>ABT450/r+ABT267+ ABT333+ RBV (#79)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>87%</td>
<td>ABT450/r+ABT267+ ABT333 #79</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>98%</td>
<td>ABT450/r+ABT267+ ABT333+ RBV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>88%</td>
<td>Daclatasvir + Asunaprevir + 791325 (#16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>94%</td>
<td>Daclatasvir + Asunaprevir + 791325 (#16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>39%</td>
<td>Faldaprevir + Deleobuvir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>52-69%</td>
<td>Faldaprevir + Deleobuvir + RBV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>71%</td>
<td>Mericitabine + Danoprevir + RBV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>84%</td>
<td>Sofosbuvir + RBV #25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>98%</td>
<td>Sofosbuvir + Daclatasvir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>96%</td>
<td>Sofosbuvir + Daclatasvir + RBV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**WEEKS**

- **12**
- **24**
Summary
Prior Nonresponders

SVR
Geno-1a/1b
47% ABT-450/r + ABT-333 + RBV (#17)
89% ABT-450/r + ABT-267 + RBV (#45)
93% ABT-450/r + ABT-267 + ABT-333 + RBV (#45)
36% Daclatasvir + Asunaprevir (#11)
10% Sofosbuvir + RBV (#10)
100% Sofosbuvir + Daclatasvir (#21)
95% Sofosbuvir + Daclatasvir + RBV (#20)
96% Sofosbuvir + Simeprevir + RBV (#27)
93% Sofosbuvir + Simeprevir (#14)
100% Sofosbuvir + Ledipasvir + RBV (#10)

Geno-1b only
91% Daclatasvir + Asunaprevir (#21)

Geno-2,3 only
50% Sofosbuvir + RBV (#201)
73% Sofosbuvir + RBV (#201)

Poordad et al, 2013
Kowdley et al, 2013
Kowdley et al, 2013
Lok et al, 2012
Gane et al, 2013
Sulkowski et al, 2013
Sulkowski et al, 2013
Lawitz et al, 2013
Lawitz et al, 2013
Gane et al, 2013
Suzuki et al, 2012
Jacobson et al, 2013

Weeks
12
24
**Genotype 2,3**

**Treatment Naive**

<table>
<thead>
<tr>
<th>Weeks</th>
<th>SVR</th>
<th>Treatment</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>100%</td>
<td>Sofosbuvir + RBV</td>
<td>Gane et al, 2013</td>
</tr>
<tr>
<td>12</td>
<td>60%</td>
<td>Sofosbuvir</td>
<td>Gane et al, 2013</td>
</tr>
<tr>
<td>24</td>
<td>67%</td>
<td>Sofosbuvir + RBV</td>
<td>Gane et al, 2013</td>
</tr>
<tr>
<td>24</td>
<td>100%</td>
<td>Sofosbuvir + Daclatasvir</td>
<td>Sulkowski et al, 2012</td>
</tr>
<tr>
<td>24</td>
<td>93%</td>
<td>Sofosbuvir + Daclatasvir + RBV</td>
<td>Gane et al, 2013</td>
</tr>
<tr>
<td>24</td>
<td>100%</td>
<td>Sofosbuvir + Ledipasvir + RBV</td>
<td>Gane et al, 2013</td>
</tr>
</tbody>
</table>
Rapid Evolution of HCV Regimens: Easier to Tolerate, Higher SVR, All Oral for All Patients

2013

Genotype 2 and 3:
P/R

Genotype 1:
Telaprevir + P/R
Boceprevir + P/R

P/R = Pegylated interferon alfa plus ribavirin

2014

Genotype 2 and 3:
Sofosbuvir + RBV

Genotype 1:
Sofosbuvir + P/R
Simeprevir + P/R
Daclatasvir + P/R
Faldaprevir + P/R

2015

Genotype 1:
Sofosbuvir + GS-5885 +/- RBV
ABT-450/r + ABT-267 + ABT-333 + RBV
Daclatasvir + Asunaprevir + BMS-791325

Derived from National AIDS Treatment Advocacy Project; http://www.natap.org/2012/HCV/082912_01.htm
The Future (as I see it)

PEG/RBV

PI+PEG+RBV

PI₂+PEG+RBV

DAA₁ + DAA₂ ± RBV (or)
DAA1 + DAA2 + DAA3 ± RBV
Anticipated registration dates (FDA) of phase 3, second generation DAAs ± PEG IFN

2013
- September 2013
  - Sofosbuvir/ RBV
  - Genotype 2,3
  - SVR12
- September 2013
  - Sofosbuvir/ PEG/RBV
  - Simeprevir/PEG/RBV
  - Genotype 1
  - SVR12/24

2014
- December 2013
  - Daclatasvir/RBV
  - Genotype 1
  - SVR 12
- Q2 2014
  - BI201335/PEG/RBV
  - Genotype 1
  - SVR 24
- Q2 2014
  - Sofosbuvir/GS5885/RBV
  - Genotype 1,4,5,6
  - SVR 12

Ref: clinicaltrials.gov
Gilead Reports Interim Data From Phase 2 Lonestar Study

May 2, 2013 8:31 AM ET

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment Duration</th>
<th>Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + ledipasvir</td>
<td>8 weeks</td>
<td>GT 1 treatment-naïve</td>
<td>95% (19/20) SVR 8</td>
</tr>
<tr>
<td>Sofosbuvir + ledipasvir + RBV</td>
<td>8 weeks</td>
<td>GT 1 treatment-naïve</td>
<td>100% (21/21) SVR 8</td>
</tr>
<tr>
<td>Sofosbuvir + ledipasvir</td>
<td>12 weeks</td>
<td>GT 1 treatment-naïve</td>
<td>100% (19/19) SVR 4</td>
</tr>
<tr>
<td>Sofosbuvir + ledipasvir</td>
<td>12 weeks</td>
<td>GT 1 treatment-experienced</td>
<td>95% (18/19) SVR 4</td>
</tr>
<tr>
<td>Sofosbuvir + ledipasvir + RBV</td>
<td>12 weeks</td>
<td>GT 1 treatment-experienced</td>
<td>95% (20/21) SVR 4</td>
</tr>
</tbody>
</table>

Gilead Sciences Inc. (GILD) - NasdaqGS

55.81 ↑ 0.07 (0.13%) 10:56 AM EDT - Nasdaq Real Time Price

![Graph showing stock price trend](Image)
Gilead Press Release May 21, 2013

European Medicines Agency Validates Gilead’s Marketing Application for Sofosbuvir for the Treatment of Hepatitis C

• Gilead Sciences today announced that the company’s Marketing Authorisation Application (MAA) for sofosbuvir has been fully validated and is now under assessment.

• Review of the MAA, when finalized, provides marketing authorization in all 27 member states of the European Union (EU).

• EMA has accepted Gilead’s request for accelerated assessment for sofosbuvir, a designation that is granted to new medicines of major public health interest. Accelerated assessment could shorten EMA’s review time of sofosbuvir by approximately two months.

• If approved, sofosbuvir could be available for marketing in the EU in the first half of 2014.
2015: the end of IFN for HCV?

Graphics: courtesy of Marc Bourliere
MK-3034:
A multi-centre single-arm study to evaluate the efficacy and safety of BOCEPREVIR 44 weeks in addition to standard of care (SOC) in previously treatment failure (relapser, non-responders, both partial and null) patients with chronic hepatitis C genotype 1 (G1) and cirrhosis

Inclusion Criteria

1. Age between 18 and 75 years included.
2. Weight between 40 kg and 125 Kg
3. Documented CHC genotype 1 infection. HCV-RNA ≥1,000 IU/mL
4. Previous course of treatment with standard of care (SOC: Peg-interferon alpha 2a or Peg-interferon alpha 2b + Ribavirin) with a documented non response
5. Diagnosis of cirrhosis documented by histology (Metavir score 4, Ishak score 5 to 6) or by Fibroscan® (liver stiffness > 12.5)
6. No findings suspicious for hepatocellular carcinoma (HCC) at ultrasound within 6 months of the Screening Visit
7. Use of 2 effective contraceptives for at least 2 weeks prior to Day 1 and continue until at least 6 months after last dose of study drug (7 months for male subject).
MK-3034:
A multi-centre single-arm study to evaluate the efficacy and safety of BOCEPREVIR 44 weeks in addition to standard of care (SOC) in previously treatment failure (relapser, non-responders, both partial and null) patients with chronic hepatitis C genotype 1 (G1) and cirrhosis

Exclusion criteria

1. Co-infection with HIV or HBV
2. Present or previous decompensated liver disease including a history or presence of clinical ascites, variceal bleeding or hepatic encephalopathy
3. Clinically significant ocular examination abnormalities: retinopathy, cotton wool spots, optic nerve disorder, retinal hemorrhage
4. The following laboratory values:
   - Hb <12 g/dL for females and <13 g/dL for males
   - Neutrophils <1500/ mm3 (blacks: <1200/mm3)
   - Platelets <70,000/ mm3
   - Direct bilirubin >1.5 x upper limit of normal (ULN).
   - Serum albumin < lower limit of normal (LLN)
5. Thyroid-stimulating hormone (TSH) >1.2 x ULN or <0.8 x LLN of laboratory
7. Serum glucose:
   a. For subjects not previously diagnosed with diabetes mellitus:
      ≥140 mg/dL (nonfasting) unless hemoglobin, A1c subtype (HbA1c) ≤7% OR
MK-5172 (100 mg): Response guided therapy

91% of patients (60/66) receiving MK-5172 100 mg QD had HCV-RNA TND at TW4 and were eligible for the short duration of therapy.

![Bar chart showing SVR24 and TND at last visit for different groups: All Patients, RGT-24 weeks, RGT-48 weeks.](chart)

- **All Patients**: 86% SVR24, 92% TND at TW4
- **RGT-24 weeks**: 90% SVR24, 98% TND at TW4
- **RGT-48 weeks**: 25% SVR24, 50% TND at TW4

*HCV-RNA TND at TW4 RGT = response-guided therapy

Manns M, et al. EASL 2013
• The primary reason for this amendment is to study 100 mg MK-5172 in combination with peginterferon alfa-2b and Ribavirin in treatment-naïve cirrhotic patients.

• **40 cirrhotic patients** will be enrolled in treatment Arm 1.
Sofosbuvir + Peginterferon + Ribavirin for 12 weeks in treatment-naïve genotype 1,4,5,6 HCV patients (The Neutrino Study)

No Cirrhosis (n=273)

Cirrhosis (n=54)

G1 (n=292)

G4 (n=28)

G5/6 (n=7)

IL28B CC (n=95)

IL28B non CC (n=232)

SVR12 (%)

Lawitz E, et al. EASL 2013
Simeprevir (TMC 435) with peginterferon/ribavirin (12 weeks triple + 12 to 36 dual tx) for chronic HCV genotype-1 infection in treatment-naïve patients:

Results from QUEST-1, a phase III trial

Jacobson I, et al. EASL 2013
Viral particle production is shut down by the immune system during anti-HCV therapy. Viremia decay during therapy is characterized by two phases:

1. **1st phase**: Viral particle production is shut down.
2. **2nd phase**: A slower decline in HCV RNA that must eradicate infected cells prior to treatment completion to avoid post-treatment resumption of HCV replication.

An SVR can only be achieved if therapy induces a rapid first-phase decline in HCV RNA that persists throughout treatment (dashed line) and a slower second-phase decline in HCV RNA that must eradicate infected cells prior to treatment completion if post-treatment resumption of HCV replication is to be avoided.

**Key terms**:
- **LLOD**: lower limit of detection
- **SVR**: sustained virologic response

LLOD: lower limit of detection; SVR: sustained virologic response
Barrier to Resistance

Low-barrier drug

High-barrier drug
No cross resistance between classes:
a combination of DAAs can eliminate RAVs

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>HCV Target</th>
<th>NS3 Linear</th>
<th>NS3 Macrocyclic</th>
<th>NS5A inhibitor</th>
<th>NS5B nucleoside</th>
<th>NS5B Palm</th>
<th>NS5B Thumb</th>
<th>IFN</th>
<th>RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>V36</td>
<td>NS3 Protease</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>T54</td>
<td></td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>V55</td>
<td></td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>V170</td>
<td></td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>R155</td>
<td></td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>A156</td>
<td></td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Q80</td>
<td></td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>D168</td>
<td></td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>M28</td>
<td>NS5A</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Q30</td>
<td></td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>L31</td>
<td></td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Y93</td>
<td></td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>S282</td>
<td>NS5B</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>C316</td>
<td></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>M414</td>
<td></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Y448</td>
<td></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>R422</td>
<td></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>M423</td>
<td></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>P495</td>
<td></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

R: resistant (>4-fold increase in EC\textsubscript{50})
S: susceptible (<4-fold change in EC\textsubscript{50})

*IL28B* genotype has been associated with viral kinetics during IFN-free therapy

INFORM-1: Mericitabine (NI) + danoprevir (PI), 14 days, n = 15

*Chu, Gastro, 2012*
# Investigation of Residual Hepatitis C Virus in Presumed Recovered Subjects

Kei Fujiwara, Robert D. Allison, Richard Y. Wang, Patricia Bare, Kentaro Matsuura, Cathy Schechterly, Krishna Murthy, Francesco M. Marincola, and Harvey J. Alter

**Hepatology 2013;57:483-491**

## Table 2. Summary of Results Obtained From Chronic Carriers and Presumed Recovered Subjects

<table>
<thead>
<tr>
<th>Tests Performed</th>
<th>Number of HCV^+ Results of Total Samples Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chronic Carriers</td>
</tr>
<tr>
<td>HCV RNA in plasma</td>
<td>67/67</td>
</tr>
<tr>
<td>HCV RNA in total PBMCs</td>
<td>66/67</td>
</tr>
<tr>
<td>HCV RNA in PBMC subsets</td>
<td></td>
</tr>
<tr>
<td>CD19^+</td>
<td>7/8</td>
</tr>
<tr>
<td>CD3^+</td>
<td>7/8</td>
</tr>
<tr>
<td>CD19^- CD3^-</td>
<td>7/8</td>
</tr>
<tr>
<td>HCV negative-strand in total PBMCs</td>
<td>0/25</td>
</tr>
<tr>
<td>HCV negative-strand in PBMC subsets</td>
<td></td>
</tr>
<tr>
<td>CD19^+</td>
<td>0/8</td>
</tr>
<tr>
<td>CD3^+</td>
<td>0/8</td>
</tr>
<tr>
<td>CD19^- CD3^-</td>
<td>0/8</td>
</tr>
<tr>
<td>PBMC cultures</td>
<td>34/43</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.
# Summary of Phase III Investigational Agents for HCV

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dosing</th>
<th>Genotypic Activity</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS5B nucleotide analogue polymerase inhibitor</td>
<td>Sofosbuvir (GS-7977)</td>
<td>QD</td>
<td>Pangenotypic[^1,^2]</td>
<td>Phase III*</td>
</tr>
<tr>
<td>NS3A protease inhibitor</td>
<td>Faldaprevir (BI 201335)</td>
<td>QD</td>
<td>GT 1, 4, 5, 6[^3]</td>
<td>Phase III</td>
</tr>
<tr>
<td>NS3A protease inhibitor</td>
<td>Simeprevir (TMC435)</td>
<td>QD</td>
<td>GT 1, 2, 4, 5, 6[^4]</td>
<td>Phase III*</td>
</tr>
</tbody>
</table>

*New Drug Application submitted to the FDA.

NEUTRINO: 12 Wks’ Sofosbuvir + P/R in Treatment-Naive GT 1/4/5/6 HCV Patients

- Open-label, single-arm study of sofosbuvir 400 mg QD + P/R for 12 wks in treatment-naive patients with GT 1/4/5/6 HCV
  - 17% had cirrhosis; 89% had GT 1, 9% had GT 4, < 1% had GT 5, 2% had GT 6 HCV


P/R: pegIFN alfa-2a 180 µg/wk + RBV 1000-1200 mg/day
NEUTRINO: SVR12 With Sofosbuvir + P/R According to Genotype and Fibrosis Level

SVR12 According to Genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 1</td>
<td>89</td>
</tr>
<tr>
<td>GT 4</td>
<td>96</td>
</tr>
<tr>
<td>GT 5,6</td>
<td>100</td>
</tr>
</tbody>
</table>

SVR12 According to Fibrosis Level

<table>
<thead>
<tr>
<th>Fibrosis Level</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cirrhosis</td>
<td>92</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>80</td>
</tr>
</tbody>
</table>

n/N = 261/292 GT 1, 27/28 GT 4, 7/7 GT 5,6

FISSION: Sofosbuvir/RBV vs PegIFN/RBV in Treatment-Naive GT 2/3 HCV Patients

- Randomized, controlled, open-label phase III noninferiority trial
  - 20% to 21% had cirrhosis; 72% had GT 3 HCV

FISSION: Sofosbuvir/RBV Noninferior to P/R in Tx-Naive GT 2/3 HCV Patients

FISSION: SVR12 According to Genotype and Fibrosis Level

FISSION: Better Tolerability Profile With Sofosbuvir/RBV vs PegIFN/RBV

- Grade ≥ 3 AEs: 7% with SOF/RBV vs 19% for pegIFN/RBV
- Discontinuations due to AEs: 1% for SOF/RBV vs 11% for pegIFN/RBV

<table>
<thead>
<tr>
<th>AEs Occurring in ≥ 15% in Either Arm, %</th>
<th>SOF/RBV (n = 256)</th>
<th>PegIFN/RBV (n = 243)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>25</td>
<td>44</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>29</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>17</td>
<td>.0075</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7</td>
<td>18</td>
<td>.0001</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7</td>
<td>17</td>
<td>.0009</td>
</tr>
<tr>
<td>Chills</td>
<td>3</td>
<td>18</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

FUSION: Sofosbuvir + RBV for 12 or 16 Wks in Tx-Experienced GT 2/3 HCV Pts

- Randomized, double-blind, placebo-controlled phase III trial
  - 62% to 64% had GT 3 HCV, 33% to 35% had cirrhosis, 75% to 76% were previous relapsers

FUSION: Overall Efficacy Outcomes of Sofosbuvir + RBV in GT 2/3

FUSION: SVR12 With Sofosbuvir + RBV by Genotype and Fibrosis Level

POSITRON: Sofosbuvir + RBV for 12 Wks in GT 2/3 IFN-Unwilling/Intolerant/Ineligible

- Randomized, double-blind, placebo-controlled phase III trial

<table>
<thead>
<tr>
<th>Baseline Factor, n (%)</th>
<th>Sofosbuvir + RBV (n = 207)</th>
<th>Placebo (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>31 (15)</td>
<td>13 (18)</td>
</tr>
<tr>
<td>Interferon ineligible</td>
<td>88 (43)</td>
<td>33 (47)</td>
</tr>
</tbody>
</table>

IFN unwilling, intolerant, or ineligible pts with GT 2/3 HCV (N = 278)
POSITRON: Virologic Response in GT 2/3 IFN-Unwilling/Intolerant/Ineligible

**Overall Outcomes**

- **HCV RNA < LLOQ (%)**
  - Wk 4: 99% (202/204)
  - EOT: 100% (202/202)
  - SVR12: 78% (161/207)

- **SVR12 (%)**
  - No cirrhosis: 92% (85/92)
  - Cirrhosis: 94% (16/17)

- **SVR12 0% for placebo**

# Topline Summary of Sofosbuvir Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Population</th>
<th>n</th>
<th>Regimen</th>
<th>Duration, Wks</th>
<th>SVR12, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEUTRINO</td>
<td>Tx-naive GT 1</td>
<td>292</td>
<td>SOF + P/R</td>
<td>12</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>Tx-naive GT 4</td>
<td>28</td>
<td>SOF + P/R</td>
<td>12</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>Tx-naive GT 5/6</td>
<td>7</td>
<td>SOF + P/R</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>FISSION</td>
<td>Tx-naive GT 2</td>
<td>70</td>
<td>SOF + RBV</td>
<td>12</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Tx-naive GT 3</td>
<td>183</td>
<td>SOF + RBV</td>
<td>12</td>
<td>56</td>
</tr>
<tr>
<td>POSITRON</td>
<td>IFN-UII GT 2</td>
<td>109</td>
<td>SOF + RBV</td>
<td>12</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>IFN-UII GT 3</td>
<td>98</td>
<td>SOF + RBV</td>
<td>12</td>
<td>61</td>
</tr>
</tbody>
</table>

**QUEST-1: Simeprevir + P/R RGT in Treatment-Naive GT 1 HCV**

- Randomized, double-blind, placebo-controlled phase III trial
  - 12% to 13% had cirrhosis, 56% to 57% had GT 1a HCV

*Response-guided therapy: Patients with HCV RNA < 25 IU/mL at Wk 4 and HCV RNA undetectable at Wk 12 received a total of 24 wks of therapy. Those not achieving this on-treatment response received 48 wks of therapy.*

P/R, peginterferon alfa-2a 180 µg/wk + ribavirin 1000-1200 mg/day.

**QUEST-1: Virologic Response to Simeprevir + P/R Treatment**

**Virologic Outcomes**

- **HCV RNA Undetectable (%)**
  - **Week 4**:
    - SMV + P/R: 80
    - P/R: 12
    - n/N = 202/254
  - **SVR12**:
    - SMV + P/R: 80
    - P/R: 50
    - n/N = 210/264

**SVR12 by RGT Group**

- **85% of pts in SMV arm met RGT criteria**

**SMV Arm: Total Duration of RGT**

- **24 Wks**: 203/224
- **48 Wks**: 21/28

QUEST-1: SVR12 by Fibrosis Level, Subtype, and Baseline Resistance

**QUEST-2: Simeprevir + P/R RGT in Treatment-Naive GT 1 HCV**

- Phase III, randomized, double-blind, placebo-controlled trial
  - 7% to 11% had cirrhosis, 58% had GT 1b HCV

Randomized 2:1*; stratified by GT 1 subtype, IL28B genotype

- Treatment-naive pts with GT 1 HCV (N = 391)

- **Simeprevir** 150 mg QD + P/R† (n = 257)
- **Placebo + P/R** (n = 134)

- **Wk 12**
- **Wk 24**
- **Wk 48**

*63% of patients in each arm were randomly assigned to receive pegIFN alfa-2a or pegIFN alfa-2b; the remainder were assigned pegIFN alfa-2a.
†RGT: Patients with HCV RNA < 25 IU/mL at Wk 4 and HCV RNA undetectable at Wk 12 received a total of 24 wks of therapy. Those not achieving this on-treatment response received 48 wks of therapy.

QUEST-2: Virologic Response to Simeprevir + P/R Treatment

- SMV Arm: Total Duration of RGT
  - 91% of pts in SMV arm met RGT criteria

- SMV + P/R: 209/257 = 81%
- P/R: 67/134 = 50%
- 24 wks: 202/235 = 86%
- 48 wks: 7/22 = 32%

Higher rates of SVR12 with SMV, irrespective of HCV genotype or cirrhosis
Baseline Q80K mutation not a predictor of response (unlike in QUEST-1)

STARTVerso1: Faldaprevir + P/R RGT in Treatment-Naive in GT 1 HCV

- Final results of phase III STARTVerso1 trial
  - 78% were white, 81% Europe, 19% Japan; 66% had GT 1b HCV; 39% had IL28B CC; 6% were cirrhotic

Faldaprevir 120 mg QD + P/R* (n = 261)

Placebo + P/R

Faldaprevir + P/R

Wk 12

Faldaprevir 240 mg QD + P/R (n = 262)

Placebo + P/R†

P/R

Wk 24

Placebo + P/R

P/R

Wk 48

*TGT: At Wk 12, patients with ETS continued P/R to Wk 24; patients without ETS continued triple therapy to Wk 24 followed by P/R to Wk 48.

†RGT: At Wk 24, patients with ETS stopped treatment; patients without ETS continued P/R to Wk 48.

ETS defined as HCV RNA < 25 IU/mL at Wk 4 and HCV RNA < 25 IU/mL, target not detected at Wk 8.

STARTVerso1: SVR12 According to ETS, Genotype, and Fibrosis Level

ETS defined as HCV RNA < 25 IU/mL at Wk 4 and HCV RNA < 25 IU/mL, target not detected at Wk 8.

- 23% of pts with GT 1a HCV had Q80K at baseline; not predictive of SVR12

MK-5172 combined with PEG/RIBA in naïve G1 HCV-related non cirrhotic patients: a phase 2b clinical trial

<table>
<thead>
<tr>
<th>Arm 1</th>
<th>MK-5172 100 mg QD + PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>Follow-up</td>
</tr>
<tr>
<td>PR</td>
<td>Follow-up</td>
</tr>
<tr>
<td>PR</td>
<td>Follow-up</td>
</tr>
<tr>
<td>PR</td>
<td>Follow-up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm 2</th>
<th>MK-5172 200 mg QD + PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>Follow-up</td>
</tr>
<tr>
<td>PR</td>
<td>Follow-up</td>
</tr>
<tr>
<td>PR</td>
<td>Follow-up</td>
</tr>
<tr>
<td>PR</td>
<td>Follow-up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm 3</th>
<th>MK-5172 400 mg QD + PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>Follow-up</td>
</tr>
<tr>
<td>PR</td>
<td>Follow-up</td>
</tr>
<tr>
<td>PR</td>
<td>Follow-up</td>
</tr>
<tr>
<td>PR</td>
<td>Follow-up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm 4</th>
<th>MK-5172 800 mg QD + PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>Follow-up</td>
</tr>
<tr>
<td>PR</td>
<td>Follow-up</td>
</tr>
<tr>
<td>PR</td>
<td>Follow-up</td>
</tr>
<tr>
<td>PR</td>
<td>Follow-up</td>
</tr>
</tbody>
</table>

| Arm 5: PR |
| BOC + PR |
| BOC + PR |
| PR       |

- **Arms 1-4:** MK-5172 + peginterferon and ribavirin (PR) for 12 weeks, then 12 weeks or 36 weeks PR
  - TW4 HCV-RNA target not detected (TND): 12 additional weeks of PR
  - TW4 HCV-RNA target detected quantifiable (TD(q)) or target detected unquantifiable (TD(u)): 36 additional weeks of PR

- **Arm 5:** Boceprevir (BOC) + PR response-guide therapy per product circular

*Manns M, et al. EASL 2013*
MK-5172: SVR24 and HCV-RNA TND at Last Visit*

<table>
<thead>
<tr>
<th>Dosage</th>
<th>SVR24 (%)</th>
<th>HCV-RNA TND (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-5172 100 mg+PR</td>
<td>86</td>
<td>92</td>
</tr>
<tr>
<td>MK-5172 200 mg+PR</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>MK-5172 400 mg+PR</td>
<td>91</td>
<td>96</td>
</tr>
<tr>
<td>MK-5172 800 mg+PR</td>
<td>87</td>
<td>98</td>
</tr>
<tr>
<td>BOC+PR</td>
<td>54</td>
<td>67</td>
</tr>
</tbody>
</table>

*n/N values reflect all patients with undetectable (ie, TND, <10 IU/mL) HCV-RNA. Data presented are from a March 18, 2013 database extract.
- All patients have completed therapy
- 254 of 266 (95%) MK-5172 patients have reached follow-up week 24 or have discontinued before follow-up week 24
- *HCV RNA TND at last visit: patients who discontinued for reasons other than virologic failure, who completed therapy and are in follow-up, or who completed therapy but did not return for the follow-up week 24 visit

Manns M, et al. EASL 2013
## HCV Pipeline: Merck

<table>
<thead>
<tr>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Licensed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MK-5172</strong>&lt;br&gt;2nd generation NS3/4A protease inhibitor</td>
<td><strong>MK-7009</strong>&lt;br&gt;NS3/4A protease inhibitor – Japan</td>
<td><strong>Boceprevir</strong>&lt;br&gt;1st generation NS3/4A protease inhibitor</td>
</tr>
<tr>
<td><strong>MK-8742</strong>&lt;br&gt;2nd generation NS5A inhibitor</td>
<td></td>
<td><strong>Peginterferon – α2b</strong>&lt;br&gt;Immunomodulator</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Ribavirin</strong>&lt;br&gt;Non-specific anti-viral</td>
</tr>
</tbody>
</table>
Each class appears to have some characteristic features

<table>
<thead>
<tr>
<th>NS3/4A Protease Inhibitors</th>
<th>NS5A Replication Complex Inhibitors</th>
<th>NS5B Nucleos(t)ide Inhibitors</th>
<th>NS5B Non-nucleos(t)ide Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• Poor/no activity against G3</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>• Picomolar activity against multiple genotypes in vitro</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td><strong>• Broad genotype coverage</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>• Most are genotype/subtype specific</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>• Low-to-medium barrier to resistance</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>• Low-to-medium barrier to resistance</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>• High barrier to resistance</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>• Low barrier to resistance</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>• Extensive cross-resistance</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>• qd dosing</strong>&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td><strong>• qd or bid dosing</strong>&lt;sup&gt;8&lt;/sup&gt;</td>
<td><strong>• qd or bid dosing</strong>&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>• Extensive cross-resistance</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>• Potential for CYP-mediated DDIs</strong>&lt;sup&gt;7&lt;/sup&gt;</td>
<td><strong>• Limited potential for CYP-mediated DDIs</strong></td>
<td><strong>• Limited potential for CYP-mediated DDIs</strong>&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>• qd, bid or tid dosing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>• Potential for CYP-mediated DDIs</strong>&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DDI = drug–drug interactions; HTA = host-targeted antiviral; G = genotype

Future HCV treatment strategies

2013

2014

2015
2016

2017

Peg IFN a

Containing Regimens

IFN free regimens

Phase III

2nd. Generation PI Triple

Faldaprevir

Simeprevir

NUC Triple

Sofosbuvir

Next wave of triple quadruple regimens

Asunaprevir (2nd gen PI)

MK 5172 (3rd gen PI)

Daclatasvir (1st gen NS5A)

Asunaprevir (2nd gen PI) + Daclatasvir

GS 5885 (NS5A) + GS59451 (PI)
## Summary of Phase III Investigational Agents for HCV

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dosing</th>
<th>Genotypic Activity</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS5B nucleotide analogue polymerase inhibitor</td>
<td>Sofosbuvir (GS-7977)</td>
<td>QD</td>
<td>Pangenotypic[^{1,2}]</td>
<td>Phase III*</td>
</tr>
<tr>
<td>NS3A protease inhibitor</td>
<td>Faldaprevir (BI 201335)</td>
<td>QD</td>
<td>GT 1, 4, 5, 6[^{3}]</td>
<td>Phase III</td>
</tr>
<tr>
<td>NS3A protease inhibitor</td>
<td>Simeprevir (TMC435)</td>
<td>QD</td>
<td>GT 1, 2, 4, 5, 6[^{4}]</td>
<td>Phase III*</td>
</tr>
</tbody>
</table>

\[^{1,2}\] New Drug Application submitted to the FDA.

---

2. Herbst DA. *Expert Opin Investig Drugs* 2013
Can a once-daily DAA further improve outcome in easy-to-treat patients?
How effective is a once-daily DAA regimen in more difficult-to-treat patients?
Vaniprevir (MK-7009) combined with PEG/RIBA in treatment-experienced G1 HCV-related cirrhotic patients: a phase 2b clinical trial

Study design

- 76 cirrhotic patients
- 26 (35%) prior null responders

Rodriguez-Torres M, et al. EASL 2013
Vaniprevir (MK-7009) combined with PEG/RIBA in treatment-experienced G1 HCV-related cirrhotic patients: a phase 2b clinical trial

Rodriguez-Torres M, et al. EASL 2013
MK-5172 combined with PEG/RIBA in naïve G1 HCV-related non cirrhotic patients: a phase 2b clinical trial

- Arm 1: MK-5172 100 mg QD + PR
- Arm 2: MK-5172 200 mg QD + PR
- Arm 3: MK-5172 400 mg QD + PR
- Arm 4: MK-5172 800 mg QD + PR
- Arm 5: Boceprevir (BOC) + PR response-guide therapy per product circular

Arms 1-4: MK-5172 + peginterferon and ribavirin (PR) for 12 weeks, then 12 weeks or 36 weeks PR
- TW4 HCV-RNA target not detected (TND): 12 additional weeks of PR
- TW4 HCV-RNA target detected quantifiable (TD(q)) or target detected unquantifiable (TD(u)): 36 additional weeks of PR

Arm 5: Boceprevir (BOC) + PR response-guide therapy per product circular

Manns M, et al. EASL 2013
MK-5172: SVR24 and HCV-RNA TND at Last Visit*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR24</th>
<th>HCV-RNA TND at last visit*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-5172 100 mg+PR</td>
<td>86</td>
<td>92</td>
</tr>
<tr>
<td>MK-5172 200 mg+PR</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>MK-5172 400 mg+PR</td>
<td>91</td>
<td>99</td>
</tr>
<tr>
<td>MK-5172 800 mg+PR</td>
<td>87</td>
<td>98</td>
</tr>
<tr>
<td>BOC+PR</td>
<td>54</td>
<td>67</td>
</tr>
</tbody>
</table>

n/N values reflect all patients with undetectable (ie, TND, <10 IU/mL) HCV-RNA.
Data presented are from a March 18, 2013 database extract.
- All patients have completed therapy
- 254 of 266 (95%) MK-5172 patients have reached follow-up week 24 or have discontinued before follow-up week 24
- *HCV RNA TND at last visit: patients who discontinued for reasons other than virologic failure, who completed therapy and are in follow-up, or who completed therapy but did not return for the follow-up week 24 visit

Manns M, et al. EASL 2013
*IL28B* genotype has been associated with viral kinetics during IFN-free therapy.

INFORM-1: Mericitabine (NI) + danoprevir (PI), 14 days, n = 15
What’s the ideal future therapy?

• Characteristics of an ideal therapy:
  – Interferon-free
  – High barrier to resistance
  – Once daily oral combination
  – Pan-genotype (genotypes 1-4, at least)
  – “Reasonably” safe; minimal DDI
  – Short duration (~12 weeks)
  – SVR rates >90%
  – Affordable
Better understanding of the lifecycle of HCV has revealed several potential innovative drug targets.

### Viral targets
- **NS3**: The NS3/4A serine protease is essential for post-translational processing of HCV polyproteins.¹
- **NS5A**: Multifunctional membrane-associated phosphoprotein essential component of the HCV-RNA replication complex.²,³
- **NS5B**: NS5B is an HCV-specific, RNA-dependent RNA polymerase.¹

### Host targets
- **Cyclophilin A**: Host protein involved in HCV replication through interaction with NS5A and the HCV polymerase.⁴

### Drug Targets
- **Boceprevir Telaprevir**: ABT-450/r, ACH-1625
- **Asunaprevir**: TMC-435 (Simeprevir), BI-201335
- **Danoprevir**: GS-945 MK-5172

### Nucleos(t)ide analogue
- Daclatasvir
- GS-5885
- ABT-267
- PPI-668
- Nucleos(t)ide analogue
- GS-7977, Mericitabine, IDX-184*
- Non-nucleoside analogue
- BI-207127, ABT-333
- ABT-072, BMS-791325
- Tegobuvir, Setrobuvir
- VX-222, Filibuvir
- Alisporivir†
- SCY-635

* On clinical hold, Idenix press release; † On clinical hold, Novartis press release.

Viral particle production is shut down

Destruction of infected hepatocytes by immune system

Viremia decay during anti-HCV therapy

An SVR can only be achieved if therapy induces a rapid first-phase decline in HCV RNA that persists throughout treatment (dashed line) and a slower second-phase decline in HCV RNA that must eradicate infected cells prior to treatment completion if post-treatment resumption of HCV replication is to be avoided.

LLOD: lower limit of detection; SVR: sustained virologic response
## Long-term outcomes of sofosbuvir (SOF) for the treatment of chronic hepatitis C infected (CHC) patients

<table>
<thead>
<tr>
<th>Indication</th>
<th>SOF vs.</th>
<th>Cirrhosis avoided</th>
<th>HCC avoided</th>
<th>LT avoided</th>
<th>Deaths avoided</th>
<th>LY gained</th>
<th>QALY gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 1 TN</td>
<td>TVR PR48</td>
<td>-557 -2,664</td>
<td>-212 -1,068</td>
<td>-74 -363</td>
<td>-37 -182</td>
<td>0.49</td>
<td>0.48 2.12</td>
</tr>
<tr>
<td>GT 4/5/6 TN</td>
<td>PR48</td>
<td>-813</td>
<td>-241</td>
<td>-69</td>
<td>-39</td>
<td>0.32</td>
<td>0.65</td>
</tr>
<tr>
<td>GT 2 TNI</td>
<td>No treatment</td>
<td>-4,450</td>
<td>-1,441</td>
<td>-505</td>
<td>-263</td>
<td>3.36</td>
<td>3.03</td>
</tr>
<tr>
<td>GT 2 TN</td>
<td>PR24</td>
<td>-1,284</td>
<td>-456</td>
<td>-163</td>
<td>-78</td>
<td>1.17</td>
<td>1.02</td>
</tr>
<tr>
<td>GT 2 TE</td>
<td>No treatment</td>
<td>-3,487 -950</td>
<td>-1,003 -255</td>
<td>-350 -74</td>
<td>-188 -43</td>
<td>2.23</td>
<td>2.24 0.62</td>
</tr>
<tr>
<td>GT 3 TNI</td>
<td>No treatment</td>
<td>-3,689</td>
<td>-1,183</td>
<td>-415</td>
<td>-217</td>
<td>2.74</td>
<td>2.50</td>
</tr>
<tr>
<td>GT 3 TN</td>
<td>PR24</td>
<td>-2,452</td>
<td>-776</td>
<td>-276</td>
<td>-137</td>
<td>1.93</td>
<td>1.77</td>
</tr>
<tr>
<td>GT 3 TE</td>
<td>No treatment</td>
<td>-2,926 -389</td>
<td>-940 -193</td>
<td>-330 -54</td>
<td>-173 -27</td>
<td>2.17</td>
<td>1.98 0.36</td>
</tr>
</tbody>
</table>

Cure S, et al. AASLD 2013
FISSION: Better Tolerability Profile With Sofosbuvir/RBV vs PegIFN/RBV

- Grade ≥ 3 AEs: 7% with SOF/RBV vs 19% for pegIFN/RBV
- Discontinuations due to AEs: 1% for SOF/RBV vs 11% for pegIFN/RBV

<table>
<thead>
<tr>
<th>AEs Occurring in ≥ 15% in Either Arm, %</th>
<th>SOF/RBV (n = 256)</th>
<th>PegIFN/RBV (n = 243)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>55</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Headache</td>
<td>25</td>
<td>44</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>29</td>
<td>.0057</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>29</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Rash</td>
<td>9</td>
<td>17</td>
<td>.0052</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>17</td>
<td>.0075</td>
</tr>
<tr>
<td>Irritability</td>
<td>10</td>
<td>17</td>
<td>.0328</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7</td>
<td>18</td>
<td>.0001</td>
</tr>
<tr>
<td>Myalgia</td>
<td>8</td>
<td>17</td>
<td>.0060</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7</td>
<td>17</td>
<td>.0009</td>
</tr>
<tr>
<td>Influenza like symptoms</td>
<td>3</td>
<td>18</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Chills</td>
<td>3</td>
<td>18</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>
Do baseline characteristics still influence treatment outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Easy to treat</th>
<th>Difficult to treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV genotype</td>
<td>2 3 4 1b 1a</td>
<td></td>
</tr>
<tr>
<td>Host <em>IL28B</em> genotype</td>
<td>CC CT TT</td>
<td></td>
</tr>
<tr>
<td>Fibrosis stage</td>
<td>F0–F2 F3 F4 Decompensated</td>
<td></td>
</tr>
<tr>
<td>Treatment history</td>
<td>Naive Peg-IFN/RBV failure DAA failure</td>
<td></td>
</tr>
</tbody>
</table>
Foster City, CA, October 25, 2013

Gilead Sciences announced that the Antiviral Drugs Advisory Committee of the U.S. Food and Drug Administration (FDA) approved sofosbuvir:

• in combination with ribavirin, for the treatment of chronic hepatitis C in adult patients with genotype 2 and 3 infection
• in combination with pegylated interferon and ribavirin for the treatment of chronic hepatitis C in treatment-naïve adult patients with genotype 1 and 4 infection.
**QUEST-2: Simeprevir + P/R RGT in Treatment-Naive GT 1 HCV**

- Phase III, randomized, double-blind, placebo-controlled trial
  - 7% to 11% had cirrhosis, 58% had GT 1b HCV

Randomized 2:1*; stratified by GT 1 subtype, IL28B genotype

*63% of patients in each arm were randomly assigned to receive pegIFN alfa-2a or pegIFN alfa-2b; the remainder were assigned pegIFN alfa-2a.

†RGT: Patients with HCV RNA < 25 IU/mL at Wk 4 and HCV RNA undetectable at Wk 12 received a total of 24 wks of therapy. Those not achieving this on-treatment response received 48 wks of therapy.

**Manns M, et al. EASL 2013**
Summary of Safety Findings From Phase III Trials

- **Sofosbuvir**[^1-4]
  - Generally well tolerated; low rates of grade 3/4 AEs, serious AEs, and treatment discontinuation due to AEs; improved profile with SOF/RBV vs pegIFN/RBV
  - Greatly improved Hb profile with simeprevir and faldaprevir vs boceprevir/telaprevir with no significant increase over pegIFN/RBV[^5-7]

- **Simeprevir**[^5,6]
  - Generally well tolerated; no added safety signals with triple therapy

- **Faldaprevir**[^7]
  - Generally well tolerated (clinically benign and transient bilirubin increases with 240 mg dose; higher incidence of gastrointestinal events and rash)

Summary of Resistance Findings From Phase III Trials

- **Sofosbuvir**\(^{[1-4]}\)
  - No S282T mutations identified; other NS5B genetic variants not associated with change in phenotypic susceptibility

- **Simeprevir**\(^{[5,6]}\)
  - Baseline Q80K polymorphism present in 41% of patients with GT 1a HCV and associated with lower SVR12 rate in QUEST-1\(^{[5]}\)
  - Emergent NS3 protease mutations in > 90% of patients without SVR (GT 1a: R155K alone, with mutations at positions 80 and/or 168; GT 1b: most common mutation D168V, Q80R + D168E)\(^{[5,6]}\)

- **Faldaprevir**\(^{[7]}\)
  - Baseline Q80K present in 23% of patients with GT 1a HCV but not associated with SVR12 rate

Once daily Sofosbuvir/Ledipasvir fixed dose combination with or without Ribavirin resulted in >95% SVR in patients with HCV genotype 1, including patients with cirrhosis:

The LONESTAR trial

![Graph showing SVR rates](image-url)

- **Naïve (no cirrhosis):**
  - SOF/LDV 8 weeks: 19/20 (95%)
  - SOF/LDV+RBV 8 weeks: 21/21 (100%)
  - SOF/LDV 12 weeks: 18/19 (95%)
  - SOF/LDV+RBV 12 weeks: 21/21 (100%)

- **PI failures (50% cirrhosis):**
  - SOF/LDV 12 weeks: 18/19 (95%)

*Lawitz E, et al. AASLD 2013, 215*
Once Daily Sofosbuvir/Ledipasvir Fixed Dose Combination with or without Ribavirin: the ELECTRON trial

54 HCV patients were enrolled in 4 arms:
1. prior null-responder GT-1 cirrhotic patients were randomized to receive open-label fixed-dose combination tablet of SOF + LDV (SOF/LDV FDC) ± RBV for 12 weeks;
2. naïve GT-1 patients without cirrhosis received SOF/LDV FDC + RBV for 6 weeks;
3. naïve non-GT-1 patients without cirrhosis received SOF/LDV FDC + RBV for 12 weeks.

*One subject was lost to follow up without post-treatment data.

<table>
<thead>
<tr>
<th>Randomized GT 1 Prior Null Responders (Cirrhotics)</th>
<th>GT 1 Treatment Naive (Non-Cirrhotics)</th>
<th>GT 2/3 Treatment Naive (Non-Cirrhotics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/LDV FDC x 12 weeks (n=10)</td>
<td>SOF/LDV FDC+RBV x 12 weeks (n=9)</td>
<td>SOF/LDV FDC+RBV x 6 weeks (n=25)</td>
</tr>
<tr>
<td>RVR</td>
<td>80%</td>
<td>100%</td>
</tr>
<tr>
<td>EOTR</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>SVR4</td>
<td>80%</td>
<td>88%</td>
</tr>
<tr>
<td>SVR12</td>
<td>Pending</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80%</td>
</tr>
</tbody>
</table>

*Gane EJ, et al. AASLD 2013*