The CLDF and IC-HEP would like to thank our supporters for providing an educational grant to support this program:

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Lisa D. Pedicone, PhD - No Relevant Relationships
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Educational Objectives

• Identify the risk factors and overall disease processes in chronic liver diseases

• Describe current and evolving treatment strategies for chronic liver diseases in order to optimize patient outcomes

• Effectively adhere to long-term surveillance recommendations outlined in the AASLD guidelines
Primary Biliary Cirrhosis (PBC)
What is PBC?

- Approved name change to “Primary Biliary Cholangitis”
- Chronic cholestatic disease with a progressive course which may extend over many decades
- Rate of progression varies greatly
- Asymptomatic in early disease
- Often leads to fatigue, pruritus and Sicca syndrome (dry eyes and/or dry mouth)
- Primary biliary cirrhosis (PBC) affects about 1/1000 women age >40 years and is a leading indication for liver transplantation

Causes and Markers of PBC

- Autoimmune disease thought to be due to a combination of genetic predisposition and environmental triggers.
- High degree of specificity for involvement of the small intrahepatic bile ducts.
- Serologic hallmark of PBC is the AMA, a highly disease-specific autoantibody found in 90-95% of patients and less than 1% of controls.
Elevated serum alkaline phosphatase (ALP) activity

Exclude other causes of liver disease including alcohol and drugs

Cross sectional imaging of liver to exclude biliary obstruction

AMA (Antimitochondrial antibody), ANA (antinuclear antibody), ASMA (anti-smooth muscle antibody)

Consider liver biopsy, especially if AST>5x ULN or AMA -
Ursodeoxycholic Acid (UDCA)

- Orally administered nontoxic bile acid
- Replaces the bile acids normally produced by the liver, which are more toxic and can harm the liver
- UDCA in a dose of 13-15 mg/kg/day is the only currently FDA approved therapy for PBC
- UDCA is initiated gradually and given BID
- Improvement in liver tests will be seen within a few weeks and 90% of the improvement usually occurs within 6-9 months
Ursodeoxycholic Acid (UDCA)

- Safe, may improve clinical symptoms, delay progression of disease and survival, and improve QOL
- However, up to 40% of PBC patients treated with UDCA have a suboptimal response

Pares A, Gastroenterology, 2006; Marschall HU, Gastroenterology, 2005.
ALP <1.67 x ULN and Normal Bilirubin after 1 Year of UDCA is Highly Predictive of Outcome

Global PBC Study Group (N=4845)

Cum LTx-free Survival (%)

Follow up after 1 year of treatment with UDCA (yr)

Responder
Non-Responder

Lammers, EASL, AASLD. 2013.
Ursodeoxycholic Acid (UDCA)

- Backbone of therapy in PBC in the past 20 years
- Early treatment provides the most benefit
- Can improve the outcome but does not cure PBC
Obeticholic Acid (OCA): A Modified Bile Acid and FXR Agonist
OCA in Patients with PBC: POISE Study Design

- **Randomization Strata**
  Subjects stratified 1:1:1 by:
  1) ALP >3x ULN and/or AST >2x ULN and/or total bilirubin >ULN (Paris I)
  2) Not receiving UDCA treatment

- **OCA Titration at 6 Months**: Subjects in OCA titration arm titrated from 5 mg to 10 mg at Month 6 if they met any of the following criteria at the Month 6 assessment:
  1. The primary endpoint (ALP <1.67x ULN or bilirubin ≤ULN) was not achieved
  2. No evidence of tolerability issues, e.g. pruritus
To assess the proportion of patients achieving ALP <1.67 xULN and a decrease of ≥ 15% and total bilirubin ≤ULN

**Inclusion**
- PBC diagnosis (EASL and AASLD guidelines)
- ALP ≥1.67 xULN and/or total bilirubin >ULN to <2 xULN
- Stable UDCA or unable to tolerate UDCA

**Exclusion**
- Concomitant liver diseases, decompensation, severe pruritus requiring treatment

**Randomization Strata**
- UDCA (yes/no)
- Paris I

Percent Achieving Primary Endpoint

Response:
Achieving ALP <1.67x ULN with bilirubin ≤ULN and ≥15% reduction in ALP

p values obtained using Cochran-Mantel-Haenszel stratified by randomization strata factor

Titration OCA group: 5 mg OCA for 6 months □ 10 mg OCA if well tolerated & ALP >1.67x ULN or bilirubin >ULN
A Significantly Greater Proportion of OCA-treated Subjects Had a ≥10, 20 or 40% ALP Reduction

**10% Reduction**

- **Month 6**: Placebo (n=73) - 40%, Titration (n=70) - 40%, 10 mg OCA (n=73) - 80%
- **Month 12**: Placebo (n=73) - 20%, Titration (n=70) - 80%, 10 mg OCA (n=73) - 80%

**20% Reduction**

- **Month 6**: Placebo (n=73) - 20%, Titration (n=70) - 60%, 10 mg OCA (n=73) - 80%
- **Month 12**: Placebo (n=73) - 0%, Titration (n=70) - 80%, 10 mg OCA (n=73) - 80%

**40% Reduction**

- **Month 6**: Placebo (n=73) - 0%, Titration (n=70) - 40%, 10 mg OCA (n=73) - 80%
- **Month 12**: Placebo (n=73) - 0%, Titration (n=70) - 40%, 10 mg OCA (n=73) - 80%

***p<0.0001 vs. placebo; p values obtained using Cochran-Mantel-Haenszel stratified by randomization strata factor

**Titration OCA group**: 5 mg OCA for 6 months then titrated to 10 mg OCA if tolerated & ALP ≥1.67x ULN or bilirubin >ULN
OCA Treatment Resulted in Significant Decreases in Markers of Hepatobiliary Damage

**Month 6**
- GGT (U/L)
  - Placebo (n=73) vs. Titration (n=70): ***p<0.001 vs. placebo
  - 10 mg OCA (n=73): ***

**Month 12**
- GGT (U/L)
  - Placebo (n=73) vs. Titration (n=70): ***p<0.001 vs. placebo
  - 10 mg OCA (n=73): ***

**Month 6**
- ALT (U/L)
  - Placebo (n=73) vs. Titration (n=70): ***p<0.001 vs. placebo
  - 10 mg OCA (n=73): ***

**Month 12**
- ALT (U/L)
  - Placebo (n=73) vs. Titration (n=70): ***p<0.001 vs. placebo
  - 10 mg OCA (n=73): ***

**Month 6**
- AST (U/L)
  - Placebo (n=73) vs. Titration (n=70): ***p<0.001 vs. placebo
  - 10 mg OCA (n=73): ***

**Month 12**
- AST (U/L)
  - Placebo (n=73) vs. Titration (n=70): ***p<0.001 vs. placebo
  - 10 mg OCA (n=73): ***

**Titration OCA group:** 5 mg OCA for 6 months then titrated to 10 mg OCA if tolerated & ALP ≥1.67x ULN or bilirubin >ULN
OCA Treatment Decreased Bilirubin Over Time

**Baseline Direct Bilirubin (mean ± SE, µmol/L):**
- Placebo: 5.5 ± 0.7
- Titrated OCA: 4.5 ± 0.5
- 10 mg OCA: 4.9 ± 0.5

**Baseline Total Bilirubin (mean ± SE, µmol/L):**
- Placebo: 11.8 ± 0.9
- Titrated OCA: 10.3 ± 0.7
- 10 mg OCA: 11.3 ± 0.8

**Titration OCA group:** 5 mg OCA for 6 months then titrated to 10 mg OCA if tolerated & ALP ≥1.67x ULN or bilirubin >ULN

* p<0.05 vs. placebo

**Charts:**
- **Total Bilirubin**
- **Direct Bilirubin**
Adverse Events

- Pruritus, generally mild to moderate, was the most common and dose related AE
  - Few subjects treated with OCA withdrew due to pruritus (<6%)
- The incidence of AEs other than pruritus was no worse with OCA (Placebo, 90%, 5/10 mg OCA, 89%, 10 mg OCA, 86%)
Overall Findings

- The effect of OCA was consistent independent of age at diagnosis, duration of PBC and baseline ALP.
- Titration from 5 to 10 mg based on clinical response improved tolerance, minimized dropouts due to pruritus, and showed comparable efficacy to 10 mg OCA after 1 year. Thus, starting patients on OCA 5 mg with titration to 10 mg based on the clinical response appears to be an appropriate dosing strategy.
- OCA given to individuals with PBC with an inadequate response to or unable to tolerate UDCA produced a significant clinically meaningful improvement in liver biochemistry, which have been shown to correlate strongly with clinical benefit.
Long-term Management of Patients with PBC (AASLD Guidance)

- Liver tests every 3-6 months
- Thyroid status (TSH) annually
- Bone mineral densitometry every 2-4 years
- Vitamins A, D, K annually if bilirubin >2.0
- Upper endoscopy every 1-3 years if cirrhotic or Mayo risk score >4.1
- Ultrasound ± AFP every 6 months in patients with known or suspected cirrhosis
Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)
Adult Obesity in America 2014

Percent of Obese Adults (Body Mass Index of 30+)

- 20 - 24.9%
- 25 - 29.9%
- 30-34.9%
- 35%+

http://stateofobesity.org/adult-obesity/

Adult Obesity in America 2011-12

- Obese: 34.9%
- Overweight or Obese: 68.5%

Childhood Obesity in America 2011-12

- Obese: 16.9%
- Overweight or Obese: 31.8%

http://stateofobesity.org/adult-obesity/
Visceral Obesity

Dyslipidemia
Hypertension

Endothelial Dysfunction

Atherosclerosis

Insulin Resistance

Type 2 Diabetes

Polycystic Ovarian Syndrome (PCOS)

Coronary Artery Disease (CAD)

Non-alcoholic Fatty Liver Disease (NAFLD)

NAFLD is Closely Associated with Visceral Obesity and Insulin Resistance

Diseases Associated with Visceral Obesity
The Spectrum of NAFLD

- Exclusion of liver diseases (HCV & ETOH)
- Requires specific pathologic criteria for NASH
- Important for prognosis

Prevalence of NAFLD & NASH


Prevalence (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD overall</td>
<td>46%</td>
</tr>
<tr>
<td>NAFLD Hispanic</td>
<td>58.3%</td>
</tr>
<tr>
<td>NAFLD Caucasian</td>
<td>45%</td>
</tr>
<tr>
<td>NAFLD African American</td>
<td>44.4%</td>
</tr>
<tr>
<td>NASH overall</td>
<td>35.1%</td>
</tr>
<tr>
<td>NASH among diagnosed NAFLD</td>
<td>24%</td>
</tr>
</tbody>
</table>
Prevalence of NAFLD in Children

- Using surrogate markers, prevalence of NAFLD in children is 2.6-17.3%
- Autopsy study from UCSD (N=742)
  - Prevalence: 9.6%, rates increasing with age
  - More common in boys
  - Highest rate in Hispanics

Schwimmer JB 2006, Argo C 2009
Summary of Outcomes of NASH

NAFLD Patients With Components of MS are at Highest Risk for Advanced Fibrosis

- NAFLD with liver biopsy (N=432)
- In multivariate analysis, elevated AST and ALT, presence of diabetes mellitus, male gender and Caucasian ethnicity were associated with moderate to severe fibrosis (p-value<0.0001)

209 NAFLD patients with liver biopsy slides, clinical data and mortality data were included

- Median follow up = 146 months (max 342 months)
- During follow-up, 31% of patients died with 9% dying of LRM

Regardless of the pathologic criteria used, NASH patients had higher LRM than non-NASH NAFLD

- (13.0% vs. 1.3% for Original NAFLD NASH, p = 0.0047)

On multivariate analysis, only significant fibrosis (grade > 2) was an independent predictor of LRM
Long-term Outcomes of Diabetics with NAFLD

- NAFLD & DM (n=44) vs. NAFLD alone (n=88)
- Patients with NAFLD and DM have*:
  - Higher rate of cirrhosis (25% vs. 10.2%, p=0.04)
  - Higher liver-related mortality (RR=22.83, p=0.003)
  - Higher mortality (RR=3.3, p=0.002)

*Average follow up = 10 years
Younossi et al. Clin Gastro and Hepatology 2004
No lab test or imaging study will be able to predict with 100% accuracy. The more risk factors... the more concern.

Red Flags for NASH

- Age
- Gender
- Hispanic
- HT
- Obesity
- Diabetes
- ALT and AST level
- AST/ALT ratio
- Insulin level
- PNPLA3
Treatment and Intervention
Fibrosis (45%)  
NASH Resolution (64-90%)*  
Ballooning/Inflammation (41-100%)*  
Steatosis (35-100%)*

Weight Loss ≥ 10%\(^1\)  
Weight Loss ≥ 7%\(^1\)  
Weight Loss ≥ 5%\(^{1,2,3}\)  
Weight Loss ≥ 3%\(^{1,2,3,4}\)


*Depending on degree of weight loss
NAFLD Guideline Recommendations

• Weight loss generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity (Strength - 1, Evidence - A)

• Loss of at least 3-5% of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10%) may be needed to improve necroinflammation (Strength - 1, Evidence - B)

• Exercise alone in adults with NAFLD may reduce hepatic steatosis but its ability to improve other aspects of liver histology remains unknown (Strength - 1, Evidence - B)
NAFLD Guideline Recommendations

• Metformin has no significant effect on liver histology and is not recommended as a specific treatment for liver disease in adults with NASH. (Strength - 1, Evidence - A)

• Pioglitazone can be (?) used to treat steatohepatitis in patients with biopsy-proven NASH. (Strength - 1, Evidence - B)
  – However, the majority of patients who participated in clinical trials that investigated pioglitazone for NASH were non-diabetic
  – Long term safety and efficacy of pioglitazone in patients with NASH is not established
NAFLD Guideline Recommendations

• Vitamin E (α-tocopherol) administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore should be considered as a first-line pharmacotherapy for this patient population. (Strength - 1, Quality - B)

• Until further data supporting its effectiveness become available, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis (Strength - 1, Quality - C)
FLINT Trial Design- Obeticholic Acid (OCA)

N=283
Patients w/ Histological Evidence of NASH*

OCA 25 mg QD
Placebo QD

Follow-up
Follow-up

Screening (Biopsy)

72-week treatment period

24 week off treatment

Primary endpoint: liver histological improvement defined as decrease in NAFLD Activity Score (NAS) of ≥2 points with no worsening in fibrosis

*Entry was based upon histologic diagnosis of nonalcoholic steatohepatitis (NASH) based on local CRN site pathologist’s read (end-of-study blinded central read of baseline biopsies revealed 80% of patients enrolled had definite NASH); interim analysis was conducted when ≥50% of patients completed treatment and had repeat liver biopsy; NAFLD: nonalcoholic fatty liver disease; Neuschwander-Tetri B, et al. Lancet. 2014:S0140-6736(14)61933-4.
FLINT primary endpoint

- Improvement in NAFLD activity score* (NAS) ≥ 2 pts
  - * NAS = steatosis grade (0-3) + inflammation grade (0-3) + ballooning grade (0-2)
- No worsening of fibrosis
- Results:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>21% (23/109)</td>
</tr>
<tr>
<td>OCA 25 mg/day</td>
<td>46% (50/110)</td>
</tr>
</tbody>
</table>

\[ p = 0.0002 \]

Improvement in Fibrosis and NASH Resolution

**Fibrosis**
- Placebo: 19%
- OCA: 35%
- p = 0.004

**NASH Resolution**
- Placebo: 13%
- OCA: 22%
- p = 0.08 (NS)

Lipid Concentrations

1. Data from Tetri et al. *The Lancet* and Supplementary Appendix. Published online November 7, 2014.
2. All *p*-values compared to placebo. *p*<0.05
3. Converted mean values using factor of 38.6 for cholesterol and 88.5 for triglycerides.
Adverse Events

- 6 severe adverse events in obeticholic acid group
  - 4 severe pruritus (1 stopped treatment)
  - 1 hypoglycemia
  - 1 possible cerebral ischemia (dysarthria and dizziness)
- Moderate or severe pruritus
  - 23% in obeticholic acid
  - 6% in placebo

\[ P < 0.0001 \]

NAFLD and NASH

- NAFLD is a complex disease tied closely to obesity and diabetes
- NASH patients with fibrosis most likely to progress
  - NAFLD/NASH in the setting of DM/MS has adverse outcomes
- Personalized targeted treatment may be the best future option to treat NASH
- Some considerations for current patients with NASH:
  - Life style modifications for all
  - Vitamin E for non-DM NASH
  - ??Pio for DM with NASH but be aware of safety concerns
  - Clinical trials (OCA and others)
  - Consider bariatric surgery for morbidly obese+/-DM with NASH
- Multiple clinical trials underway in the USA to treat NASH
Chronic Hepatitis C
HCV Can Now Be Cured in Most Patients

• Unlike HIV and HBV infection, HCV infection is a curable disease
  – HCV does not archive its genome

• What defines cure?
  – Undetectable HCV RNA 12 weeks after completion of antiviral therapy for chronic HCV infection
  – SVR12 is almost invariably durable

SVR Was Associated With Reduced Long-Term Risk of All-Cause Mortality in an International, Multicenter Study

International, multicenter, long-term follow-up study from 5 large tertiary care hospitals in Europe and Canada. Patients with chronic HCV infection started an interferon-based treatment regimen between 1990 and 2003 (n=530).

Global Distribution and Prevalence of HCV Genotypes

Approved Direct-Acting Antiviral Agents from Multiple Classes: Combination Regimens for HCV

Note the common root name for each drug class
Principles of All Oral Regimens for HCV

• Combine drugs from different classes
  – Target multiple targets to increase efficacy
  – Decrease risk of viral resistance

• Near universal efficacy

• Shortened duration

• Adverse events have minimal impact on patient’s quality of life
General Concepts About Selecting HCV Regimens

• Choice of regimen, treatment duration, and use of ribavirin depends on:
  – Presence of cirrhosis
  – Prior treatment experience
    • PEG-RBV or DAA exposure
  – Genotype and Subgenotype
## Fibrosis Assessment / Diagnosing Cirrhosis

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Physical exam (firm liver edge, splenomegaly) Low platelets (&lt;160 x 10³/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal images</td>
<td>Surface abnormalities (eg, nodularity) Features of portal HTN and ascites</td>
</tr>
<tr>
<td>Liver fibrosis imaging</td>
<td>Ultrasonography, ARFI, MRE, MRI, CT scan, etc.</td>
</tr>
<tr>
<td>Transient elastography</td>
<td>FibroScan</td>
</tr>
<tr>
<td>Serum markers of fibrosis</td>
<td>APRI, FIB-4, Fibrosure, FibroTest, HepaScore</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>Useful in establishing the stage but invasive</td>
</tr>
</tbody>
</table>

See online calculators for APRI, FIB-4, Child-Pugh, MELD, etc. ([eg, www.gihep.com](http://www.gihep.com))

APRI = aspartate aminotransferase-to-platelet ratio index; ARFI = acoustic radiation force imaging; MRE = magnetic resonance elastography; MRI = magnetic resonance imaging; CT = computed tomography.

Approved Treatments for Patients with GT 1 Infection
Paritaprevir/r (protease inhibitor/ritonavir) + ombitasvir (NS5A inhibitor) + dasabuvir (non-nucleoside polymerase inhibitor) ± RBV

(PTV/RTV/OMV + DSV ± RBV) (PrOD ± RBV)
Integrated Efficacy: SVR12 in GT 1a Non-cirrhotic Patients Treated with PTV/RTV/OMV + DSV for 12 Weeks (+/- RBV) (SAPPHIRE-I and –II, PEARL-IV)

Integrated Efficacy: SVR12 in GT 1a Cirrhotic Patients Treated with PTV/RTV/OMV + DSV + RBV for 12 vs 24 Weeks (TURQUOISE-II)

SVR12 in GT 1b Non-cirrhotic Patients Treated with PTV/RTV/OMV + DSV for 12 Weeks (+/- RBV)

- Pooled analysis of Phase 3 trials

**Overall**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR12 (%)</th>
<th>Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ RBV</td>
<td>100</td>
<td>301 / 301</td>
</tr>
<tr>
<td>- RBV</td>
<td>98.3</td>
<td>562 / 572</td>
</tr>
</tbody>
</table>

**Treatment naive**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR12 (%)</th>
<th>Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ RBV</td>
<td>100</td>
<td>210 / 210</td>
</tr>
<tr>
<td>- RBV</td>
<td>98.9</td>
<td>357 / 361</td>
</tr>
</tbody>
</table>

**Relapse**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR12 (%)</th>
<th>Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ RBV</td>
<td>100</td>
<td>33 / 33</td>
</tr>
<tr>
<td>- RBV</td>
<td>98.5</td>
<td>67 / 68</td>
</tr>
</tbody>
</table>

**Partial response**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR12 (%)</th>
<th>Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ RBV</td>
<td>100</td>
<td>26 / 26</td>
</tr>
<tr>
<td>- RBV</td>
<td>98.1</td>
<td>52 / 53</td>
</tr>
</tbody>
</table>

**Null response**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR12 (%)</th>
<th>Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ RBV</td>
<td>100</td>
<td>32 / 32</td>
</tr>
<tr>
<td>- RBV</td>
<td>95.6</td>
<td>86 / 90</td>
</tr>
</tbody>
</table>

*Includes 1 treatment-naive G1b pt who was enrolled in PEARL-IV study

Colombo M, et al. AASLD 2014, Boston. #1931
SVR12 in GT 1b Cirrhotic Patients Treated with PTV/RTV/OMV + DSV for 12 Weeks

• TURQUOISE III trial
  – 60 GT 1b patients with cirrhosis received PTV/RTV/OMV + DSV (no RBV) for 12 weeks
  – SVR12=100% (60/60)
  – Recommended regimen in AASLD/IDSA guidance document (August 2015)

Feld J, et al. J of Vir Hep. 2015 (suppl 2); pp. 134-135
## Label-Recommended Regimen

<table>
<thead>
<tr>
<th>Subgenotype</th>
<th>Patients without Cirrhosis</th>
<th>Patients with Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GT1a</td>
<td>GT1b</td>
</tr>
<tr>
<td>Regimen</td>
<td>3D + RBV</td>
<td>3D</td>
</tr>
<tr>
<td>Duration, weeks</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

USPI and EU SmPC recommended regimens for subject with GT1 infection

Among >2000 patients in the phase 3 studies, 1083 patients received the label-recommended regimen
Ledipasvir (LDV) (NS5A inhibitor) + sofosbuvir (SOF) (nucleotide polymerase inhibitor) (LDV/SOF)
LDV/SOF ± RBV for 12 vs 24 Weeks: SVR12 in GT 1 Treatment-naïve Patients (ION-1)

GT 1 Treatment Naïve Non-Cirrhotics With BL Viral Load <6 Million IU/mL: 8 Weeks Can Be Considered But May Impact Insurance Coverage (ION-3)

<table>
<thead>
<tr>
<th></th>
<th>LDV/SOF 8 Weeks (N=215)</th>
<th>LDV/SOF 12 Weeks (N=216)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SVR12 (Overall)</strong></td>
<td>94% (202/215)</td>
<td>96% (208/216)</td>
</tr>
<tr>
<td><strong>SVR12 (BL viral load &lt;6M IU/mL)</strong></td>
<td>97% (119/123)</td>
<td>96% (126/131)</td>
</tr>
<tr>
<td><strong>Relapse Rates (Overall)</strong></td>
<td>5% (11/215)</td>
<td>1% (3/216)</td>
</tr>
<tr>
<td>&lt;6M IU/mL</td>
<td>2% (2/123)</td>
<td>2% (2/131)</td>
</tr>
<tr>
<td>≥6M IU/mL</td>
<td>10% (9/92)</td>
<td>1% (1/85)</td>
</tr>
</tbody>
</table>

Ledipasvir/sofosbuvir (HARVONI™) Prescribing Information. Gilead Sciences, Foster City, CA. March, 2015 (Adapted from Table 6).
LDV/SOF ± RBV for 12 vs 24 Weeks: SVR12 in GT 1 Treatment-experienced Patients (ION-2)

SVR12 (%)

12 Weeks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No cirrhosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF</td>
<td>95/83/87</td>
<td>86/19/22</td>
</tr>
<tr>
<td>LDV/SOF + RBV</td>
<td>100/89/89</td>
<td>82/18/22</td>
</tr>
</tbody>
</table>

24 Weeks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No cirrhosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF</td>
<td>99/86/87</td>
<td>100/22/22</td>
</tr>
<tr>
<td>LDV/SOF + RBV</td>
<td>99/88/89</td>
<td>100/22/22</td>
</tr>
</tbody>
</table>

Afdhal EASL Abst O109
## Integrated Analysis of Cirrhotic Patients From the LDV/SOF Development Program, n=513

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Treatment Naïve</th>
<th>Treatment Experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall SVR12</strong></td>
<td></td>
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<tr>
<td>12 wk</td>
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<td>24 wk</td>
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<tr>
<td><strong>Regimen</strong></td>
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<tr>
<td>LDV/SOF</td>
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<tr>
<td>LDV/SOF + RBV</td>
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<tr>
<td><strong>Duration ± RBV</strong></td>
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<tr>
<td>LDV/SOF 12 wk</td>
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<tr>
<td>LDV/SOF + RBV 12 wk</td>
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<tr>
<td>LDV/SOF 24 wk</td>
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</tbody>
</table>

Ledipasvir (LDV) + Sofosbuvir (SOF): GT 1

- Very manageable safety profile
- One pill once a day
- Duration
  - Non-cirrhotics
    - LDV/SOF x 12 weeks (consider 8 weeks for some treatment naïve patients)
  - Cirrhotics
    - LDV/SOF x 24 weeks or
    - LDV/SOF + RBV x 12 weeks
- Potential drug:drug interactions (e.g., P-gp inducers, amiodarone)
- Not recommended in patients with severe or ESRD requiring dialysis
Simeprevir (SMV) (protease inhibitor) + sofosbuvir (SOF)
(nucleotide polymerase inhibitor)

(SMV/SOF)
SMV/SOF x 12 Weeks
SVR12 in GT 1 Non-cirrhotics (OPTIMIST-1)

Proportion of patients (%)

Treatment-naïve

112/115
88/103

SMV+SOF 12 weeks
SMV+SOF 8 weeks

Proportion of patients (%)

Treatment-experienced

38/40
40/52

Kwo et al. Abstract #LP-14, EASL 2015.
SMV/SOF x 12 Weeks
SVR12 in GT 1 Cirrhotics (OPTIMIST-2)

**SVR12: SMV + SOF 12 weeks**

- Treatment-naive: 88%
  - 44/50
- Treatment-experienced: 79%
  - 42/53

*Implication: SMV+SOF insufficient for GT1 cirrhotics*

Lawitz E, et al. EASL 2015, Vienna. #LP04
Simeprevir (SMV) + Sofosbuvir (SOF): GT 1

• Ribavirin may be necessary for some patients
• Manageable safety profile
• One tablet and one capsule once daily
• Regimens (+/- RBV)
  – SMV/SOF x 12 weeks for patients without cirrhosis
  – SMV/SOF x 24 weeks for patients with cirrhosis
• Not recommended in patients with moderate or severe hepatic impairment (Child-Pugh Class B and C)
• No dosage adjustment of SMV required in patients with mild, moderate or severe renal impairment (remember SOF warning in severe renal impairment)
• Drug:drug interactions (e.g., moderate/strong inducers or inhibitors of CYP3A, amiodarone due to the SOF component)
Approved Treatments for Patients with GT 2 or GT 3 Infection
SOF+PEG/RBV x 12 Wks vs SOF + RBV x 24 Weeks: SVR12 in GT 2 vs GT 3 Patients (BOSON Study)

- **GT 2 Treatment Experienced, Cirrhotic**
  - SOF + RBV 16 weeks: 87%
  - SOF + RBV 24 weeks: 100%
  - SOF + PEG/RBV 12 weeks: 94%

- **GT 3 Treatment Naïve or Experienced, With or Without Cirrhosis**
  - SOF + RBV 16 weeks: 71%
  - SOF + RBV 24 weeks: 84%
  - SOF + PEG/RBV 12 weeks: 93%

Error bars represent 95% confidence intervals.
Foster et al., Abstract #L-05, EASL 2015
SOF+PEG/RBV x 12 Wks vs SOF+RBV x 24 Weeks: SVR12 in GT 3 Patients By Subgroup (BOSON Study)

Foster et al., Abstract #L-05, EASL 2015
Daclatasvir/Sofosbuvir for GT 3: SVR12 in Treatment-naïve and Treatment-experienced Patients Treated for 12 Weeks (ALLY-3) (FDA Approval: July 2015)

Daclatasvir/Sofosbuvir for GT 3: SVR12 in Patients With and Without Cirrhosis Treated for 12 Weeks (ALLY-3) (FDA Approval: July 2015)

Treatment of GT 3 Patients

• In July 2015, daclatasvir (DCV) + sofosbuvir (SOF) for GT 3 was approved by the FDA

• Recommended regimens in guidance document
  – SOF + PEG/RBV x 12 weeks
  – DCV + SOF x 12 weeks without cirrhosis
  – DCV + SOF + RBV x 24 with cirrhosis

• GT 3 infected patients with cirrhosis remain the biggest challenge to cure
Conclusions

• One time testing of all baby boomers is essential
• HCV is a curable disease and eradication decreases all-cause mortality
• Linkage to liver experts that can assess disease progression and treatment options
• Highly efficacious, short duration regimens with favorable safety profiles are available
• Rapidly evolving field…
The CLDF and IC-HEP would like to thank our supporters for providing an educational grant to support this program:

*AbbVie, Bristol-Myers Squibb, Gilead, Intercept Pharmaceuticals, and Merck*