AASLD 2014: Nucleoside Regimens (sofosbuvir)

Fred Poordad, MD
Professor of Medicine
University of Texas Health Science Center
VP, Academic and Clinical Affairs
Texas Liver Institute
San Antonio, TX

Disclosures

- Grant/Research support: Abbott Laboratories, Achillion Pharmaceuticals, Anadys Pharmaceuticals, Biolex Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, GlobeImmune, Idenix Pharmaceuticals, Idera Pharmaceuticals, Inhibitex Pharmaceuticals, Intercept Pharmaceuticals , Janssen, Medarex, Medtronic, Merck & Co., Novartis, Pharmasset, Roche, Schering-Plough, Santaris Pharmaceuticals, Scynexis Pharmaceuticals, Vertex Pharmaceuticals, ViroChem Pharma, ZymoGenetics; Speaker: Gilead, Merck, Vertex; Consultant/Advisor: Abbott Laboratories, Achillion Pharmaceuticals, Anadys Pharmaceuticals, Biolex Therapeutics, GlobeImmune, Inhibitex Pharmaceuticals, Merck & Co., Pharmasset, Santaris Pharmaceuticals, Tibotec, Theravance.

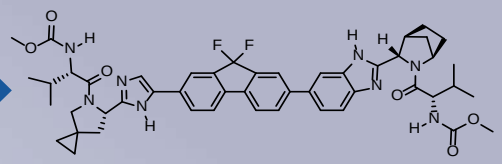
Texas Liver Institute

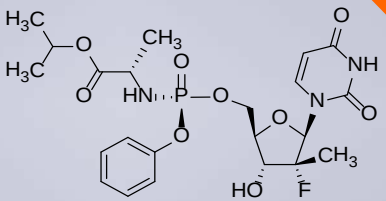
UT Health Science Center

Ledipasvir/Sofosbuvir

- **Ledipasvir**
  - Once-daily, oral, 90-mg NS5A inhibitor
- **Sofosbuvir**
  - Once-daily, oral, 400-mg NS5B inhibitor
- **Ledipasvir/Sofosbuvir FDC**
  - Once-daily, oral, fixed-dose (90/400 mg) combination tablet
  - Single-tablet regimen for hepatitis C

LDV NS5A inhibitor





SOF nucleotide polymerase inhibitor

LDV NS5A inhibitor

SOF nucleotide polymerase inhibitor

FDC, fixed-dose combination.

Texas Liver Institute

UT Health Science Center

An Integrated Safety and Efficacy Analysis of >500 Patients with Compensated Cirrhosis Treated with Ledipasvir/ Sofosbuvir with or without Ribavirin

Marc Bourlière[1]; Mark S. Sulkowski[2]; Masao Omata[3]; Stefan Zeuzem[4]; Jordan J. Feld[5]; Eric Lawitz[6]; Patrick Marcellin[7]; Robert H. Hyland[8]; Xiao Ding[8]; Jenny C. Yang[8]; Steven J. Knox[8]; Phillip S. Pang[8]; Mani Subramanian[8]; William T. Symonds[8]; John G. McHutchison[8]; Alessandra Mangia[9]; Edward J. Gane[10]; K. Rajender Reddy[11]; Masashi Mizokami[12]; Stanislas Pol[13]; Nezam H. Afdhal[14]

1. Hôpital Saint Joseph, Marseilles, France
2. Johns Hopkins University, Baltimore, MD
3. Yamanashi Prefectural Hospital Organization, Yamanashi, Japan
4. Johann Wolfgang Goethe University, Frankfurt am Main, Germany
5. Sandra Rotman Centre for Global Health, University of Toronto, Toronto, ON, Canada
6. Texas Liver Institute, University of Texas Health Science Center, San Antonio, TX
7. Hôpital Beaujon, University of Paris, Paris, France
8. Gilead Science, Inc, Foster City, CA
9. Liver Unit, Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Italy
10. New Zealand Liver Transplant Unit, Auckland City Hospital, Auckland, New Zealand
11. University of Pennsylvania, Philadelphia, PA
12. Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine, Chiba, Japan
13. Department of Hepatology, Université Paris-René Descartes, Paris, France
14. Beth Israel Deaconess Medical Center, Boston, MA

Texas Liver Institute

UT Health Science Center

Abstract #82

Methods

- 513 patients with GT 1, compensated cirrhosis
- Pooled data from Phase 2 and 3 LDV/SOF ± RBV studies
  - LONESTAR, ELECTRON, ELECTRON-2, 337-0113, ION-1, ION-2, SIRIUS

Bourlière M, et al. Abstract #82, AASLD 2014

Texas Liver Institute

UT Health Science Center

Baseline Demographics

Patients, %	Treatment Naïve (n=161)	Treatment Experienced (n=352)	Total (n=513)
Male	63%	68%	67%
Black	8%	4%	5%
Asian	17%	15%	15%
GT 1a	53%	63%	60%
Prior PI Failure	NA	68%	47%
Region			
US	50%	31%	37%
Ex-US	50%	69%	63%

Bourlière M, et al. Abstract #82, AASLD 2014

Texas Liver Institute

UT Health Science Center

SVR12: LDV/SOF for 12 vs 24 Weeks in Compensated Cirrhotics

Bourlière M, et al. Abstract #82, AASLD 2014

Texas Liver Institute

UT Health Science Center

Subgroup Observations

- Among treatment-experienced patients, 12 weeks of LDV/SOF without RBV resulted in only 90% SVR rate
- Adding RBV or extending treatment duration increased this rate to ≥96%
- Platelet count <75 x 10^3/uL was associated with a lower SVR rate among treatment-experienced patients with cirrhosis

Bourlière M, et al. Abstract #82, AASLD 2014

Texas Liver Institute

UT Health Science Center

Ledipasvir/Sofosbuvir with Ribavirin for the Treatment of HCV in Patients with Decompensated Cirrhosis: Preliminary Results of a Prospective, Multicenter Study

Steven L. Flamm[1]; Gregory T. Everson[2]; Michael Charlton[3]; Jill M. Denning[4]; Sarah Arterburn[4]; Theo Brandt-Sarif[4]; Phillip S. Pang[4]; John G. McHutchison[4]; K. Rajender Reddy[5]; Nezam H. Afdhal[6]

1. Northwestern Feinberg School of Medicine, Chicago, IL
2. University of Colorado Denver, Aurora, CO
3. Intermountain Medical Center, Murray, UT
4. Gilead Sciences, Raleigh, NC
5. University of Pennsylvania School of Medicine, Philadelphia, PA
6. Beth Israel Deaconess Medical Center, Boston, MA

Texas Liver Institute

UT Health Science Center

Abstract #239

Study Design

- 108 GT 1 or 4 treatment naïve or treatment experienced patients with decompensated cirrhosis (Child-Pugh class B[7-9]) or C[10-12])

- Inclusion/exclusion
  - No history of major organ transplant, including liver
  - No HCC
  - Total bili $\leq$10 mg/dL, hemoglobin $\geq$10 g/dL
  - CL_{cr} $\geq$40 mL/min, platelets >30,000 x 10^3/uL

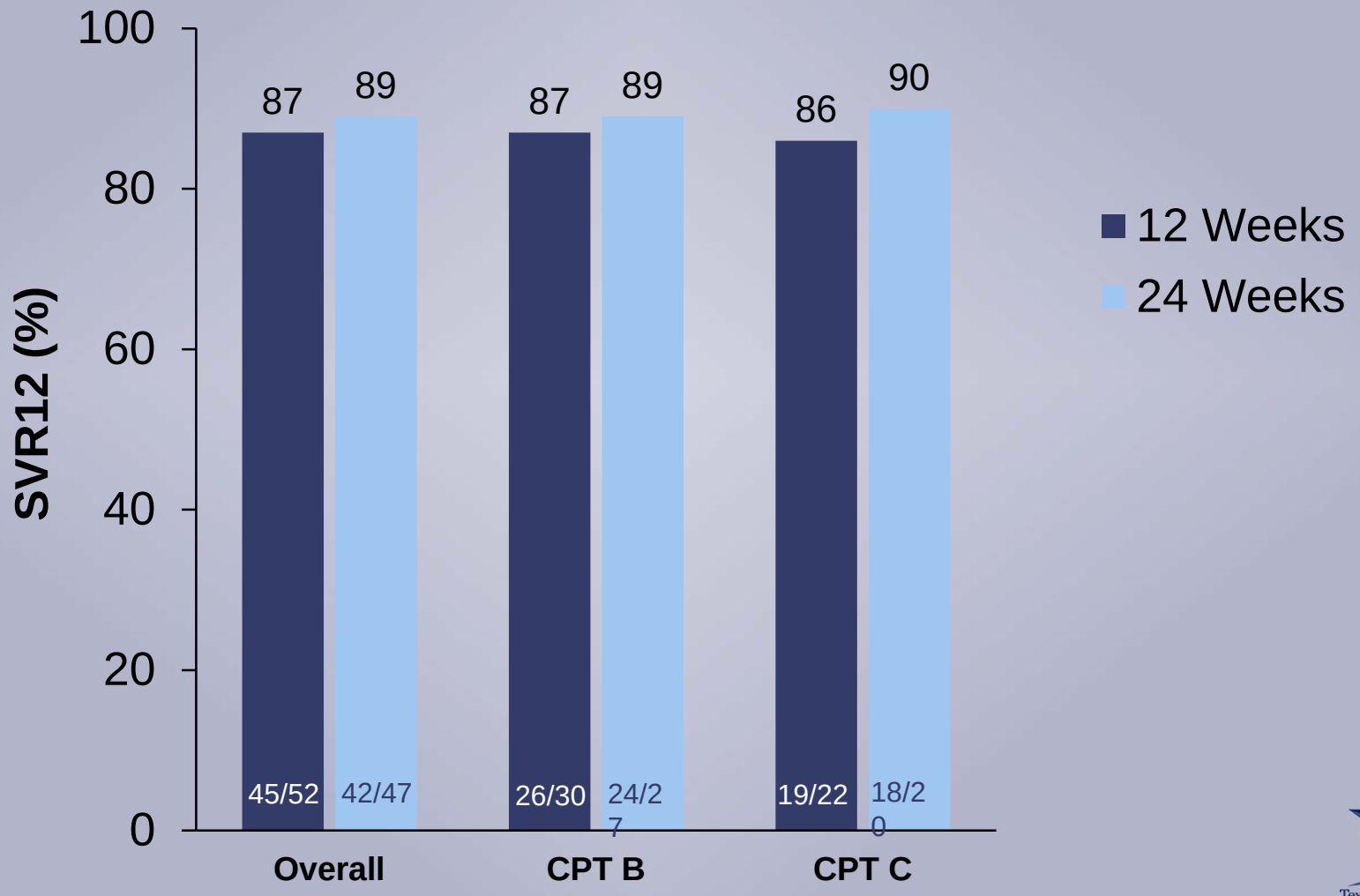
- LDV/SOF (ledipasvir/sofosbuvir)+ RBV for 12 or 24 weeks

Flamm S, et al. Abstract #239, AASLD 2014

Texas Liver Institute

UT Health Science Center

LDV/SOF + RBV in Decompensated Cirrhosis: SVR12



Flamm S, et al. Abstract #239, AASLD 2014

Texas Liver Institute

UT Health Science Center

Overall Safety Summary

	CPT B		CPT C	
Patients, %	**12 Weeks (n=30)**	**24 Weeks (n=29)**	**12 Weeks (n=23)**	**24 Weeks (n=26)**
Adverse Events (AE)	97%	93%	100%	100%
Grade 3-4 AE	7%	28%	26%	42%
Serious AE	10%	34%	26%	42%
Serious and Related AEs	7%	0	0	8%
Treatment discontinuation due to AE	0	3%	0	8%
Death	3%	7%	9%	4%

Related SAEs: Anemia, hepatic encephalopathy, peritoneal hemorrhage

Flamm S, et al. Abstract #239, AASLD 2014

Texas Liver Institute

UT Health Science Center

Conclusions

- Extending treatment duration to 24 weeks did not increase SVR rate
- LDV/SOF + RBV was generally safe and well tolerated in decompensated cirrhotics

Flamm S, et al. Abstract #239, AASLD 2014

Texas Liver Institute

UT Health Science Center

High Efficacy of LDV/SOF Regimens for 12 Weeks for Patients with HCV Genotype 3 or 6 Infection

E. J. Gane[1]; R. H. Hyland[2]; D. An[2]; E. S. Svarovskaia[2]; P. S. Pang[2]; W. T. Symonds[2]; J. G. McHutchison[2]; C. A. Stedman[3]

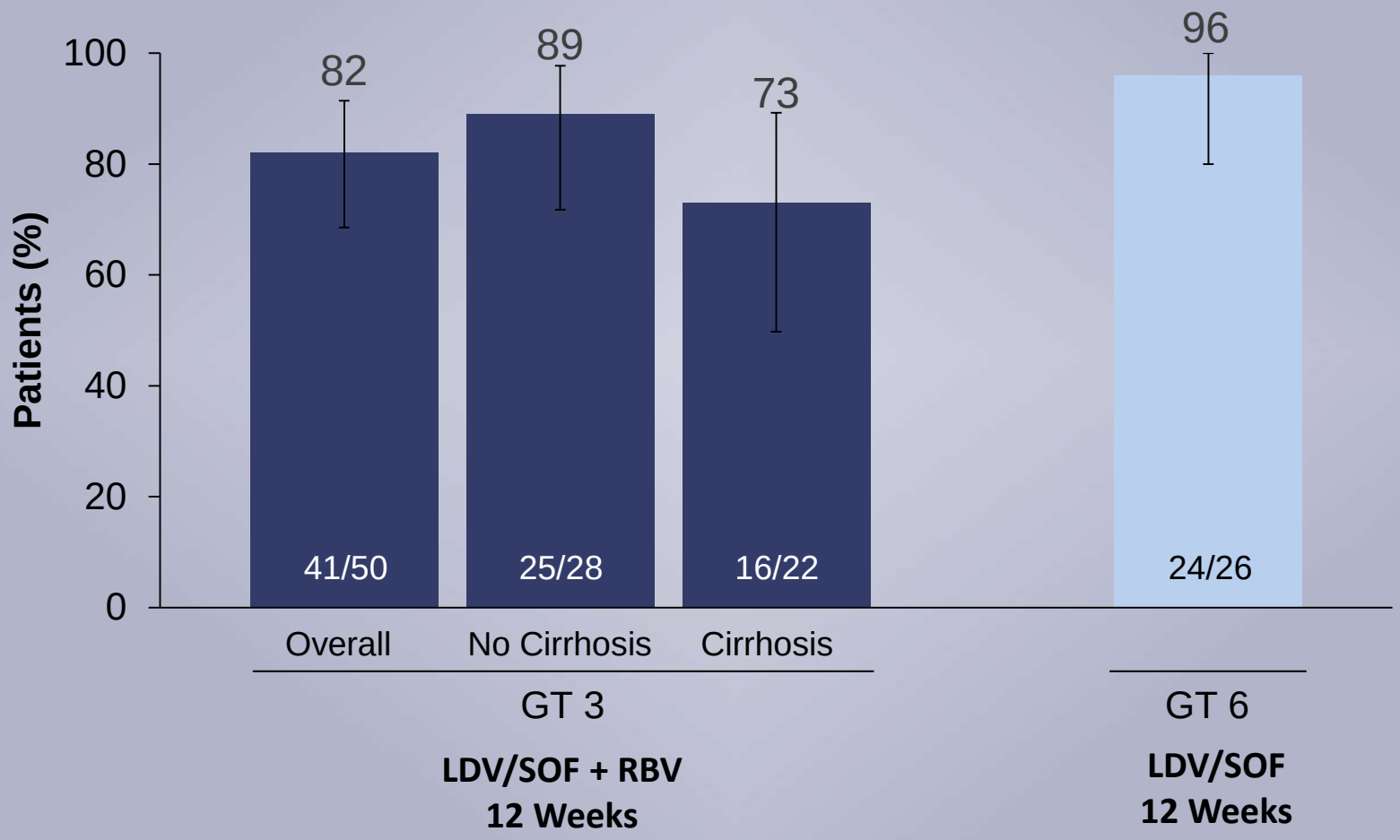
1. Auckland Clinical Studies, Auckland, New Zealand
2. Gilead Science, Inc., Foster City, CA, United States
3. Christchurch Clinical Studies Trust, Christchurch, New Zealand

Texas Liver Institute

UT Health Science Center

Abstract #LB-11

SVR12 in GT3 Treatment Experienced and GT 6 Treatment Naïve/Treatment Experienced Patients



Gane E, et al. Abstract #LB-11, AASLD 2014

Texas Liver Institute

UT Health Science Center

Conclusions

- LDV/SOF + RBV for 12 weeks resulted in SVR12 rates of 73% and 89% in treatment-experienced GT3 patients with and without cirrhosis, respectively
  - Similar SVR12 to previous reports of SOF + RBV (24 weeks) and SOF + PEG/RBV (12 weeks)
- LDV/SOF for 12 weeks without RBV is first reported safe, effective, all-oral regimen for GT6 patients

Gane E, et al. Abstract #LB-11, AASLD 2014

Texas Liver Institute

UT Health Science Center

All Oral Treatment for Genotype 4 Chronic Hepatitis C Infection with Sofosbuvir and Ledipasvir: Interim Results from the NIAID SYNERGY Trial

Rama Kapoor[1]; Anita Kohli[1]; Sreetha Sidharthan[2]; Zayani Sims[2]; Tess L. Petersen[2]; Anu Osinusi[3]; Amy K. Nelson[3]; Rachel Silk[1]; Colleen Kotb[1]; Kate Sugarman[4]; Brian P. Lam[5]; Phillip S. Pang[6]; Mani Subramanian[6]; John G. McHutchison[6]; Henry Masur[2]; Shyam Kottilil[3]; Vinod K.

1. Leidos Biomedical Research, Inc. (formerly SAIC–Frederick, Inc.), Frederick National Laboratory for Cancer Research, Frederick, MD
2. Critical Care Medicine Department, National Institutes of Health Clinical Center, National Institutes of Health, Bethesda, MD
3. Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD
4. Unity Health Care, Inc., Washington, DC
5. Center for Liver Diseases, Inova Fairfax Medical Campus, Falls Church, VA
6. Gilead Sciences Inc., Foster City, CA
7. University of Pittsburgh Medical Center, Pittsburgh, PA

Texas Liver Institute

UT Health Science Center

Abstract #240

Summary

- Patient population
  - GT4 infected patients with any stage of liver fibrosis
  - Treatment naïve or treatment experienced
- Regimen
  - SOF/LDV for 12 weeks
- SVR12: 19 of 20 patients (95%)

Kapoor R, et al. Abstract #240, AASLD 2014

Texas Liver Institute

UT Health Science Center

Retreatment of Patients Who Failed Prior Sofosbuvir-Based Regimens with All Oral Fixed-Dose Combination Ledipasvir/Sofosbuvir Plus Ribavirin for 12 Weeks

David L. Wyles[1]; Paul J. Pockros[2]; Jenny C. Yang[3]; Yanni Zhu[3]; Phillip S. Pang[3]; John G. McHutchison[3]; Steven L. Flamm[4]; Eric Lawitz[5]

1. University of California, San Diego, La Jolla, CA
2. Scripps Translational Science Institute, La Jolla, CA
3. Gilead Sciences, Inc, Foster City, CA
4. Northwestern University, Chicago, IL
5. The Texas Liver Institute, San Antonio, TX

Texas Liver Institute

UT Health Science Center

Abstract #235

Objective and Patient Demographics

- Evaluate whether LDV/SOF + RBV for 12 weeks is effective in GT 1 treatment-experienced patients who have failed prior SOF-based therapy
- 51 patients
  - 16% African American
  - 59% GT 1a
  - 29% cirrhosis
  - Prior HCV treatment
    - SOF + PEG/RBV: 49%
    - SOF ± RBV*: 41%
    - SOF placebo**: 5%

*1 patient received SOF monotherapy. **SOF placebo plus PEG/RBV or GS-0938 plus PEG/RBV
Wyles D, et al. Abstract #235, AASLD 2014

Texas Liver Institute

UT Health Science Center

Results

- 50/51 (98%) of patients achieved SVR12
- 1 patient who failed was a GT 3a patient who relapsed (inadvertently genotyped as GT 1a at baseline)
- No patients had SOF-associated variant, S282T, detected at baseline
  - 2 patients had NS5B treatment-emergent variant L159F at baseline and achieved SVR

Texas Liver Institute

UT Health Science Center

Once Daily Sofosbuvir with GS-5816 for 8 Weeks with or without Ribavirin In Patients with HCV Genotype 3 without Cirrhosis Result in High Rates of SVR12: The ELECTRON2 Study

Edward J. Gane[1]; Robert H. Hyland[2]; Di An[2]; John McNally[2]; Diana M. Brainard[2]; William T. Symonds[2]; John G. McHutchison[2]; Catherine A. Stedman[3]

1. Auckland Clinical Studies, Auckland, New Zealand
2. Gilead Science, Inc, Foster City, CA
3. Christchurch Clinical Studies Trust, Christchurch, New Zealand

Texas Liver Institute

UT Health Science Center

Abstract #79

Background & Aims

- Sofosbuvir (SOF) is an approved nucleotide polymerase inhibitor with activity against HCV GT 1-6
- GS-5816 is an investigational inhibitor of the HCV NS5A protein with picomolar antiviral activity across all HCV genotypes 1-6
- In a Phase 2 study, 12 week treatment with SOF + GS-5816 at a dose of 25 or 100 mg/day with or without RBV was found to be safe and effective
- Evaluate safety and efficacy in treatment naïve non-cirrhotic GT 3 patients when administered for 8 weeks

Gane E, et al. Abstract #79, AASLD 2014

Texas Liver Institute

UT Health Science Center

SVR12: SOF/GS-5816 + RBV for 8 Weeks in GT 3 Treatment-naïve Non-cirrhotics

Texas Liver Institute

UT Health Science Center

Conclusions

- SOF + GS-5816 (25 mg or 100 mg) ± RBV for 8 weeks resulted in high SVR12 rates in treatment naïve non-cirrhotic GT3 patients
- Regimen was well tolerated with no identified safety signal due to SOF or GS-5816
- SOF 400 mg + GS-5816 100 mg have been co-formulated in a fixed-dose combo for Phase 3

Gane E, et al. Abstract #79, AASLD 2014

Texas Liver Institute

UT Health Science Center

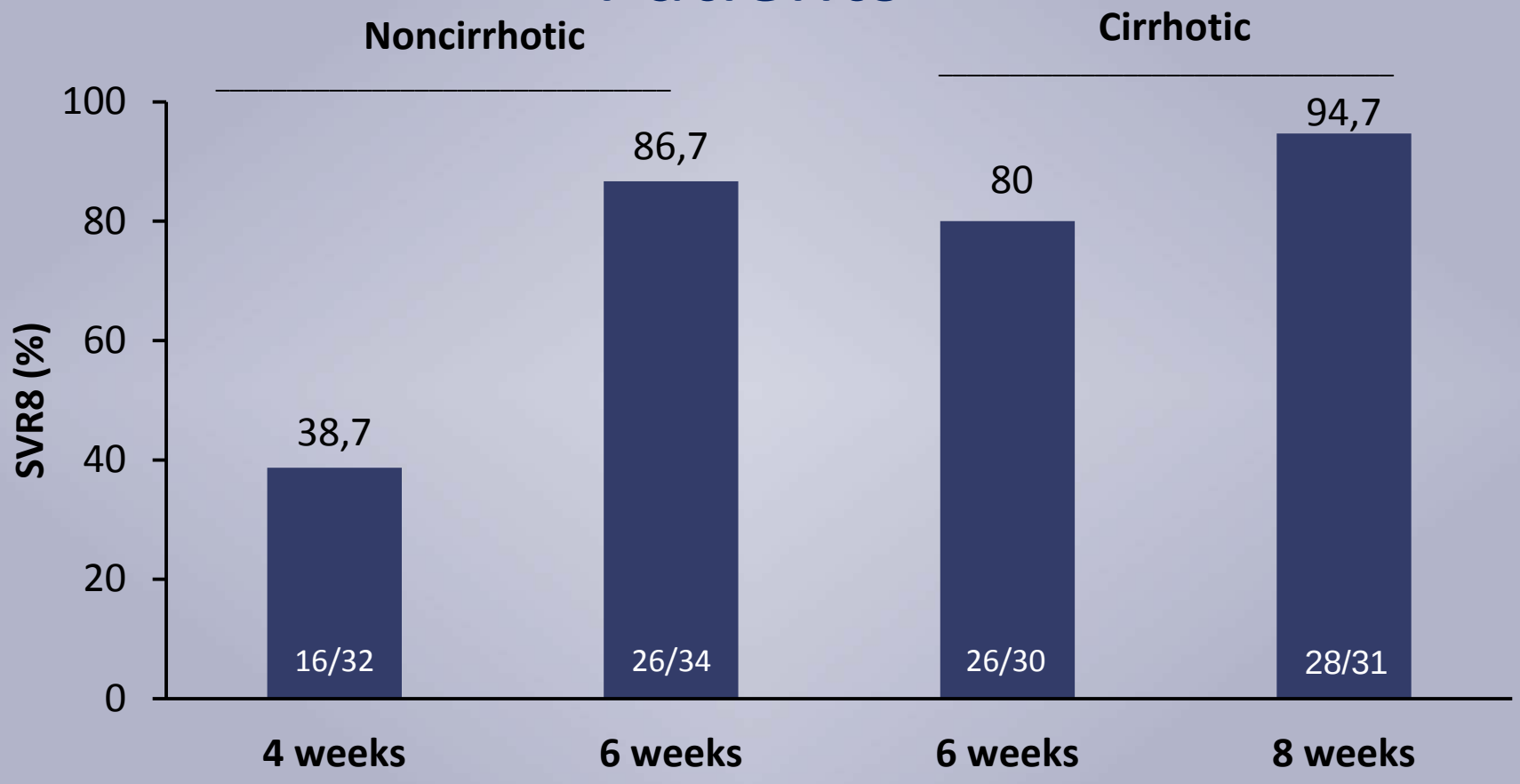
C-SWIFT: Grazoprevir (MK-5172) + Elbasvir (MK-8742) +Sofosbuvir in Treatment-naïve Patients With Hepatitis C Virus Genotype 1 Infection, With and Without Cirrhosis, for Durations of 4, 6, or 8 Weeks (Interim Results)

Eric Lawitz[1]; Fred Poordad[1]; Julio A. Gutierrez[1]; Barbara Evans[2]; Peggy Hwang[2]; Anita How[2]; Hwa-Ping Feng[2]; Michael Robertson[2]; Janice Wahl[2]; Eliav Barr[2]; Barbara Haber[2]

1. The Texas Liver Institute, University of Texas Health Science Center, San Antonio TX, USA
2. Merck & Co.

Abstract #LB-33

SVR8* in GT 1 Treatment-naïve Patients



*SVR8 results available for 98/102 patients; for remaining 4 patients SVR4 results are used. Excludes 2 cirrhotics in 8 week arm who discontinued unrelated to viral failure.

Lawtiz E, et al. Abstract #LB-33, AASLD 2014

Texas Liver Institute

UT Health Science Center

Summary

- Combined regimens of 3 potent antivirals may be able to shorten treatment duration to 6-8 weeks among cirrhotic and noncirrhotic GT1 infected patients
- Factors that may have impacted likelihood of SVR in 4 and 6 week arms
  - GT 1a vs 1b
  - Baseline viral load
  - IL28B status
  - PK of component medicines in the regimen

Lawtiz E, et al. Abstract #LB-33, AASLD 2014

Texas Liver Institute

UT Health Science Center

All-oral 12-week Combination Treatment With Daclatasvir (DCV) and Sofosbuvir (SOF) in Patients Infected with HCV Genotype (GT) 3: ALLY-3 Phase 3 Study

D. R. Nelson[1]; J. N. Cooper[2]; J. P. Lalezari[i,3]; E. Lawitz[4]; P. J. Pockros[5]; N. Gitlin[6]; B. Freih·ch[7]; Z. Younes[8]; W. Harlan[9]; R. H. Ghall[10]; G. I. Oguchi[11]; P. J. Thuluvath[12]; G. Ortiz-Lasanta[13]; M. Rabinovitz[14]; D. Bernstein[15]; M. Bennett[16]; T. Hawkins[17]; N. Ravendhran[8]; A. M. Sheikh[19]; P. Varunok; K. V. Kowdley; D. Hennicken; F. McPhee; K. Rana; E. A. Hughes[22]

1. University of Florida, Gainesville, FL, United States
2. !nova Fairfax Hospital, Falls Church, VA, United States
3. Quest Clinical Research, San Francisco, CA, United States
4. Texas Liver Institute, University of Texas Health Science Center, San Antonio, TX, United States
5. Scripps Clinic, La Jolla, CA, United States
6. Atlanta Gastroenterology Associates, Atlanta, GA, United States
7. Kansas City Research Institute, Kansas City, MO, United States
8. Gastro One, Germantown, TN, United States
9. Asheville Gastroenterology Associates, Asheville, NC, United States
10. Texas Clinical Research Institute, Arlington, TX, United States
11. Midland Florida Clinical Research Center, DeLand, FL, United States
12. Mercy Medical Center, Baltimore, MD, United States
13. Fundacion de Investigacion de Diego, Santurce, Puerto Rico, United States
14. University of Pittsburgh, Pittsburgh, PA, United States
15. Hofstra North Shore-Long Island Jewish School of Medicine, Manhasset, NY, United States
16. Medical Associates Research Group, San Diego, CA, United States
17. Southwest CARE Center, Santa Fe, NM, United States
18. Digestive Disease Associates, Baltimore, MD, United States
19. Gastrointestinal Specialists of Georgia, Marietta, GA, United States
20. Premier Medical Group of Hudson Valley, Poughkeepsie, NY, United States
21. Swedish Medical Center, Seattle, WA, United States
22. Bristol-Myers Squibb Research and Development, Princeton, NJ, United States

Abstract #LB-3

Texas Liver Institute

UT Health Science Center

Background & Aims

- HCV genotype (GT) 3 is common worldwide and remains a significant disease burden
- GT 3 infection is associated with increased risk of fibrosis progression, steatosis, and hepatocellular carcinoma in patients with cirrhosis
- Current therapies for patients with GT 3 infection include
  - US and Europe
    - 24 week sofosbuvir (SOF) + ribavirin (RBV)
    - 12 week SOF + PEG/RBV
  - Europe
    - 24-week daclatasvir (DCV) + SOF ± RBV

Nelson D, et al. Abstract #LB-3, AASLD 2014

Texas Liver Institute

UT Health Science Center

Methods

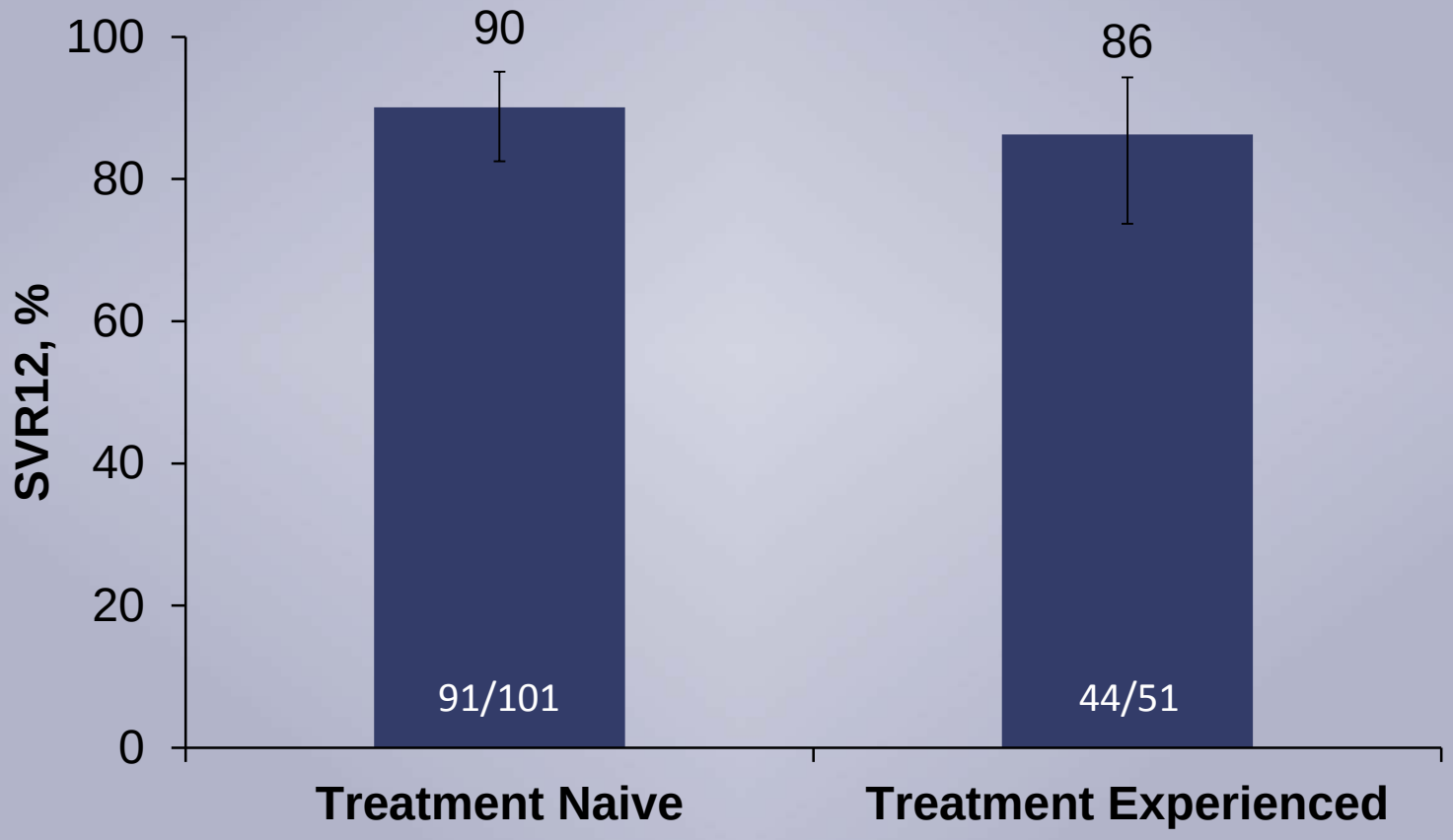
- Two cohorts consisting of GT 3 treatment naive or treatment experienced patients received open-label DCV + SOF once daily for 12 weeks
- 21% of patients were cirrhotic

Nelson D, et al. Abstract #LB-3, AASLD 2014

Texas Liver Institute

UT Health Science Center

SVR12: DCV + SOF for 12 Weeks in GT 3 Patients

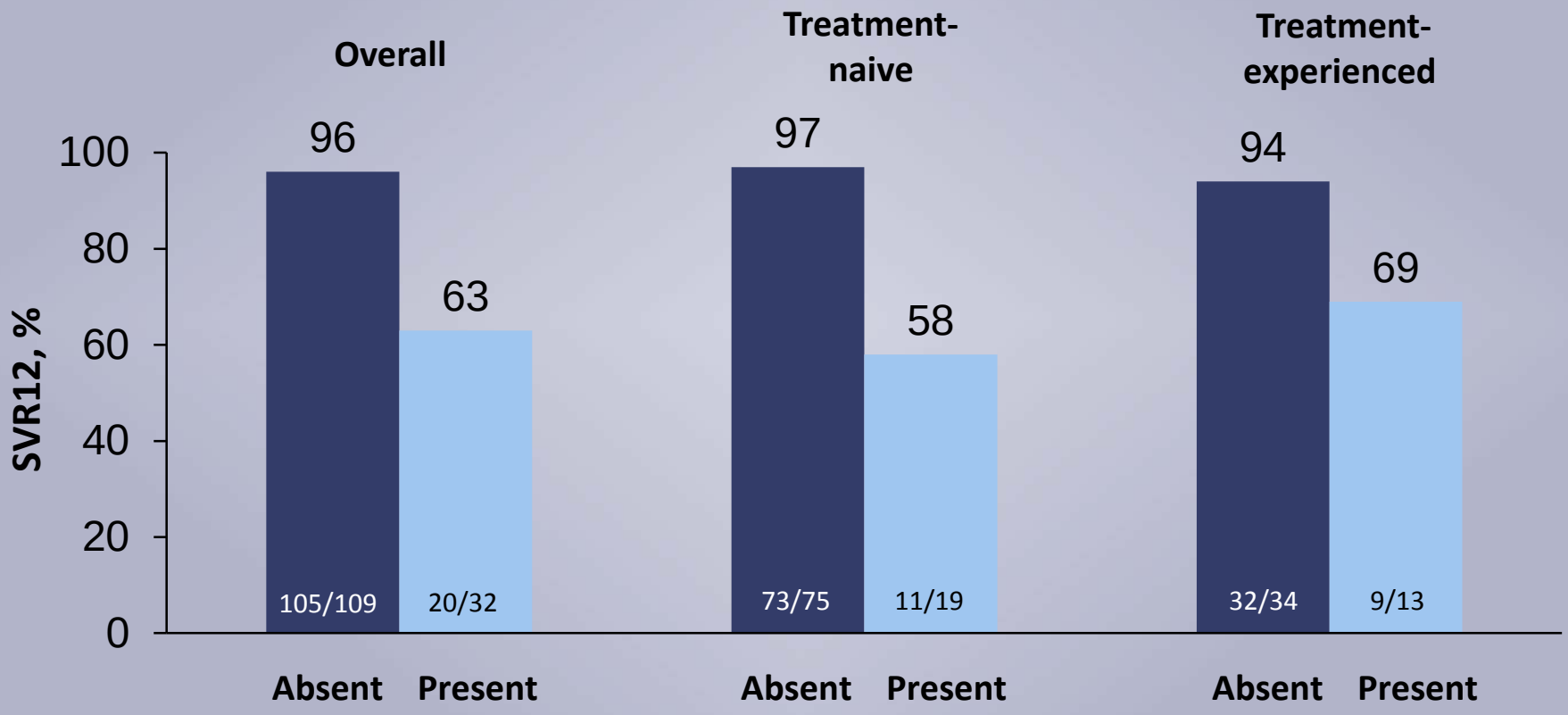


Nelson D, et al. Abstract #LB-3, AASLD 2014

Texas Liver Institute

UT Health Science Center

SVR12: DCV + SOF for 12 Weeks in GT 3 Patients With Cirrhosis



Nelson D, et al. Abstract #LB-3, AASLD 2014

Texas Liver Institute

UT Health Science Center

Conclusion

- DCV + SOF for 12 weeks achieved high SVR rates
  - 90% in treatment naïve
  - 86% in treatment experienced
  - 96% in non-cirrhotics
  - 63% in cirrhotics (further optimization being evaluated)
- DCV + SOF was safe and well tolerated

Nelson D, et al. Abstract #LB-3, AASLD 2014

Texas Liver Institute

UT Health Science Center

Conclusion

- Nucleoside based regimens using Sofosbuvir have high overall SVR rates
- Well tolerated
- Genotype 3 cirrhosis remains difficult population to cure
- Future regimens with nucleosides may emerge

Texas Liver Institute

UT Health Science Center