What is the Optimized Treatment Duration?
To Overtreat versus Undertreat

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Learning Objectives:

1. Discuss patient populations appropriate for shorter duration therapy
2. Review the impact on SVR of shorter duration therapy by treatment regimen
3. Discuss the potential “cost” of shortened therapy
Expectations Based on Phase 2/3 Clinical Trials

- Ideal duration is a moving target
- Not all types of patients have been considered for studies that evaluate truncated treatment duration
- Not all patients will be appropriate for shortened therapy
**Premise:** Patients with easier to treat characteristics can be treated for shorter duration

- PEG-RBV data suggested that some populations may be able to shorten therapy
  - Low viral load
  - IL28B CC

- Shorter therapy is desirable as duration drives cost and may impact compliance

SVR12 by Number of Negative Predictors

Derived from Multivariate Analysis (combined dataset)

*Prior treatment, sex, weight IL28B, cirrhosis, and HCV RNA level. Phase 3 studies of sofosbuvir regiments (ATOMIC, NEUTRINO, FISSION, POSITRON, FUSION, VALENCE).
Ledipasvir (NS5A inhibitor) + sofosbuvir (nucleotide polymerase inhibitor)

GT 1
LDV/SOF + RBV for 12 vs 24 Weeks: SVR12 in GT 1 Treatment-naïve Patients (ION-1)

LDV/SOF + RBV for 12 vs 24 Weeks: SVR12 in GT 1 Treatment-experienced Non-cirrhotic Patients (ION-2)

LDV/SOF + RBV for 12 vs 24 Weeks: SVR12 in GT 1 Treatment-experienced Cirrhotic Patients (ION-2)

Ledipasvir (NS5A inhibitor) + sofosbuvir (nucleotide polymerase inhibitor)

Cirrhosis matters
Treatment failure matters
Additive
ION-3: LDV/SOF ± RBV in HCV GT 1 Treatment-Naïve, Non-Cirrhotic Patients

647 patients randomized 1:1:1 across three arms

LDV/SOF

LDV/SOF + RBV

LDV/SOF

Wk 0 Wk 8 Wk 12 Wk 20 Wk 24

SVR12

SVR12

SVR12

ION-3 (GT 1, Treatment-Naive, Non-Cirrhotic, LDV/SOF±RBV x 8 or 12 weeks)

Primary Endpoint (ITT Analysis)

<table>
<thead>
<tr>
<th></th>
<th>SVR 12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF 8 weeks</td>
<td>94/202/215</td>
</tr>
<tr>
<td>LDV/SOF + RBV 8 weeks</td>
<td>93/201/216</td>
</tr>
<tr>
<td>LDV/SOF 12 weeks</td>
<td>96/208/216</td>
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Relapse Rates

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>LDV/SOF 8 weeks</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>LDV/SOF+RBV 8 weeks</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>LDV/SOF 12 weeks</td>
<td>3 (1%)</td>
</tr>
</tbody>
</table>

- All three treatment arms met the primary endpoint of superiority over the historical response rate of 60% (P<0.001 for all comparisons)
- 8 weeks of LDV/SOF was non-inferior to 8 weeks of LDV/SOF + RBV and 12 weeks LDV/SOF

Error bars represent 95% confidence intervals

Data on File, Gilead Sciences, Inc. Data on File, Gilead Sciences, Inc.
ION-3 (GT 1, Treatment-Naive, Non-Cirrhotic, LDV/SOF±RBV x 8 or 12 weeks)

Efficacy in Subjects with Baseline HCV RNA < 6 Million IU/mL

Relapse Rates by Baseline Viral Load

<table>
<thead>
<tr>
<th>HCV RNA &lt; 6M IU/mL</th>
<th>LDV/SOF 8 weeks</th>
<th>LDV/SOF 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>2% (2/123)</td>
<td>2% (2/131)</td>
<td></td>
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</tbody>
</table>

8 weeks of LDV/SOF was non-inferior to 12 weeks for patients with HCV RNA < 6M IU/ml and in the overall population

Data on File, Gilead Sciences, Inc.
Sofosbuvir (NUC) + Ledipasvir (NS5A) in Genotype 1
ION-3: Shorter Duration is Possible but how short?

ION-3

- Treatment Naive
- No cirrhosis

- N=215
  - SOF + LDV
  - SVR: 94%

- N=216
  - SOF + LDV + RBV
  - SVR: 93%

- N=216
  - SOF + LDV
  - SVR: 95%

ELECTRON*

- Treatment Naive
- No cirrhosis

- N=25
  - SOF+LDV+RBV
  - SVR: 68%

Treatment Duration > 6 weeks is needed for this combination

NIH SYNERGY: HCV Treatment Naïve G1
SOF+LDV (NPI-NS5A)+/- NNPI or PI

Paritaprevir/r (protease inhibitor/ritonavir) + ombitasvir (NS5A inhibitor) + dasabuvir (non-nucleoside polymerase inhibitor) ± RBV (3D ± RBV)

GT 1
3D + RBV for 12 Weeks: SVR12 in Treatment-naïve Non-cirrhotic Patients (SAPPHIRE-I)

<table>
<thead>
<tr>
<th></th>
<th>SVR12 (%)</th>
<th>All Patients</th>
<th>GT1a</th>
<th>GT1b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>96.2</td>
<td>455/473</td>
<td>95.3</td>
<td>307/322</td>
</tr>
<tr>
<td></td>
<td>98.0</td>
<td>148/151</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3D + RBV for 12 Weeks: SVR12 in Treatment-experienced Non-cirrhotic Patients (SAPPHIRE-II)

3D + RBV for 12 vs 24 Weeks: SVR12 in GT 1 Patients With Compensated Cirrhosis (Treatment-naïve and experienced)

TURQUOISE-II: ITT SVR12 by Prior Treatment Response in HCV GT 1b

TURQUOISE-II: ITT SVR12 by Prior Treatment Response in HCV GT 1a

Paritaprevir/r (protease inhibitor/ritonavir) + ombitasvir (NS5A inhibitor) + dasabuvir (non-nucleoside polymerase inhibitor) + RBV (3D + RBV)

Cirrhosis matters
Treatment experience matters
Varies by HCV Subtype and prior response
Sofosbuvir (nucleotide polymerase inhibitor)+RBV

GT 2 and GT 3 Patients
SOF + RBV for 12 Weeks: SVR12 in Treatment-Naive Patients (FISSION)

SOF + RBV for 24 weeks: SVR12 in GT 3 Treatment-naïve and Treatment-experienced Patients (VALENCE)

SOF + PEG/RBV for 12 Weeks in GT 3 Treatment-experienced Patients (LONESTAR-2)

Strategies to Optimize Therapy

• Simplify the regimen
• Decrease toxicity
• Shorten duration
• Improve efficacy
SOF(NI) + GS-5816 (NS5A) ± RBV x 8 or 12 Wks in Tx-Naive Noncirrhotic Pts With GT1-6 HCV

**Part A**

12 wks

Pts followed to Wk 24

**Tx-naive noncirrhotic pts**

- GT1 HCV (N = 55)
- GT3 HCV (N = 54)
- GT2, 4, 5, 6 HCV (N = 45)

**SOF + GS-5816 25 mg/day**

**SOF + GS-5816 100 mg/day**

SOF + GS-5816 ± RBV x 8 or 12 Wks in Tx-Naive Noncirrhotic Pts With GT1-6 HCV

Part B
Tx-naive noncirrhotic pts

GT1 HCV (N = 120)

GT2 HCV (N = 103)

8 wks

SOF + GS-5816 25 mg/day
SOF + GS-5816 25 mg/day + RBV
SOF + GS-5816 100 mg/day
SOF + GS-5816 100 mg/day + RBV

Pts followed to Wk 20

SVR Rates Reduced With 8-Wk Regimen in GT1 & 2; 12 Wks Effective in GT1, 2 and 3

8-Wk Duration: Impact of Baseline NS5A RAVs on Efficacy

- Response rate lower in GT2 pts with baseline NS5A RAVs

C-WORTHY: Grazoprevir (PI) + Elbasvir (NS5A) ± RBV x 12 or 18 Weeks in GT1 HCV

Treatment-naive cirrhotic GT1 HCV (N = 123)
Cirrhotic + noncirrhotic GT1 + previous null response to pegIFN/RBV (N = 130)

Grazoprevir + Elbasvir
Grazoprevir + Elbasvir + RBV
Grazoprevir + Elbasvir
Grazoprevir + Elbasvir + RBV

Wk 12
Wk 18

All pts followed for SVR12

Grazoprevir 100 mg once daily; elbasvir 50 mg once daily; weight-based RBV 800, 1200, or 1400 mg daily.
C-WORTHY: Efficacy of Grazoprevir + Elbasvir ± RBV x 12 or 18 Weeks

C-SWIFT: Grazoprevir/Elbasvir + SOF x 4, 6, or 8 Weeks in Tx-Naive GT1 HCV

- Randomized, open-label phase II trial
- Primary endpoint: SVR12


Grazoprevir/elbasvir 100/50 mg QD FDC; sofosbuvir 400 mg QD
C-SWIFT Interim Results: Modified ITT SVR4/8 With Grazoprevir/Elbasvir + SOF

Short Is NOT Simple

1. Identify appropriate patients
   – Cirrhosis
   – Prior treatment response
   – Baseline RAV’s

2. Understand rules of regimen

Less errors with a simple one-size-fits all rule
Why would we shorten therapy?

• Cost
  – If treatment priced by duration not course
• Adherence
• Management
Cost-Effectiveness
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• All-oral HCV treatment is considered cost-effective

• Analysis based on 12 v. 8/12 weeks of LDV/SOF
  – Treatment naive
  – “Treat all” strategy
  – Assumed 67% of treatment naïve would be able to truncate to 8 weeks

Cost-Effective

Table 14. Cost-effectiveness of Alternative Treatment Regimens for Hepatitis C, for Treatment-naïve Patients and a “Treat All” Strategy

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Net cost</th>
<th>Incr Net cost</th>
<th>Eff</th>
<th>Incr Eff</th>
<th>ICER</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx naïve, treat all</td>
<td>$45,313</td>
<td>$ -</td>
<td>11.82</td>
<td>0.00</td>
<td>$ -</td>
<td>undominated</td>
</tr>
<tr>
<td>No Treatment</td>
<td>$62,540</td>
<td>$ 17,227</td>
<td>13.34</td>
<td>1.51</td>
<td>$ 11,385</td>
<td>undominated</td>
</tr>
<tr>
<td>PR (48 weeks)</td>
<td>$90,991</td>
<td>$ 28,451</td>
<td>14.75</td>
<td>1.41</td>
<td>$ 20,132</td>
<td>undominated</td>
</tr>
<tr>
<td>LDV/SOF (8/12 weeks)</td>
<td>$107,942</td>
<td>$ 16,951</td>
<td>14.52</td>
<td>-0.23</td>
<td>$(73,572)</td>
<td>abs. dominated</td>
</tr>
<tr>
<td>SOF+PR (12 weeks)</td>
<td>$108,619</td>
<td>$ 17,628</td>
<td>14.81</td>
<td>0.06</td>
<td>$ 283,927</td>
<td>undominated</td>
</tr>
<tr>
<td>LDV/SOF (12 weeks)</td>
<td>$163,336</td>
<td>$ 54,717</td>
<td>14.74</td>
<td>-0.08</td>
<td>$(719,351)</td>
<td>abs. dominated</td>
</tr>
<tr>
<td>SMV/SOF (12 weeks)</td>
<td>$186,513</td>
<td>$ 77,894</td>
<td>13.99</td>
<td>-0.82</td>
<td>$(95,006)</td>
<td>abs. dominated</td>
</tr>
</tbody>
</table>

ICER = Incremental cost-effectiveness ratio

- PR $11,385 compared to no treatment
- LDV/SOF (8/12 w) added 1.41 QALYs ICER of $20,132
- LDV/SOF (12 w) additional 0.06 QALYs ICER ~300,000

ICER=$50,000 per QALY threshold to be considered highly cost-effective
Figure 6: One-way Sensitivity Analyses for Treatment-naïve Patients and “Treat All” Strategy

**Tornado Analysis ICER (LDV/SOF 8/12 weeks vs. PR)**

- Weekly cost of Sofosvir + Ledipasvir (3937.5 to 11812.5)
- Weekly cost of Peg-Interferon (412.5 to 1237.5)
- Percent of patients eligible for the 8-week therapy (0.3 to 0.9)
- PegINF+R discontinuation rate, Tx Naive (all causes, omits EVR 12) (0.121 to 0.363)
- Annual cost of CHC health state F4 (1258.0 to 10064.0)
- Utility in F2 stage (0.72 to 1.0)
- Annual cost of CHC health state F3 (1075.0 to 8600.0)
- PegINF+R SVR, Tx Naive, among completers (48-weeks) (0.85 to 0.95)
- Probability of F2 to F3 (0.077 to 0.133)
- Probability of F3 to HCC (0.0 to 0.026686)
- Probability of F4 to HCC (0.017 to 0.055)
- Probability of F4 to DC (0.03 to 0.048)

**EV: 20132.48753**

**ICER ($/QALY)**

- -10000
- -5000
- 0
- 5000
- 10000
- 15000
- 20000
- 25000
- 30000
- 35000
- 40000
- 45000
- 50000
Figure 7: One-way Sensitivity Analyses for Treatment-naïve Patients and “Treat at F3, F4” Strategy

Tornado Analysis ICER (LDV/SOF 8/12 weeks vs. PR)

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- Utility in F2 stage (0.72 to 1.0)

EV: 15939.94473
Adherence

Business & Market Trends

Pharmacy data show high drop-out rate for new hepatitis C drug

• Data from CVS Health Research Institute showed > 8% discontinuation rate among hepatitis C patients taking sofosbuvir. Forbes(9/18)
Patient Buy-in More Important Than Duration of Therapy

- Patient motivation is the most important factor in medical adherence
  - ~25% of adults have <90% adherence to ART
  - Demographic factors do not accurately predict suboptimal adherence
- Motivational interviewing and printed adherence information do not improve medication adherence

What is the cost of failure?

1. Monetary
2. Resistance
3. Access to retreatment
   - Data limited [Delay for approved regimen]
   - Some payer systems may not approve more than one treatment regimen
What Happens when SVR does not Occur After SOF-Based Therapy?

Potential routes to failure

- Failure to suppress
- Viral breakthrough
- Post-treatment relapse

SOF Failure = Relapse

What virus is left behind in the wake of failure?

No resistance left behind
# No Resistance to Sofosbuvir in Combination Therapy

<table>
<thead>
<tr>
<th>Study*</th>
<th>SOF + RBV</th>
<th>SOF + PEG-IFN + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEUTRINO¹ (n=28)</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>FISSION¹ (n=74)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>FUSION² (n=72)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>POSITRON² (n=40)</td>
<td>0%</td>
<td></td>
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</tbody>
</table>

*n = number of patients analyzed for resistance

- S282T is the “signature mutation” in vitro
- No SOF-mutations in NS5B detected by deep or population sequencing in any subject receiving SOF + RBV or SOF + PEG-IFN + RBV in Phase 2 and 3 studies
- No “virologic price to pay” for failure
- Implications for ability to retreat with SOF

Reasons for Not Achieving SVR

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>8 Weeks</th>
<th>12 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDV/SOF n=215</td>
<td>LDV/SOF+RBV n=216</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>1 (&lt;1)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Withdrew Consent</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Relapse Rates by Baseline Viral Load

<table>
<thead>
<tr>
<th></th>
<th>HCV RNA &lt; 6M IU/mL</th>
<th>HCV RNA ≥ 6M IU/mL</th>
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<tbody>
<tr>
<td></td>
<td>1.6% (2/123)</td>
<td>9.8% (9/92)</td>
</tr>
<tr>
<td></td>
<td>1.5% (2/131)</td>
<td>1.2% (1/85)</td>
</tr>
</tbody>
</table>

- All virologic failures in this study were due to relapse (n=23)
- 9 subjects had baseline NS5A resistance-associated polymorphisms and 8 subjects did not; 6 subjects had new RAVs at relapse
- 18% of subjects had baseline NS5A resistance-associated polymorphisms, and 90% achieved SVR12

Kowdley K, EASL, 2014, O56
Data on File, Gilead Sciences, Inc.
Conclusions

• Treatment duration will depend on
  – Regimen utilized
  – Baseline factors

• The benefit of short duration therapy could include lower cost but may add complexity
  – Emerging regimens may impact current assumptions of cost as competitive pricing and healthcare system contracting become a reality

• The cost of failing treatment
  – RAVs
  – Access to salvage regimens
  – Lack of data to support guideline statements