Hepatitis C: Update in Clinical Management

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Disclosure Slide

- Dr. Bacon has a financial relationship with Merck, Kadmon, Vertex, Gilead, Abbott, Roche/Genentech, ISIS, and Bristol-Myers Squibb.
The Hepatitis Epidemic

- US prevalence of chronic hepatitis C
  - 5 million exposed
  - 3.5 million with chronic viremia
- Worldwide prevalence of chronic hepatitis C-170 million
- Most patients with hepatitis C are asymptomatic until irreversible liver damage occurs
- Diagnosis depends upon a high index of suspicion and proper screening
- New guidelines from CDC for screening

Why Treat Chronic Hepatitis C?

- The disease
  - Common, chronic, and potentially progressive
  - Complications are becoming more common
    - Liver failure
    - Hepatocellular carcinoma (HCC)
- The treatment
  - Viral cure, or sustained virologic response (SVR), is achievable
  - SVR associated with histologic improvement and gradual regression of fibrosis\(^1\)
  - SVR leads to lower risk for liver failure and HCC, and improved survival\(^2,3\)

Histologic Improvement After Successful Anti-HCV Therapy

Pretreatment biopsy: Trichrome stain with Ishak stage 3 fibrosis (portal-to-portal bridging)

Long-term, follow-up biopsy obtained from the same patient 57 months after end of treatment: Trichrome stain with Ishak stage 1 fibrosis


SVR Is Equivalent to Viral Cure

Nearly 100% of patients who achieve SVR remain undetectable during long-term follow-up.1-4

Is Risk-Based HCV Screening the Best Approach?

- High HCV prevalence in “baby boomer” population (born 1946-1964)
  - HCV may have been acquired decades ago
  - Individuals no longer identified as high risk
  - Aging of population anticipated to yield ↑ advanced liver disease
- Study investigated impact of targeted “birth cohort screening”
  - 1-time screening of all US persons born 1946-1964 vs risk-based screening through 70 yrs of age
  - Utilized Markov model of natural history of HCV and liver disease, incorporating diagnosis and treatment, to estimate HCV-associated outcomes for both screening approaches


Birth Cohort vs Risk-Based HCV Screening

<table>
<thead>
<tr>
<th>Outcome Estimate, n</th>
<th>Birth Cohort Screening</th>
<th>Risk-Based Screening</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total screened</td>
<td>78,700,000</td>
<td>8,000,000</td>
<td>+70,700,000</td>
</tr>
<tr>
<td>Diagnosed</td>
<td>1,312,391</td>
<td>427,030</td>
<td>+885,361</td>
</tr>
<tr>
<td>Treated</td>
<td>742,329</td>
<td>234,689</td>
<td>+507,640</td>
</tr>
<tr>
<td>SVR</td>
<td>404,274</td>
<td>124,650</td>
<td>+279,624</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>238,500</td>
<td>291,200</td>
<td>-52,700</td>
</tr>
<tr>
<td>HCC</td>
<td>137,400</td>
<td>166,000</td>
<td>-28,600</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>28,700</td>
<td>34,700</td>
<td>-6000</td>
</tr>
<tr>
<td>HCV death</td>
<td>233,200</td>
<td>281,200</td>
<td>-48,000</td>
</tr>
</tbody>
</table>

- Limitations of analysis: model is simplified view of disease and treatment; validity dependent on model assumptions; data combined from various sources; incident infection and transmission not included in model; new HCV treatments not considered


Targets for New Hepatitis C Drugs

5′- Core E1 E2 P 7 NS2 NS3 NS4A NS4B NS5A NS5B

Protease inhibitors

Linear
- Telaprevir
- Boceprevir
- ACH-1625
- GS-9256

Macro cyclic
- Danoprevir (RG7227)
- TMC 4355350
- BI-201335
- BMS-650032
- Vaniprevir

Polymerase inhibitors

Active site (nucleosides)
- RG7128
- IDX184
- PSI-7977

Non-nucleosides
- ABT-333
- ABT-072
- GS 9190
- ANA598
- VCH-759
- VCH-916
- VX-222
- Filibuvir
- BI-207127

Cyclophilin

Debio 025
SCY-635

Not all-inclusive
To Treat or not to Treat:  
A Constellation of Considerations

- Genotype virus Genotype Patient (IL28)  
- Histologic stage 20%+ lifetime risk of cirrhosis  
- Duration of infection  
- Personal plans (marriage, pregnancy)  
- Age  
- Family and other support  
- Patient “mindset”  
- ALT  
- Occupation  
- Extrahepatic Features (Fatigue, EMC, PCT)  
- HIV coinfection  
- Contraindications & comorbidities Insulin Resistance

Boceprevir and Telaprevir Clinical Trials

- Phase III trials leading to approval
  - Boceprevir plus pegIFN/RBV
    - SPRINT-2: treatment-naive patients[^1]
  - Telaprevir plus pegIFN/RBV
    - ADVANCE: treatment-naive patients[^3]
    - ILLUMINATE: treatment-naive patients[^4]
    - REALIZE: treatment-experienced patients[^5]

**SPRINT-2: Boceprevir in GT1 Treatment-Naive Patients**

Treatment-naive patients with genotype 1 HCV (2 cohorts: N = 938 nonblack and 159 black)

- PR* (n = 316, 52)
- BOC + PR* (n = 316 nonblack, 52 black)
- PR* (n = 311, 55)
- BOC + PR* (n = 311 nonblack, 55 black)

**Follow-up**

*BOC 800 mg q8h, pegIFN alfa-2b 1.5 µg/kg/wk, weight-based RBV 600-1400 mg/day.*


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**Treatment With Boceprevir**

- All patients initiate therapy with 4-wk pegIFN/RBV lead-in phase
- After completion of lead-in phase, boceprevir should be added to continued pegIFN/RBV
  - Boceprevir: 800 mg TID, every 7-9 hrs
  - Boceprevir should be administered with food (light snack or meal)

SVR and Relapse Rates

**SPRINT-2: BOC + PegIFN/RBV in GT1 treatment-naïve patients**

![Bar chart showing SVR and Relapse Rates](image)

**P < .001**


**SPRINT-2 Subanalysis: Response to 4-Wk PegIFN/RBV Lead-in**

- Response to 4-wk lead-in phase with pegIFN/RBV strongest predictor of SVR in multivariate analysis (OR: 9.0; P < .001)
  - When 4-wk lead-in phase included as continuous variable, *IL28B* genotype no longer significantly predictive of SVR

![Bar chart showing SVR and Relapse Rates](image)

Boceprevir: Duration of Therapy for Noncirrhotic Treatment-Naive Patients

- HCV RNA levels at Wks 8, 12, and 24 used as decision points
  - HCV RNA assay should have 25 IU/mL limit of quantification

<table>
<thead>
<tr>
<th>HCV RNA Levels</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 8</td>
<td>Wk 12</td>
</tr>
<tr>
<td>Undetectable</td>
<td>&lt; 100 IU/mL</td>
</tr>
<tr>
<td>Detectable</td>
<td>&lt; 100 IU/mL</td>
</tr>
<tr>
<td>Detectable</td>
<td>≥ 100 IU/mL</td>
</tr>
</tbody>
</table>

1) Continue all 3 drugs through Wk 36, then
2) continue pegIFN/RBV through Wk 48

Discontinue all 3 drugs at Wk 12


ADVANCE: Telaprevir + PegIFN/RBV in GT1 Treatment-Naive Patients

TVR 750 mg q8h, pegIFN alfa-2a 180 µg/wk, weight-based RBV 1000-1200 mg/day.

eRVR: extended rapid virologic response = undetectable HCV RNA at Wks 4 and 12.

Treatment With Telaprevir

• All patients initiate therapy with 12-wk period of triple therapy with telaprevir plus pegIFN/RBV
  – Telaprevir: 750 mg TID, every 7-9 hrs
  – Telaprevir should be administered with food (standard or high fat)
    ▪ Standard fat meal would be 21 g, such as 2 oz of cheese or 1/2 cup of nuts


ADVANCE: Overall SVR and Relapse Rates

- P < .0001 for both treatment arms vs control
- 8-wk TVR/PR + 16/40-wk PR (n = 364)
- 12-wk TVR/PR + 12/36-wk PR (n = 363)
- 48-wk PR (n = 361)

Jacobson IM, et al. AASLD 2010. Abstract 211. These data are available in unpresented abstract format only, and will be presented in full during the AASLD meeting. We encourage you to review the presented data before making conclusions.
Response-Guided Approach With TVR in Tx-Naive Patients Supported by 2 Studies

- ADVANCE: suggested 24 wks of therapy sufficient for patients with eRVR
  - Among patients in T12PR48 arm who achieved an eRVR and received 24 wks therapy, SVR was 89%


Response-Guided Approach With TVR in Tx-Naive Patients Supported by 2 Studies

- Robustness of response-guided therapy confirmed by ILLUMINATE
  - 92% of those who received 24 wks of total therapy following eRVR achieved SVR
    \[ \Delta 4.5\% \]

Telaprevir: Duration of Therapy for Treatment-Naive Patients

- After 12 wks, telaprevir should be discontinued and pegIFN/RBV continued
  - Cirrhotic patients with undetectable HCV RNA at Wks 4 and 12 may nevertheless benefit from additional 36 wks of pegIFN/RBV (48 wks total) rather than response-guided therapy

<table>
<thead>
<tr>
<th>HCV RNA</th>
<th>Triple Therapy: TVR + PegIFN/RBV</th>
<th>Dual Therapy: PegIFN/RBV</th>
<th>Total Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetectable at Wks 4 and 12</td>
<td>First 12 wks</td>
<td>Additional 12 wks</td>
<td>24 wks</td>
</tr>
<tr>
<td>Detectable (but ≤ 1000 IU/mL) at Wks 4 and/or 12</td>
<td>First 12 wks</td>
<td>Additional 36 wks</td>
<td>48 wks</td>
</tr>
</tbody>
</table>

**Stopping Rules**

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Criteria</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 4 or 12</td>
<td>HCV RNA &gt; 1000 IU/mL</td>
<td>Discontinue all therapy</td>
</tr>
<tr>
<td>Wk 24</td>
<td>HCV RNA detectable</td>
<td>Discontinue pegIFN/RBV</td>
</tr>
<tr>
<td>Any</td>
<td>Discontinuation of pegIFN/RBV for any reason</td>
<td>Discontinue TVR</td>
</tr>
</tbody>
</table>


Retreatment With BOC + PegIFN/RBV in Treatment-Experienced Patients

<table>
<thead>
<tr>
<th>SVR (%)</th>
<th>PR48</th>
<th>BOC RGT</th>
<th>BOC/PR48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous partial response</td>
<td>73/101</td>
<td>29/51</td>
<td>40/62</td>
</tr>
<tr>
<td>Previous relapse</td>
<td>7/29</td>
<td>72/152</td>
<td>52/105</td>
</tr>
</tbody>
</table>


BOC, BOC+PR48
SVR in Previous Relapsers, Partial Responders, Null Responders

REALIZE: TVR + PegIFN/RBV in G1 Previous Relapsers and Partial/Null Responders

![Graph showing SVR in Previous Relapsers, Partial Responders, Null Responders]

*P < .001 vs PR48.


SVR in Poorly IFN-Responsive Patients by Wk 4 PR Lead-in Response

RESPOND-2: BOC + PegIFN/RBV in GT 1 Treatment-Experienced Patients

Poorly Responsive to IFN: < 1 log_{10} HCV RNA decline at Wk 4

Responsive to IFN: ≥ 1 log_{10} HCV RNA decline at Wk 4

![Graph showing SVR in Poorly IFN-Responsive Patients]

SVR in Poor IFN Responders Based on TW8 Response (Log Decline in VL Compared to BL VL) (BOC Arms Combined)

Efficacy of boceprevir in prior null responders to peginterferon/ribavirin: the PROVIDE study*

*Of 48 prior null responders from SPRINT-2 and RESPOND-2, 3 discontinued during the 4-week lead-in phase, 2 are ongoing treatment (1 entering TW3, 1 entering TW18 of BOC/PR) and 1 is in follow-up phase

Relapse: an undetectable HCV RNA level at EOT but with a detectable HCV RNA level during the follow-up period

Telaprevir in Patients With Bridging Fibrosis or Cirrhosis

SVR was defined as HCV RNA <25 IU/mL at last observation within the Week 72 visit window. In cases of missing data, the last HCV RNA data point from Week 12 of follow-up onwards was used.

Key for Waves of New Gents: Direct-Acting Anti-Virals (DAAs) and Host-Targeting antiviral (HTAs)

**DAAs**
- **First Wave 1st**
  - Telaprevir
  - Boceprevir
- **Second Wave 2nd**
  - TMC435
  - BI 201335
  - BMS-790052
  - PSI-7977
- **Third Wave 3rd**
  - BI 201335/BI 207127
  - BMS-790052/BMS-650032
  - Mericitabine/MK-5172

**HTAs**
- Alisporivir/DEB 025
- SCY635
HCV Pipeline by Mechanism of Action and Stage of Development

**Mechanism**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Direct acting antiviral agents</th>
<th>Host targeting agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Inhibitor of polyprotein processing</td>
<td>Inhibitor of HCV replication</td>
</tr>
<tr>
<td>NS3 or NS3/NS4A protease</td>
<td>NS3A</td>
<td>NS5A polymerase</td>
</tr>
</tbody>
</table>

**Recently approved**

- **Phase III**
  - Telaprevir (Merck) 800 mg twice daily (BID) (designated agent)
  - Boceprevir (Viagra) 1000 mg three times daily (TID) (designated agent)

- **Phase II**
  - TMC-435 (Schering-Plough) 200 mg QD (once daily)
  - BI-201335 (Boehringer Ingelheim) 240 mg QD (once daily)

- **Phase I**
  - SCH-200354 (Schering-Plough) 200 mg QD (once daily)
  - ONZ-75 (Onze) 140 mg QD (once daily)
  - BMV-001 (Boehringer Ingelheim) 75 mg QD (once daily)

**Preliminary**

- ACH-268 (Achillion) 200 mg QD (once daily)
- BI-201335 (Boehringer Ingelheim) 280 mg QD (once daily)

**Antiviral Efficacy of 2nd Wave NS3 PIs**

- **Danoprevir**
  - 200 mg TID: Mean HCV RNA Decline (log10 IU/mL) = 3.8
- **TMC435**
  - 200 mg QD: Mean HCV RNA Decline (log10 IU/mL) = 3.9
- **BI-201335**
  - 240 mg QD: Mean HCV RNA Decline (log10 IU/mL) = 4.2
- **Vaniprevir**
  - 700 mg BID: Mean HCV RNA Decline (log10 IU/mL) = 4.6
- **BMS-650032**
  - 400 mg QD: Mean HCV RNA Decline (log10 IU/mL) = 3.3
- **PHX1766**
  - 800 mg BID: Mean HCV RNA Decline (log10 IU/mL) = 1.8

*Only represents a sample of agents in development for HCV.

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Goals for Hepatitis C Therapy

• Compared to PegIFN/RBV, new products should offer:
  – Improved efficacy
  – Efficacy in all patient types including previously treated patients, cirrhotic and black patients
  – Orally effective regimen, IFN free
  – Shorter treatment duration
  – Improved side-effect profile

Selected Oral Directing Acting Antivirals for the Treatment of Chronic Hepatitis C, 2012

<table>
<thead>
<tr>
<th>Compound</th>
<th>Sponsor</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-267</td>
<td>Abbott</td>
<td>NS5A inhibitor</td>
</tr>
<tr>
<td>ABT-333</td>
<td>Abbott</td>
<td>Non-nucleoside NS5B polymerase inhibitor</td>
</tr>
<tr>
<td>ABT-450</td>
<td>Abbott</td>
<td>NS3/4A protease inhibitor</td>
</tr>
<tr>
<td>Faldaprevir</td>
<td>Boehringer Ingelheim</td>
<td>NS3/4A protease inhibitor</td>
</tr>
<tr>
<td>(BI201335)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BI207127</td>
<td>Boehringer Ingelheim</td>
<td>Non-nucleoside NS5B polymerase inhibitor</td>
</tr>
</tbody>
</table>
### Selected Oral Directing Acting Antivirals for the Treatment of Chronic Hepatitis C, 2012 (cont)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Sponsor</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asunaprevir</td>
<td>Bristol-Myers Squibb</td>
<td>NS3 protease inhibitor</td>
</tr>
<tr>
<td>(BMS-650032)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Bristol-Myers Squibb</td>
<td>NS5A replication complex inhibitor</td>
</tr>
<tr>
<td>(BMS-790052)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMS-791325</td>
<td>Bristol-Myers Squibb</td>
<td>Non-nucleoside NS5B polymerase inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Gilead</td>
<td>Uridine nucleotide analog NS5B polymerase inhibitor</td>
</tr>
<tr>
<td>(GS-7977)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GS-5885</td>
<td>Gilead</td>
<td>NS5A protein inhibitor</td>
</tr>
</tbody>
</table>

*Not all-inclusive, but indicates drugs covered in this presentation*

### SOUND-C2 Trial Update: BI 201335 + BI 207127 ± RBV

- Five arm study that evaluated different doses and durations in regimens with faldaprevir (PI) and BI207127 (non-nuc) with or without RBV
  - Durations: 16, 28 or 40 weeks
  - BID vs TID
- Randomization was stratified by genotype (1a vs 1b) and IL28B
  - 9% of patients had cirrhosis
- SVR12 ranged between 52% to 69% in RBV-containing arms and 39% without RBV
  - SVR in cirrhotics is 54%*
- IL28B CC, genotype 1b and female gender were favorably associated with SVR12

SOUND-C2 Trial Update: Faldaprevir + BI 207127 ± RBV

Primary endpoint: SVR12 (ITT and per protocol)


ELECTRON Trial

Objective
- To evaluate sofosbuvir (SOF; formerly GS-7977), a uridine nucleotide analog, plus ribavirin (RBV) in additional ELECTRON study arms:
  - SOF + RBV in treatment-naïve genotype 1 patients
  - SOF + RBV in null responder genotype 1 patients
  - SOF + RBV in treatment experienced (Prior null response, breakthrough, or relapse) in genotype 2/3 patients
- To determine feasibility of shorter duration or reduced dose of RBV in treatment naïve genotype 2/3 patients
- To evaluate the efficacy and safety of adding GS-5885, an NS5A inhibitor, to SOF + RBV in treatment naïve and null responder genotype 1 patients

**ELECTRON Trial Update: Sofosbuvir + RBV vs. Sofosbuvir + GS-5885 + RBV in Genotype 1 HCV**

<table>
<thead>
<tr>
<th></th>
<th>SOF + RBV</th>
<th>SOF + GS-5885 + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment-Naïve</td>
<td>Null Responder</td>
</tr>
<tr>
<td></td>
<td>(n=25)</td>
<td>(n=10)</td>
</tr>
<tr>
<td><strong>SAEs</strong>*</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>AEs that led to</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ Grade 2 AEs</td>
<td>10 (40)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>0</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Ligament sprain</td>
<td>1 (4)</td>
<td>1 (10)</td>
</tr>
</tbody>
</table>

*SAEs considered unrelated to SOF
*Stopped treatment at week 8 at time of partial colectomy for diverticular perforation


**ELECTRON Trial Summary: Genotype 1 HCV**

- SOF + RBV for 12 weeks provided SVR12 in 84% of treatment-naïve, but only in 10% of null responders
- Addition of GS-5885 increased efficacy of SOF + RBV
  - 100% SVR4 in treatment-naïve patients
  - 3/3 SVR4 in null responders
  - No additional safety/tolerability issues detected

SOF in Combination with Low or Full Dose RBV in Difficult to Treat Genotype 1 HCV Patients

Objective:

• To assess the safety, tolerability, and efficacy of SOF in combination with weight-based (full) or low dose ribavirin (RBV) for 24 weeks in HCV mono-infected, genotype 1, treatment-naive subjects
• SOF is a specific nucleotide analog HCV polymerase inhibitor


SOF in Combination with Low or Full Dose RBV in Difficult to Treat Genotype 1 HCV Patients

Treatment Response: Full dose RBV (Part 1; N=10)

<table>
<thead>
<tr>
<th>ITT HCV RNA &lt;LLOQ (%)</th>
<th>Week 4</th>
<th>Week 12</th>
<th>ETR</th>
<th>SVR4</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90%</td>
<td>90%</td>
<td>90%</td>
<td>90%</td>
<td>90%</td>
</tr>
</tbody>
</table>

• mITT: 100% SVR12 (1 drop out at week 3)

SOF in Combination with Low or Full Dose RBV in Difficult to Treat Genotype 1 HCV Patients

Conclusions:
- In this inner city population of HCV genotype 1 treatment-naïve patients, SOF + RBV administered for 24 weeks resulted in:
  - Full dose RBV: SVR4 of 77%
  - Low dose RBV: SVR4 of 56%
- There were no safety signals or drug-related discontinuations in this study


All-Oral Combination of Daclatasvir Plus Sofosbuvir ± Ribavirin in Treatment Naïve HCV GT 1, 2, or 3

Objective:
- To evaluate the efficacy and safety of daclatasvir (DCV; BMS-790052) plus sofosbuvir (SOF; GS-7977) with or without RBV
  - 24 weeks in treatment-naïve patients infected with HCV GT1 (1a/1b), 2, or 3
  - 12 weeks in treatment-naïve patients infected with GT1 (1a/1b)
- DCV is an NS5A replication complex inhibitor; SOF is a nucleotide analogue NS5B polymerase inhibitor

Virologic Response is Maintained at PT Week 24 (GT 2 or 3; 24-Week Treatment Groups)

<table>
<thead>
<tr>
<th>HCV RNA &lt;LLOQ (% patients)</th>
<th>SOF LI + DCV</th>
<th>DCV + SOF</th>
<th>DCV + SOF + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>100 100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>EOT</td>
<td>94</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>SVR4</td>
<td>100</td>
<td>100</td>
<td>88</td>
</tr>
<tr>
<td>SVR12</td>
<td>86</td>
<td>86</td>
<td>100</td>
</tr>
<tr>
<td>SVR24</td>
<td>88</td>
<td>88</td>
<td>100</td>
</tr>
</tbody>
</table>


All-Oral Combination of Daclatasvir Plus Sofosbuvir ± Ribavirin in Treatment Naïve HCV GT 1, 2, or 3

Conclusions:
- DCV + SOF with or without RBV achieved SVR in ≥93% of patients with HCV genotype 1, 2, or 3
- HCV genotype 2 or 3 (N=44)
  - 24-week duration: SVR24=93% of patients
- HCV genotype 1 (N=126)
  - 12-week duration: SVR4=96%
  - 24-week duration: SVR24=98%

ABT-450/r, ABT-267, ABT-333 and RBV in Treatment Naïve and Prior Null Responders with Genotype 1 HCV

Objective
- To assess efficacy and safety of several interferon free regimens of ABT-450/r with ABT-267 and/or ABT-333 ± ribavirin (RBV)
  - ABT-450 is an HCV NS3/4 protease inhibitor that is co-administered with ritonavir (ABT-450/r) and dosed once daily
  - ABT-267 is an NS5A inhibitor that is dosed once daily
  - ABT-333 is a non-nucleoside polymerase inhibitor dosed twice daily


ABT-450/r, ABT-267, ABT-333 and RBV in Treatment Naïve and Prior Null Responders with Genotype 1 HCV

SVR12 Rates (ITT) for 8- and 12-week Arms

ABT-450/r, ABT-267, ABT-333 and RBV in Treatment Naïve and Prior Null Responders with Genotype 1 HCV

Conclusions

• The 12-week 3 DAA + RBV regimens showed the greatest efficacy in both treatment-naïve and null responder populations
• All DAA combinations studied were well tolerated through 8 - 12 weeks of treatment
• Phase 3 studies with the 3 DAA combination (with and without RBV) recently initiated


What’s In the Future? – Multiple DAAs?

Multiple DAAs + IFN Backbone + RBV

• 2nd generation PIs
• Nucleoside polymerase inhibitors
• NS5A inhibitors
• Nonnucleoside polymerase inhibitors (NNIs)

• Considerations:
  – 2 DAA programs
  – Consider replacing RBV
  – RGT
What’s In the Future? – IFN Free?

Polymerase Backbone
• Highest resistance barrier
• Pan-genotypic
• Second generation PI / NS5A / NNI / RBV
• Cyclophilin inhibitor
• 3- or 4-drug regimens
• SVR?

HCV — The Revolution Has Begun

- Antiviral activity in all HCV genotypes
- No selection of resistance
- All-oral combination regimen
- Short treatment duration
- QD (or BID) dosing
- Excellent safety and tolerability

Applicable in difficult-to-treat populations:
- Transplant
- Coinfection
- End-stage renal disease, etc.