HEPATITIS WEB STUDY HEPATITIS C ONLINE

# Ledipasvir-Sofosbuvir (*Harvoni*)

Prepared by: David H. Spach, MD and H. Nina Kim, MD MSc
Last Updated: December 15, 2015

Hepatitis web study

LEDIPASVIR-SOFOSBUVIR (*HARVONI*)

# Background and Dosing

# Ledipasvir-Sofosbuvir (*Harvoni*)

- **Approval Status**
  - Initial approval by United States FDA October 10, 2014
  - Expanded indications approved by FDA November 12, 2015

- **Indications and Usage**
  - Indicated for the treatment of chronic HCV genotypes 1, 4, 5, and 6 in adults
  - Indicated for the treatment of chronic HCV in patients co-infected with HIV

- **Class & Mechanism**
  - Ledipasvir: NS5A inhibitor
  - Sofosbuvir: Nucleotide analog NS5B polymerase inhibitor

- **Dosing:** Ledipasvir-Sofosbuvir (fixed dose 90 mg/400 mg)
  One tablet orally once daily with or without food

- **Adverse Effects (AE)**: Fatigue, headache

**Source: *Harvoni* Prescribing Information. Gilead Sciences**

# Ledipasvir-Sofosbuvir (*Harvoni*)
# Indications and Usage

| Genotype Patient Populations | Treatment Duration* |
|---|---|
| **Genotype 1** | |
| Treatment naïve with or without cirrhosis | 12 weeks |
| Treatment experienced** without cirrhosis | 12 weeks |
| Treatment experienced** with cirrhosis | 24 weeks |
| **Genotype 4, 5, or 6** | |
| Treatment naïve with or without cirrhosis | 12 weeks |
| Treatment experienced** with or without cirrhosis | 12 weeks |

*Consider treatment duration of 8 weeks in treatment-naïve patients without cirrhosis who have a pretreatment HCV RNA less than 6 million IU/mL

**Treatment-experienced patients who have failed treatment with a peginterferon alfa plus ribavirin-based regimen, with or without an HCV protease inhibitor

**Source: *Harvoni* Prescribing Information. Gilead Sciences**

# Ledipasvir-Sofosbuvir (*Harvoni*)
# Estimated Cost of Therapy

| Estimated Cost of Ledipasvir-Sofosbuvir Based on Treatment Duration | |
|---|---|
| Duration of Treatment | Estimated Cost* |
| 8 Weeks | $63,000 |
| 12 Weeks | $94,500 |
| 24 Weeks | $189,000 |

*Estimated cost based on Wholesaler Acquisition Cost in United States of $1125 per pill

# Ledipasvir-Sofosbuvir (*Harvoni*)
# Drug-Drug Interactions

- **Not recommended for coadministration with:**
  - P-gp inducers (eg. rifampin, St. John's Wort)
  - Amiodarone

- **Consult Prescribing Information Regarding Interactions with**:
  - Acid reducing agents
  - Antiarrhythmics
  - Anticonvulsants
  - Antimycobacterials
  - HIV antiretrovirals

**Source: *Harvoni* Prescribing Information. Gilead Sciences**

# Ledipasvir-Sofosbuvir (*Harvoni*)
# Adverse Effects

| Adverse Effects with Ledipasvir-Sofosbuvir Reported in ≥5% of Subjects | | | |
|---|---|---|---|
| | Ledipasvir-Sofosbuvir | | |
| | 8 Weeks | 12 Weeks | 24 Weeks |
| | N=215 | N=539 | N=326 |
| Fatigue | 16% | 13% | 18% |
| Headache | 11% | 14% | 17% |
| Nausea | 6% | 7% | 9% |
| Diarrhea | 4% | 3% | 7% |
| Insomnia | 3% | 5% | 6% |

**Source: *Harvoni* Prescribing Information. Gilead Sciences**

CLINICAL TRIALS

# Ledipasvir-Sofosbuvir

# Ledipasvir-Sofosbuvir (LDV-SOF): Summary of Key Studies

- **Treatment Naïve** (Phase 3)
  - **ION-1**: GT-1 / LDV-SOF +/- RBV x 12 or 24 weeks
  - **ION-3**: GT-1 / LDV-SOF +/- RBV x 8 weeks vs LDV/SOF x 12 weeks
- **Treatment Naïve** (Phase 2)
  - **NIAID SYNERGY (GT-1)**: GT-1 LDV-SOF +/- [GS-9669 or GS-9451]
- **Treatment Experienced** (Phase 3)
  - **ION-2**: GT-1 / LDV-SOF +/- RBV x 12 or 24 weeks
- **Treatment Experienced with Compensated Cirrhosis** (Phase 2)
  - **SIRIUS**: GT-1 / LDV-SOF + RBV x 12 weeks or LSV-SOF x 24 weeks

# Ledipasvir-Sofosbuvir (LDV-SOF): Summary of Key Studies

- **Treatment Naïve or Treatment Experienced** (Phase 2)
  - **LONESTAR**: GT-1 / LDV-SOF +/- RBV x 8 or 12 weeks
  - **ELECTRON** (Arms 12-17 & 22): LDV-SOF +/- RBV x 6 or 12 weeks
  - **ELECTRON-2**: experienced GT-1 & naïve GT-3/ LDV-SOF +/- RBV x 12 weeks
  - **New Zealand**: GT 3,6 / LDV-SOF +/- RBV x 12 weeks
  - **NIAID SYNERGY (GT-4)**: GT 4 / LDV/SOF x 12 weeks
- **Prior Sofosbuvir Failure** (Phase 2)
  - **NIAID**: GT-1 / LDV-SOF +/- RBV x 12 weeks
  - **PRIOR Failure in Sofosbuvir Trials**: GT-1 / LDV-SOF +/- RBV x 12 weeks

# Ledipasvir-Sofosbuvir (LDV-SOF): Summary of Key Studies

- **HIV Coinfection: Treatment Naïve (Phase 2)**
  - **NIAID ERADICATE**: GT 1 / LDV-SOF x 12 weeks +/- HIV antiretrovirals
- **HIV Coinfection: Treatment Naïve or Treatment Experienced**
  - **ION-4**: GT 1 or 4 / LDV-SOF x 12 weeks +/- HIV antiretrovirals
- **Advanced Liver Disease: Pre and Post Transplant** (Phase 2)
  - **SOLAR-1:** GT 1,4 / LDV-SOF + RBV x 12 or 24 wks

# Ledipasvir-Sofosbuvir in Treatment-Naïve Patients

Hepatitis web study

Treatment Naïve

# Ledipasvir-Sofosbuvir +/- Ribavirin in HCV Genotype 1

# ION-1

Afdhal N, et al. N Engl J Med. 2014;370:1889-98.

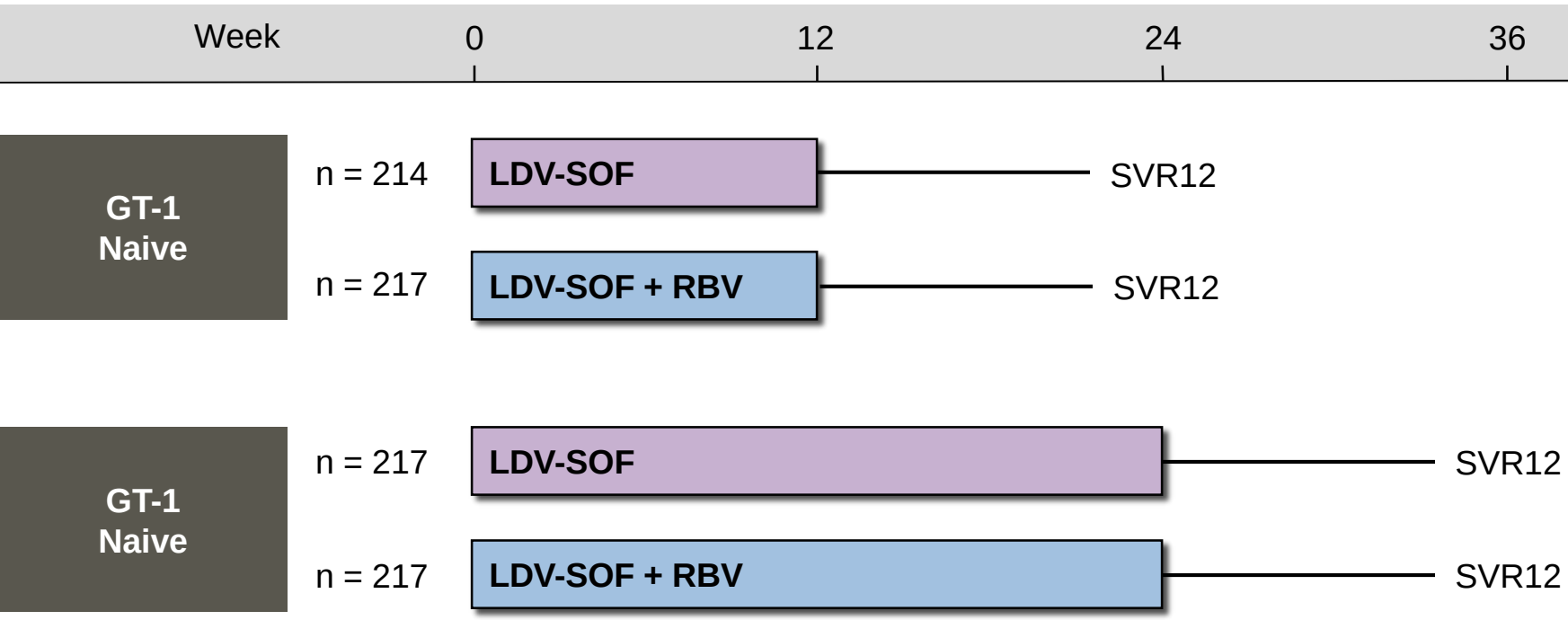
# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Naïve HCV GT 1
## ION-1 Study: Features

**ION-1 Trial**

- **Design**: Open-label, randomized, phase 3 trial using fixed-dose combination of ledipasvir-sofosbuvir +/- ribavirin for 12 or 24 weeks in treatment-naïve patients with GT1 HCV
- **Setting**: 99 sites in United States and Europe
- **Entry Criteria**
  - Chronic HCV Genotype 1 (n=865)
  - 18 years or older
  - No prior HCV treatment
  - Patients with compensated cirrhosis accepted (up to 20% of patients)
- **Primary End-Point**: SVR12

**Source: Afdhal N, et al. N Engl J Med. 2014;370:1889-98.**

# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Naïve HCV GT 1
## ION-1 Study: Study Design




**Abbreviations**: LDV-SOF= ledipasvir-sofosbuvir; RBV = ribavirin

**Drug Dosing**
Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily
Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

**Source: Afdhal N, et al. N Engl J Med. 2014;370:1889-98.**

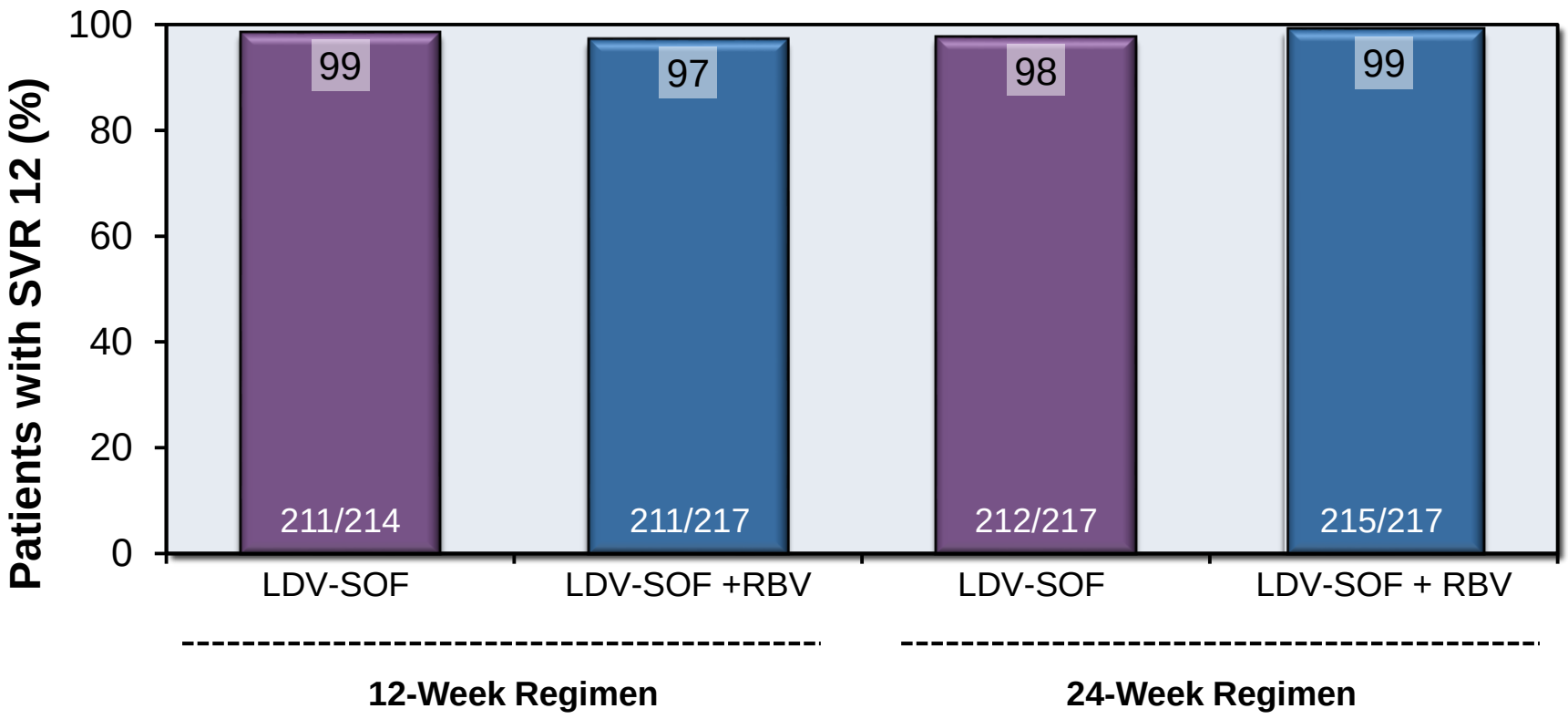
# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Naïve HCV GT 1
## ION-1 Study: Baseline Characteristics

| Baseline Characteristic | 12-Week Treatment | | 24-Week Treatment | |
|---|---|---|---|---|
| | LDV-SOF n=214 | LDV-SOF + RBV n=217 | LDV-SOF n=217 | LDV-SOF + RBV n=217 |
| Mean age, y (range) | 52 (18–75) | 52 (18–78) | 53 (22–80) | 53 (24–77) |
| BMI, kg/m$^2$ mean (range) | 27 (18–41) | 27 (18–42) | 27 (18–48) | 26 (18–48) |
| Male sex, n (%) | 127 (59) | 128 (59) | 139 (64) | 119 (55) |
| Race | | | | |
| White, n (%) | 187 (87) | 188 (87) | 177 (82) | 183 (84) |
| Black, n (%) | 24 (11) | 26 (12) | 32 (15) | 26 (12) |
| Hispanic ethnic group, n (%) | 26 (12) | 20 (9) | 29 (13) | 26 (12) |
| HCV Genotype | | | | |
| 1a, n (%) | 144 (67) | 148 (68) | 146 (67) | 143 (66) |
| 1b, n (%) | 66 (31) | 68 (31) | 68 (31) | 71 (33) |
| IL28B non CC, n (%) | 175 (76) | 141 (65) | 165 (76) | 144 (66) |
| Cirrhosis, n (%) | 34 (16) | 33 (15) | 33 (15) | 36 (17) |
| HCV RNA, $\log_{10}$ IU/ml (mean) | 6.4 | 6.4 | 6.3 | 6.3 |

**Source: Afdhal N, et al. N Engl J Med. 2014;370:1889-98.**

# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Naïve HCV GT 1
# ION-1 Study: Results

## ION-1: SVR 12* by Treatment Duration and Regimen

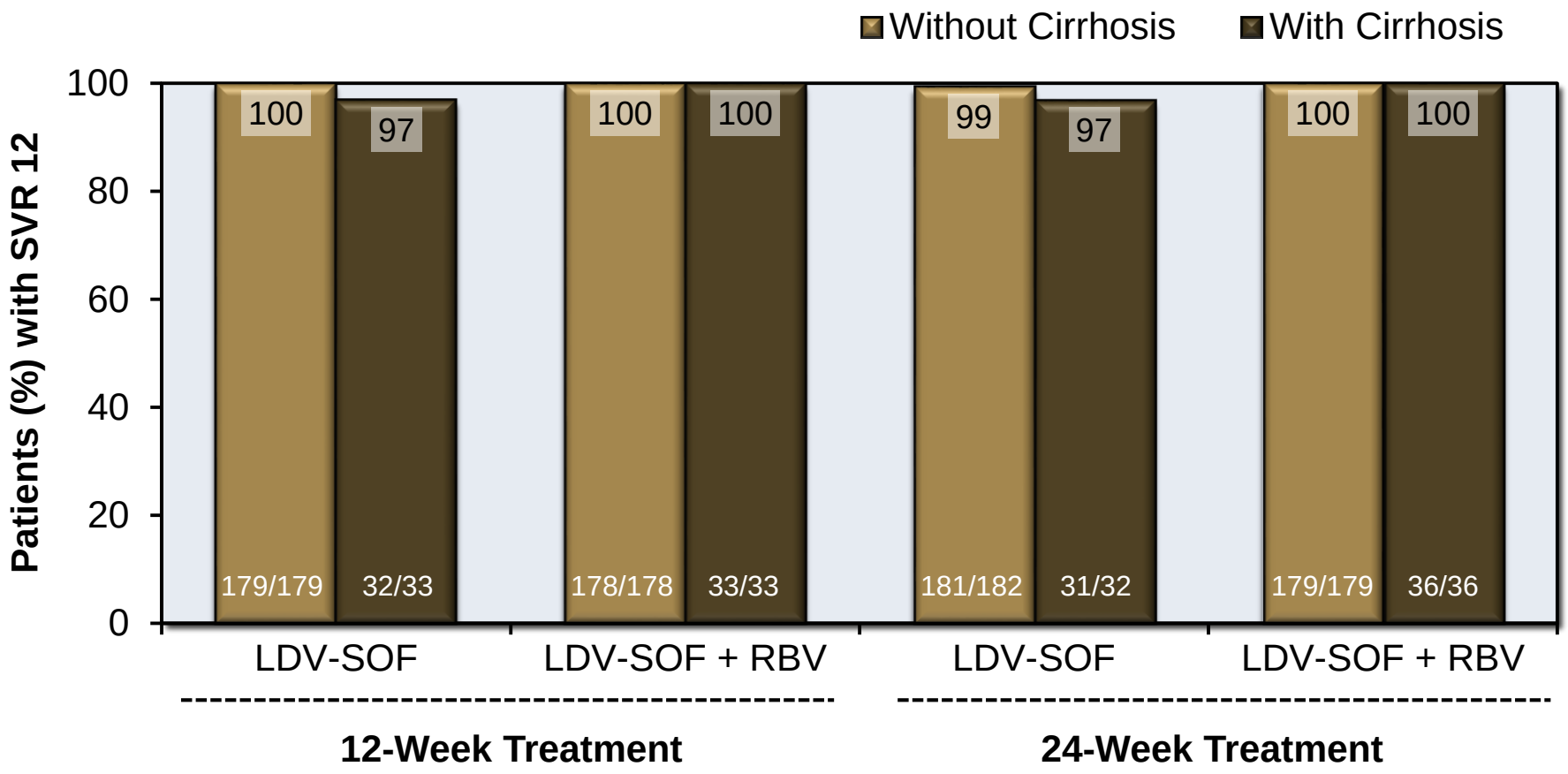



Abbreviations: LDV-SOF= ledipasvir-sofosbuvir; RBV = ribavirin
*Primary end-point by intention-to-treat analysis

**Source: Afdhal N, et al. N Engl J Med. 2014;370:1889-98.**

# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Naïve HCV GT 1
# ION-1 Study: Results

## ION-1: SVR12 by Treatment Regimen and Liver Disease



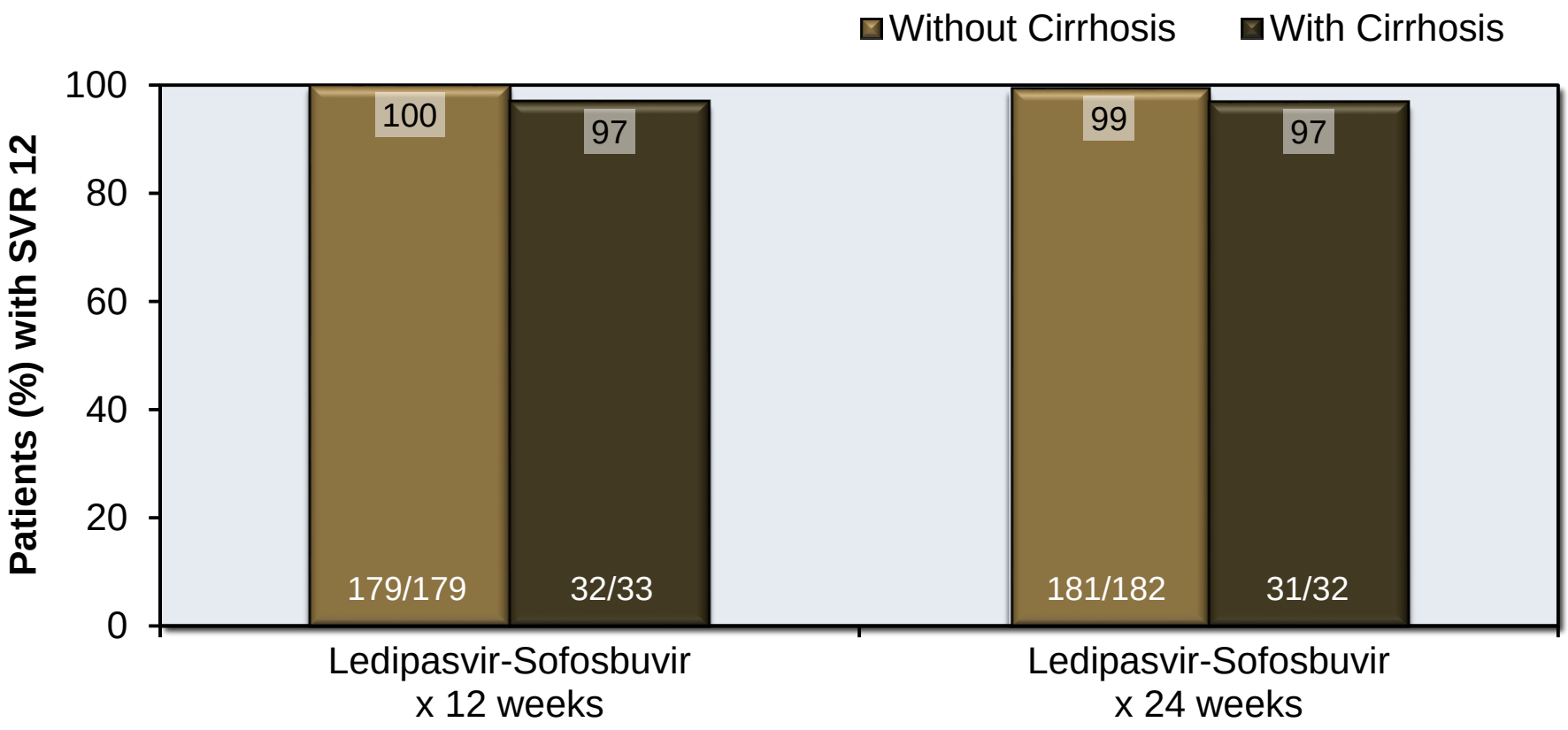

Note: subgroup results do not include patients who withdrew consent or were lost to follow-up

**Source: Afdhal N, et al. N Engl J Med. 2014;370:1889-98.**

# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Naïve HCV GT 1

## ION-1 Study: Results for Ledipasvir-Sofosbuvir

### ION-1: SVR12 by Treatment Duration and Liver Disease




**Source: Afdhal N, et al. N Engl J Med. 2014;370:1889-98.**

Hepatitis web study

# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Naïve HCV GT 1
## ION-1 Study: Resistance Data

- **NS5A resistant variants**
  - Baseline resistance in 140 (16%) of 861 patients tested
  - SVR12 in 135 (96%) of 140 patients with NS5A resistance
  - 2 of the 3 patients with virologic failure had baseline NS5A resistance

**Source: Afdhal N, et al. N Engl J Med. 2014;370:1889-98.**

# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Naïve HCV GT 1

## ION-1 Study: Conclusions

**Conclusions**: “Once-daily ledipasvir–sofosbuvir with or without ribavirin for 12 or 24 weeks was highly effective in previously untreated patients with HCV genotype 1 infection.”

**Source: Afdhal N, et al. N Engl J Med. 2014;370:1889-98.**

Treatment Naïve

# Ledipasvir-Sofosbuvir for 8 or 12 weeks in HCV GT1

# ION-3

Kowdley K, et al. N Engl J Med. 2014;370:1879-88.

# Ledipasvir-Sofosbuvir for 8 or 12 Weeks in Treatment-Naïve HCV GT 1

## ION-3 Study: Features

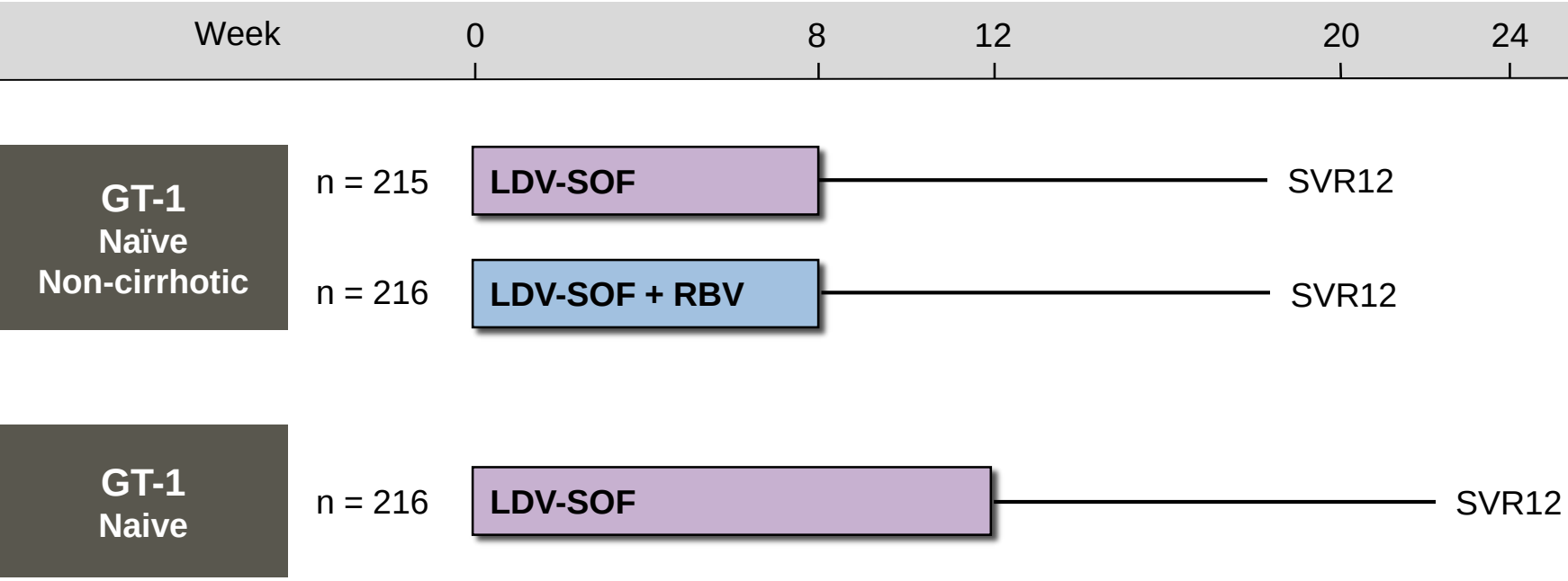
### ION-3 Trial

- **Design**: Open-label, randomized, phase 3, comparing ledipasvir-sofosbuvir with or without ribavirin for 8 weeks and ledipasvir-sofosbuvir for 12 weeks in treatment-naïve, non-cirrhotic patients with GT1 HCV
- **Setting**: 58 sites in United States
- **Entry Criteria**
  - Chronic HCV Genotype 1 (n=647)
  - 18 years or older
  - No prior HCV treatment
  - Patients with cirrhosis were excluded
  - HCV RNA ≥ 10,000 IU/ml
  - No limits on BMI
- **Primary End-Point**: SVR12

**Source: Kowdley, K, et al. N Engl J Med. 2014;370:1879-88.**

# Ledipasvir-Sofosbuvir for 8 or 12 Weeks in Treatment-Naïve HCV GT 1

## ION-3 Study: Study Design




**Abbreviations**: LDV= ledipasvir; SOF = sofosbuvir; RBV = ribavirin

**Drug Dosing**

Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily

Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

**Source: Kowdley, K, et al. N Engl J Med. 2014;370:1879-88.**

# Ledipasvir-Sofosbuvir for 8 or 12 Weeks in Treatment-Naïve HCV GT 1

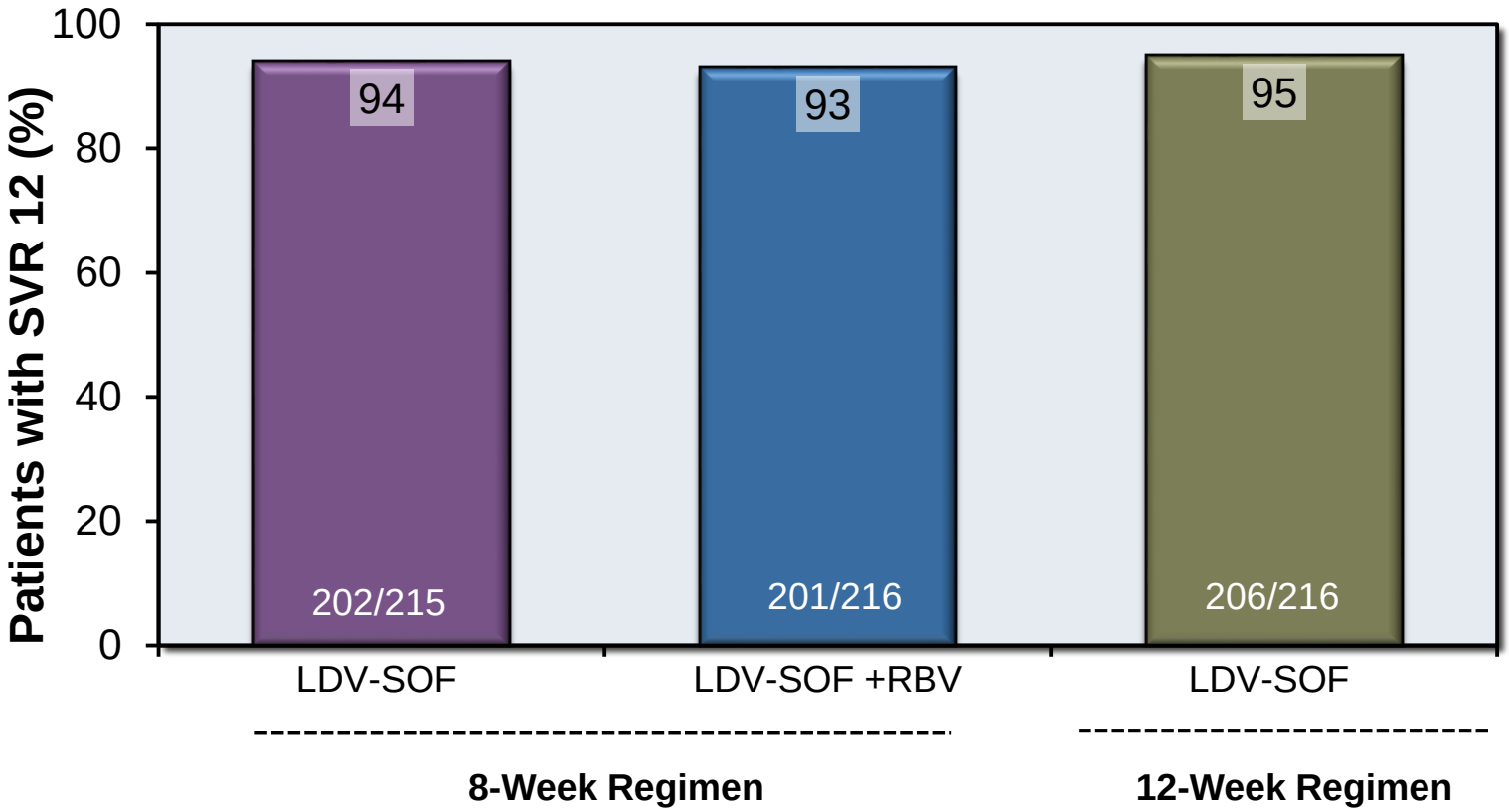
## ION-3 Study: Baseline Characteristics

| Baseline Characteristics | 8 Weeks | | 12 Week-Treatment |
|---|---|---|---|
| | LDV-SOF n=215 | LDV-SOF + RBV n=216 | LDV-SOF n=216 |
| Mean age, y (range) | 53 (22–75) | 51 (21–71) | 53 (20–71) |
| BMI, kg/m$^2$ mean (range) | 28 (18–43) | 28 (18–56) | 28 (19–45) |
| Male sex, n (%) | 130 (60) | 117 (54) | 128 (59) |
| Race | | | |
| White, n (%) | 164 (76) | 176 (81) | 177 (82) |
| Black, n (%) | 45 (21) | 36 (17) | 42 (19) |
| Other, n (%) | 6 (3) | 4 (2) | 7 (3) |
| HCV Genotype | | | |
| 1a, n (%) | 171 (80) | 172(68) | 172 (80) |
| 1b, n (%) | 43 (20) | 44 (20) | 44 (20) |
| IL28B non CC, n (%) | 159 (74) | 156 (72) | 160 (74) |
| F3 fibrosis, n (%) | 29 (13) | 28 (13) | 29 (13) |
| HCV RNA, $\log_{10}$ IU/ml, mean | 6.5 | 6.4 | 6.4 |

**Source: Kowdley, K, et al. N Engl J Med. 2014;370:1879-88.**

# Ledipasvir-Sofosbuvir for 8 or 12 Weeks in Treatment-Naïve HCV GT 1
## ION-3 Study: Results

### ION-3: SVR 12* by Treatment Duration and Regimen




Abbreviations: LDV-SOF= ledipasvir-sofosbuvir; RBV = ribavirin
*Primary end-point by intention-to-treat analysis

**Source: Kowdley, K, et al. N Engl J Med. 2014;370:1879-88.**

# Ledipasvir-Sofosbuvir for 8 or 12 Weeks in Treatment-Naïve HCV GT 1

## ION-3 Study: Results

| Response to Ledipasvir-Sofosbuvir Based on 8 or 12 Weeks of Therapy | | |
|---|---|---|
| | 8 Weeks | 12 Weeks |
| | N=215 | N=216 |
| Number of Responders at End of Treatment | 100% (215/215) | 100% (216/216) |
| SVR | 94% (202/215) | 96% (202/216) |
| Relapse | 5% (11/215) | 1% (3/216) |
| Relapse According to Baseline HCV RNA | | |
| HCV RNA ≤6 million IU/mL | 2% (2/123) | 2% (2/131) |
| HCV RNA ≥6 million IU/mL | 10% (9/92) | 1% (1/85) |

**Source: *Harvoni* Prescribing Information. Gilead Sciences**

# Ledipasvir-Sofosbuvir for 8 or 12 Weeks in Treatment-Naïve HCV GT 1
## ION-3 Study: Resistance Data

- **NS5B S282T variant (reduces susceptibility to sofosbuvir)**
  - Not observed in any patients at baseline or after treatment by deep sequencing

- **NS5A resistant variants**
  - Baseline resistance in 116 (18%) of 647 patients
  - SVR12 in 104 (90%) of 116 patients with NS5A resistance
  - Of the 23 patients who had viral relapse, 15 (65%) had NS5A-resistant variants at time of relapse

**Source: Kowdley, K, et al. N Engl J Med. 2014;370:1879-88.**

# Ledipasvir-Sofosbuvir for 8 or 12 Weeks in Treatment-Naïve HCV GT 1
## ION-3 Study: Conclusions

**Conclusions**: “Ledipasvir-sofosbuvir for 8 weeks was associated with a high rate of sustained virologic response among previously untreated patients with HCV genotype 1 infection without cirrhosis. No additional benefit was associated with the inclusion of ribavirin in the regimen or with extension of the duration of treatment to 12 weeks.”

**Source: Kowdley, K, et al. N Engl J Med. 2014;370:1879-88.**

Title changed on results slide

Treatment Naïve (unfavorable baseline treatment characteristics)

# Ledipasvir-Sofosbuvir +/- 3rd DAA in HCV Genotype 1

# NIAID SYNERGY: Genotype 1

Kohli A, et al. Lancet. 2015:385:1107-13.

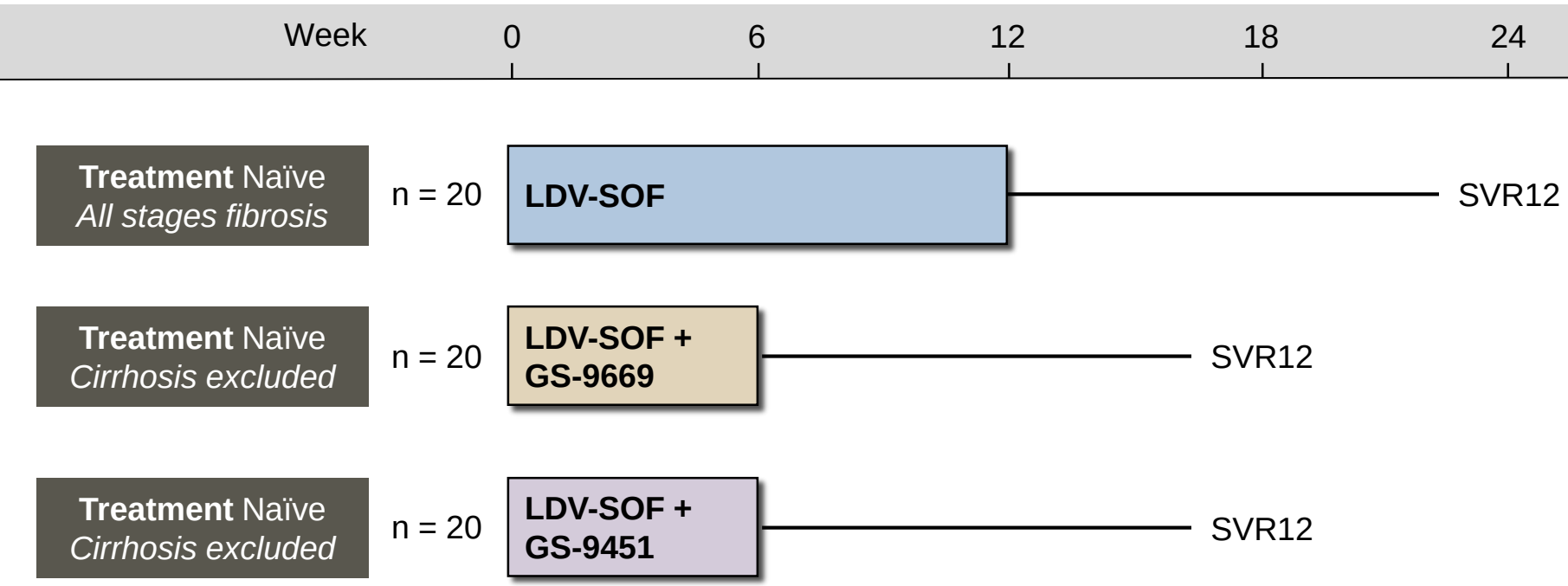
# Ledipasvir-Sofosbuvir +/- [GS-9669 or GS-9451] in Naïve GT1
## NIAID SYNERGY GT-1 Trial: Features

**NIAID SYNERGY Trial**

- **Design**: Open-label, phase 2a, using fixed dose ledipasvir-sofosbuvir alone or in combination with either GS-9669 (non-nucleoside NS5B inhibitor) or GS-9451 (NS3/4A protease inhibitor) in treatment-naïve GT 1
- **Setting**: single site, United States
- **Entry Criteria**
  - 18 years of age or older
  - Chronic HCV Genotype 1
  - Treatment naive
  - HCV RNA ≥2,000 IU/mL
  - Patients in 6 week group excluded if cirrhotic
- **Primary End-Point**: SVR12

**Source: Kohli A, et al. Lancet. 2015:385:1107-13.**

# Ledipasvir-Sofosbuvir +/- [GS-9669 or GS-9451] in Naïve GT1 NIAID SYNERGY GT-1 Trial: Features




**Abbreviations**: LDV-SOF= ledipasvir-sofosbuvir

**Drug Dosing**

Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily

GS-9669: 500 mg once daily

GS-9451: 80 mg once daily

**Source: Kohli A, et al. Lancet. 2015:385:1107-13.**

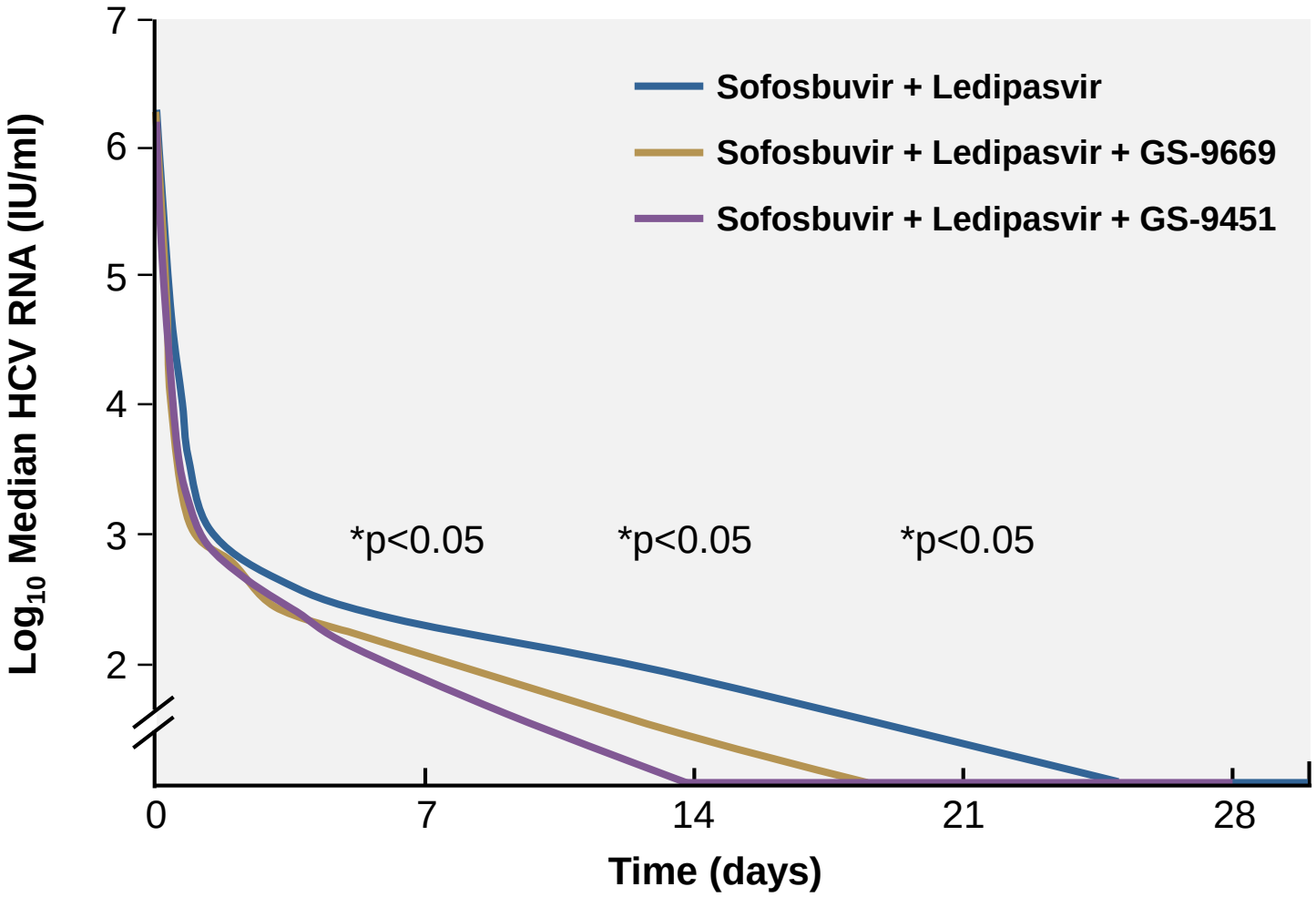
# Ledipasvir-Sofosbuvir +/- [GS-9669 or GS-9451] in Naïve GT1 NIAID SYNERGY GT-1 Trial: Participants

| Baseline Characteristic | LDV-SOF x 12 weeks (n=20) | LDV-SOF + GS-9669 x 6 weeks (n=20) | LDV-SOF + GS-9451 x 6 weeks (n=20) |
|---|---|---|---|
| Age, mean | 57 | 54 | 54 |
| Male, % | 70 | 65 | 80 |
| Black, %<br>White, % | 80<br>20 | 95<br>5 | 90<br>10 |
| HCV genotype, %<br>1A<br>1B | <br>55<br>45 | <br>70<br>30 | <br>85<br>15 |
| HCV RNA >800,000 IU/ml, % | 75 | 65 | 70 |
| IL28B CT/TT, % | 75 | 90 | 75 |
| Advanced fibrosis, %<br>Knodell score 3<br>Knodell score 4 | <br>25<br>15 | <br>25<br>0 | <br>25<br>0 |

Source: Kohli A, et al. Lancet. 2015;385:1107-13.

web study

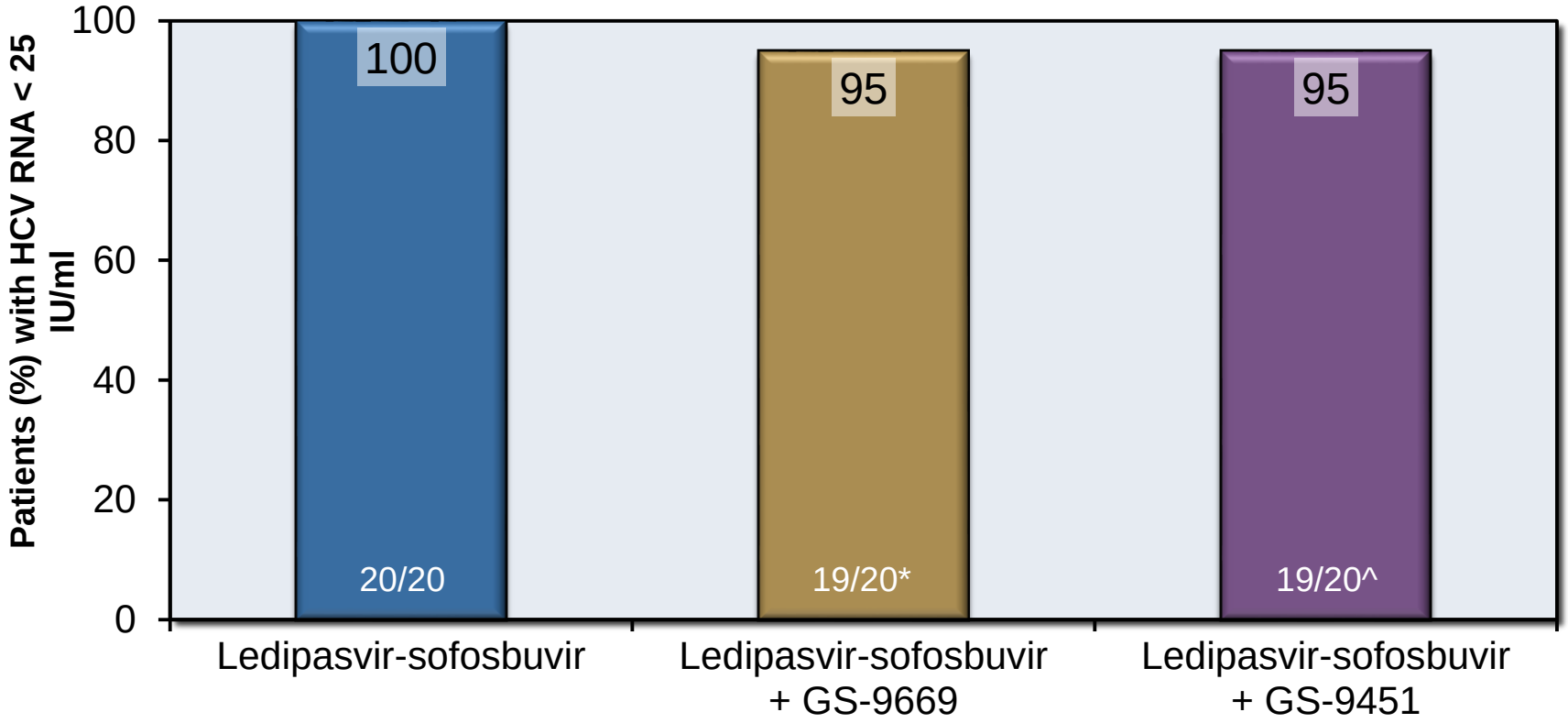
# Ledipasvir-Sofosbuvir +/- [GS-9669 or GS-9451] in Naïve GT1
## NIAID SYNERGY GT-1 Trial: Viral Kinetics




Source: Kohli A, et al. Lancet. 2015:385:1107-13.

# Ledipasvir-Sofosbuvir +/- [GS-9669 or GS-9451] in Naïve GT1 NIAID SYNERGY GT-1 Trial: Results

## NIH SYNERGY: SVR 12 by Treatment Regimen




*1 patient relapsed 2 weeks after completion of treatment

^1 patient lost to follow-up after reaching SVR at 4 weeks

**Source: Kohli A, et al. Lancet. 2015:385:1107-13.**

# Ledipasvir-Sofosbuvir +/- [GS-9669 or GS-9451] in Naïve GT1
## NIAID SYNERGY GT-1 Trial: Interpretation

**Interpretation**: “In this small proof-of-concept study, two different three-drug regimens that were given for 6 weeks resulted in high cure rates for HCV infection with excellent tolerability. Addition of a third potent direct-acting antiviral drug can reduce the duration of treatment required to achieve sustained viral response in patients with chronic HCV genotype 1 infection without cirrhosis.”

**Source: Kohli A, et al. Lancet. 2015:385:1107-13.**

# Ledipasvir-Sofosbuvir in Treatment-Experienced Patients

Hepatitis web study

Treatment Experienced

# Ledipasvir-Sofosbuvir +/- Ribavirin in HCV Genotype 1

# ION-2

Afdhal N, et al. N Engl J Med. 2014;370:1483-93.

# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Experienced HCV GT 1

## ION-2 Study: Features

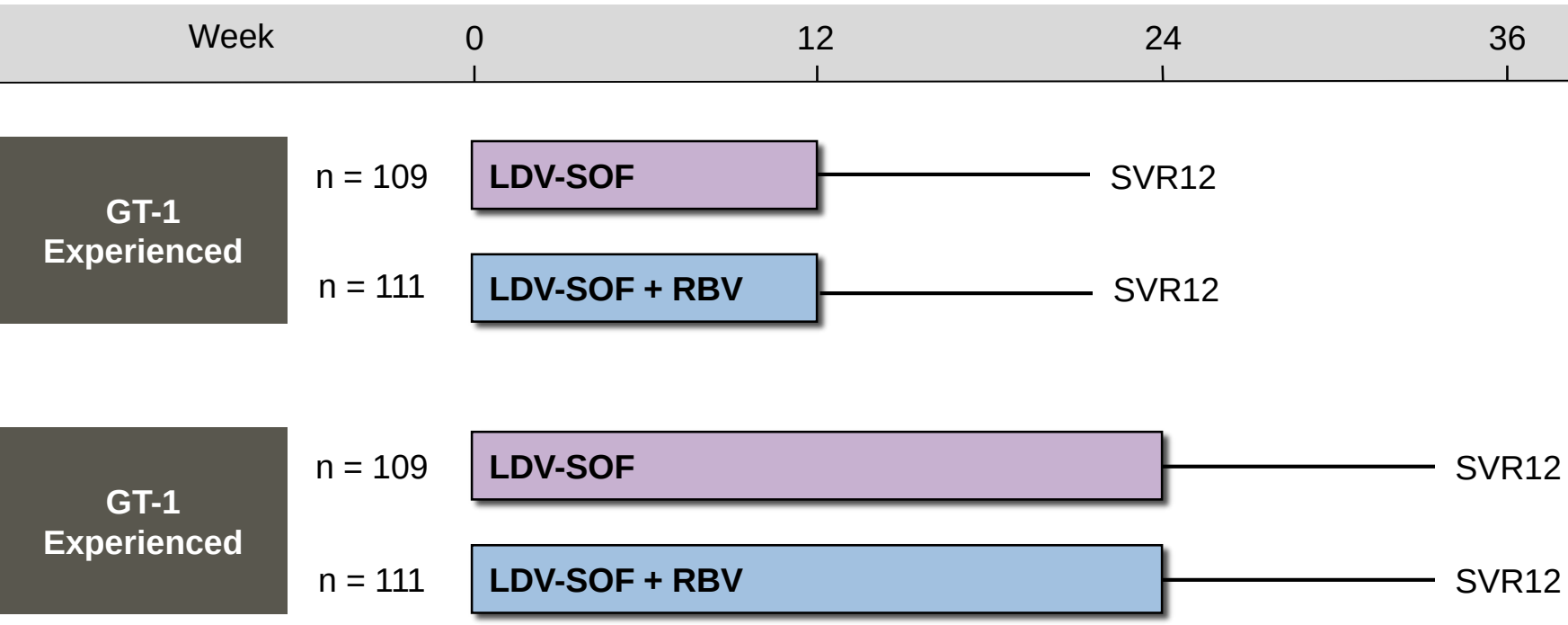
### ION-2 Trial

- **Design**: Open-label, randomized, phase 3, using fixed-dose combination of ledipasvir-sofosbuvir with or without ribavirin for 12 or 24 weeks in treatment-experienced patients with GT1 HCV
- **Setting**: 64 sites in United States
- **Entry Criteria**
  - Chronic HCV Genotype 1 (n=440)
  - 18 years or older
  - Treatment experienced
  - Did not achieved SVR with prior dual therapy (peginterferon + ribavirin), or triple therapy (NS3/4A protease inhibitor plus peginterferon + ribavirin)
  - Patients with cirrhosis accepted (up to 20% of patients)
- **Primary End-Point**: SVR12

**Source: Afdhal N, et al. N Engl J Med. 2014;370:1483-93.**

# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Experienced HCV GT 1

## ION-2 Study: Study Design




**Abbreviations**: LDV= ledipasvir; SOF = sofosbuvir; RBV = ribavirin

**Drug Dosing**

Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily

Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

**Source: Afdhal N, et al. N Engl J Med. 2014;370:1483-93.**

# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Experienced HCV GT 1

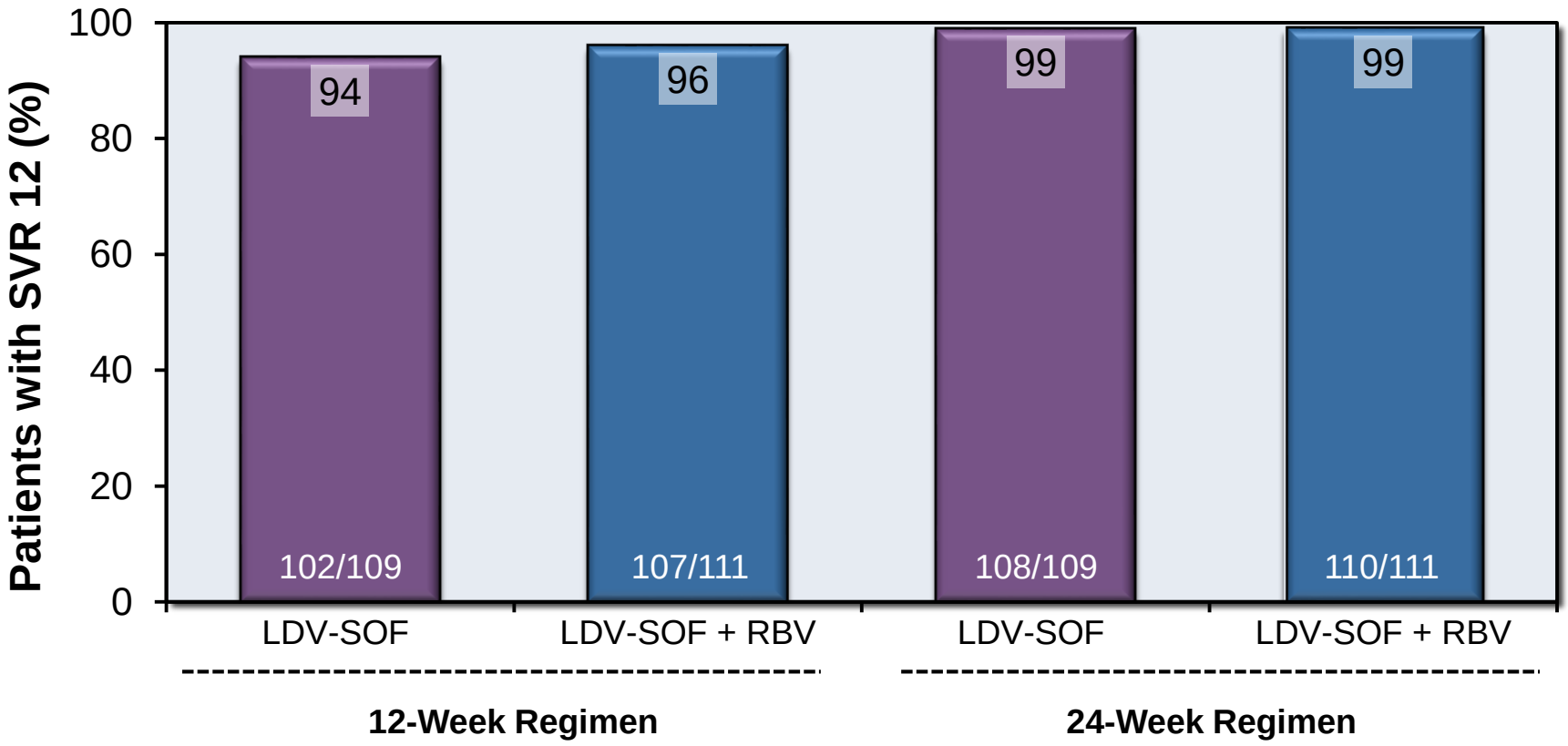
## ION-2 Study: Baseline Characteristics

| Baseline Characteristic | 12-Week Treatment | | 24-Week Treatment | |
|---|---|---|---|---|
| | LDV-SOF n=109 | LDV-SOF + RBV n=111 | LDV-SOF n=109 | LDV-SOF + RBV n=111 |
| Mean age, y (range) | 56 (24–67) | 57 (27–75) | 56 (25–68) | 55 (28–70) |
| BMI, kg/m$^2$ mean (range) | 29 (19–47) | 28 (19–45) | 28 (19–41) | 28 (19–50) |
| Male sex, n (%) | 74 (68) | 71 (64) | 74 (68) | 68 (61) |
| Race | | | | |
| White, n (%) | 84 (77) | 94 (85) | 91 (83) | 89 (80) |
| Black, n (%) | 24 (22) | 16 (14) | 17 (16) | 20 (18) |
| HCV Genotype | | | | |
| 1a, n (%) | 86 (79) | 88 (79) | 85 (78) | 88 (79) |
| 1b, n (%) | 23 (21) | 23 (21) | 24 (22) | 23 (21) |
| IL28B non CC, n (%) | 99 (91) | 100 (90) | 93 (85) | 93 (84) |
| Cirrhosis, n (%) | 22 (20) | 22 (20) | 22 (20) | 22 (20) |
| Prior nonresponse | 49 (45) | 46 (41) | 49 (45) | 51 (46) |
| HCV RNA, $\log_{10}$ IU/ml (mean) | 6.5 | 6.4 | 6.4 | 6.5 |

**Source: Afdhal N, et al. N Engl J Med. 2014;370:1483-93.**

# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-experienced HCV GT 1
## ION-2 Study: Results

### ION-2: SVR 12* by Treatment Duration and Regimen

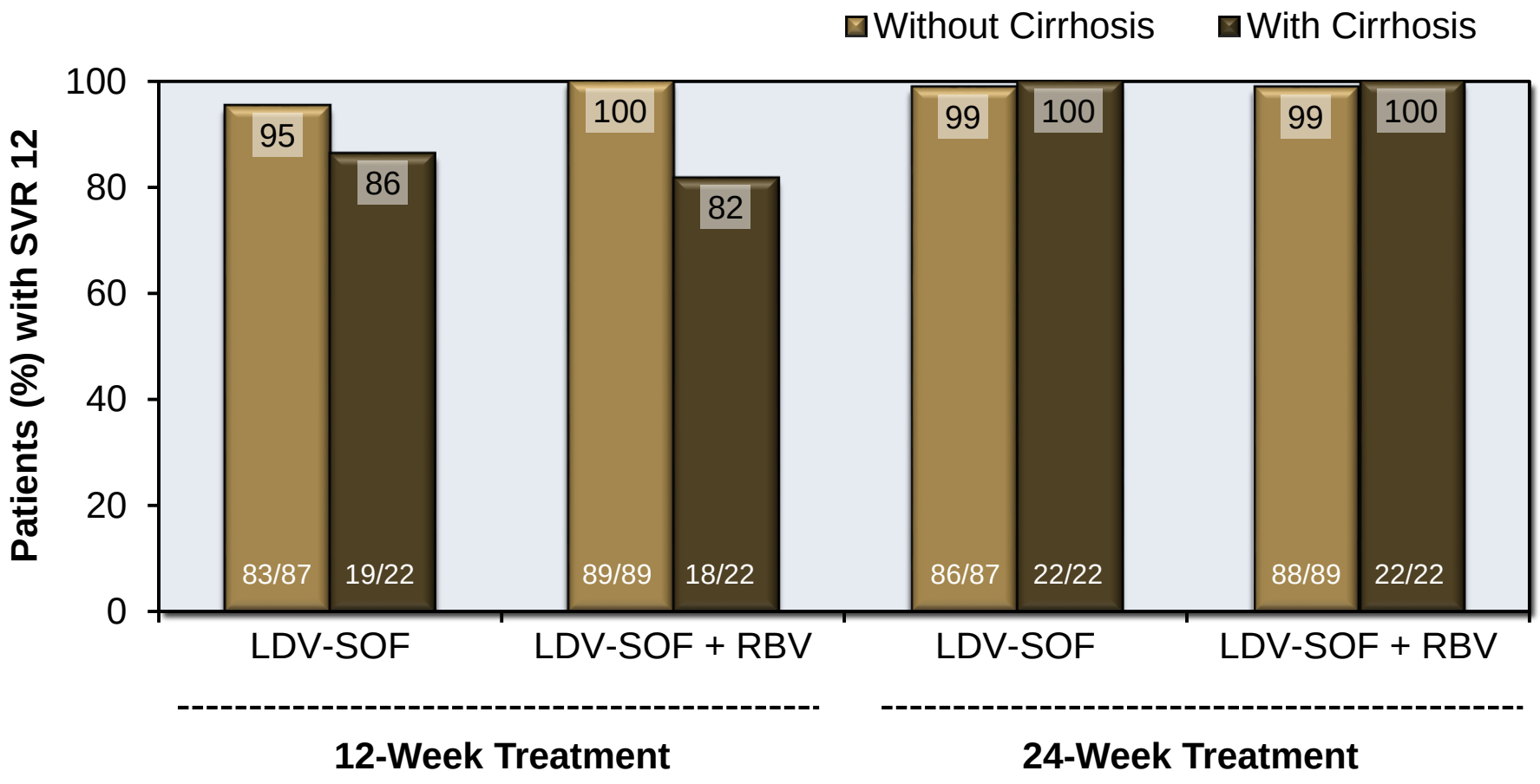



Abbreviations: LDV-SOF= ledipasvir-sofosbuvir; RBV = ribavirin
*Primary end-point by intention-to-treat analysis

**Source: Afdhal N, et al. N Engl J Med. 2014;370:1483-93.**

# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-experienced HCV GT 1
# ION-2 Study: Results

## ION-2: SVR12 by Treatment Regimen and Liver Disease

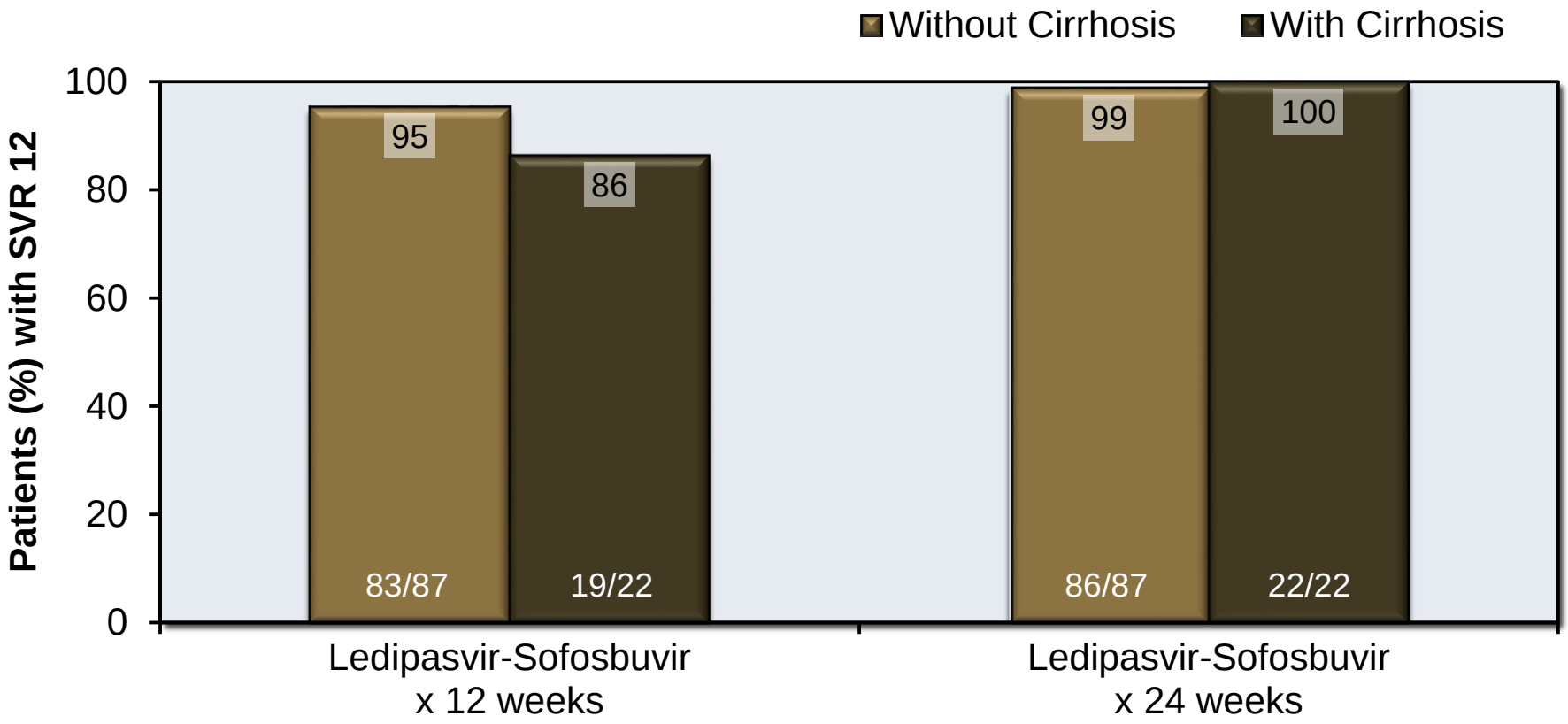



Source: Afdhal N, et al. N Engl J Med. 2014;370:1483-93.

# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-experienced HCV GT 1

## ION-2 Study: Results for Ledipasvir-Sofosbuvir

### ION-2: SVR12 by Treatment Regimen and Liver Disease




Note: subgroup results do not include patients who withdrew consent or were lost to follow-up

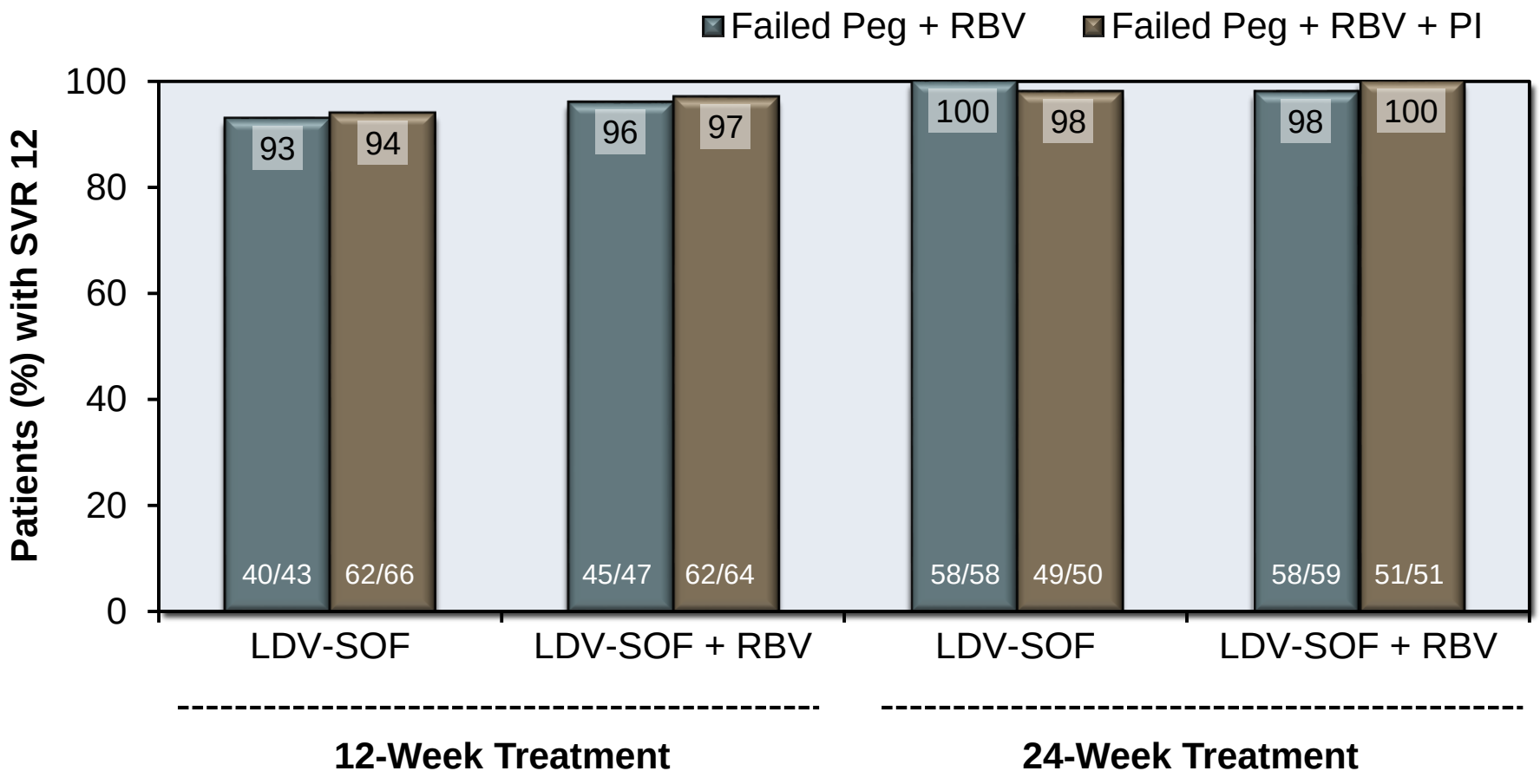
**Source: Afdhal N, et al. N Engl J Med. 2014;370:1483-93.**

Hepatitis web study

# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-experienced HCV GT 1

## ION-2 Study: Results

### ION-2: SVR12 by Prior Treatment Regimen




Source: Afdhal N, et al. N Engl J Med. 2014;370:1483-93.

# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-experienced HCV GT 1
## ION-2 Study: Resistance Data

- **NS5B S282T variant (reduces susceptibility to sofosbuvir)**
  - Not observed in any patients at baseline or after treatment

- **NS5A resistant variants**
  - Baseline resistance in 62 (14%) of 439 patients tested
  - SVR12 in 55 (89%) of 62 patients with NS5A resistance
  - All 11 patients who had viral relapse had detectable NS5A resistant variants at the time of relapse

- **NS3/4A resistant variants**
  - Baseline resistance in 163 (71%) of 228 patients tested
  - SVR12 in 159 (98%) of 163 patients with resistance

**Source: Afdhal N, et al. N Engl J Med. 2014;370:1483-93.**

# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Experienced HCV GT 1
## ION-2 Study: Conclusions

**Conclusions**: “Treatment with a once-daily, single-tablet regimen of ledipasvir and sofosbuvir resulted in high rates of sustained virologic response among patients with HCV genotype 1 infection who had not had a sustained virologic response to prior interferon-based treatment.”

**Source: Afdhal N, et al. N Engl J Med. 2014;370:1483-93.**

Treatment Experienced

# Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis

# SIRIUS

Bourliere M, et al. Lancet Infect Dis. 2015;15:397-404.

# Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis

## SIRIUS Trial: Features

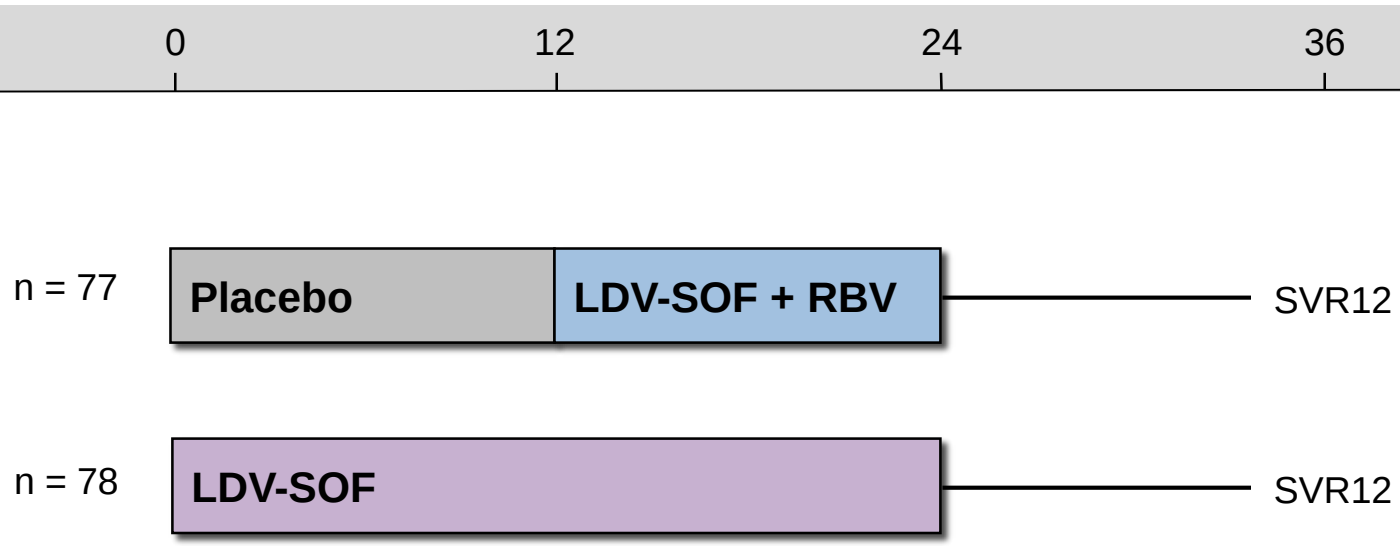
### SIRIUS Trial

- **Design**: Phase 2, double-blind, randomized, trial that evaluated ledipasvir-sofosbuvir x 24 weeks or ledipasvir-sofosbuvir plus ribavirin for 12 weeks in treatment-experienced patients with GT1 HCV and compensated cirrhosis
- **Setting**: Multiple sites in France
- **Entry Criteria**
  - Chronic HCV Genotype 1 (n = 155 randomized)
  - 18 years or older
  - Failed prior therapy with sequential PEG + RBV and PEG + RBV + PI
  - Compensated cirrhosis by: (a) biopsy, (b) FibroScan >12.5 kPa, or (c) FibroTest (FibroSURE) >0.75 and APRI >2
  - Excluded if evidence of hepatic decompensation or HCC
- **Primary End-Point**: SVR12

**Source: Bourliere M, et al. Lancet Infect Dis. 2015;15:397-404.**

# Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis

## SIRIUS Trial: Study Design




**Drug Dosing**

Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily

Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

**Abbreviations**: LDV= ledipasvir; SOF = sofosbuvir; RBV = ribavirin

**Source: Bourliere M, et al. Lancet Infect Dis. 2015;15:397-404.**

# Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis

## SIRIUS Trial: Baseline Characteristics

| | LDV-SOF + RBV 12 wks N = 77 | LDV-SOF x 24 wks N = 78 |
|---|---|---|
| Age (years) | 56 | 57 |
| BMI, kg/m$^2$ mean | 27.9 | 26.3 |
| Male sex, n (%) | 58 (75) | 56 (72) |
| White Race, n (%) | 76 (99) | 75 (96) |
| IL28B CC, n (%) | 4 (5) | 6 (8) |
| HCV RNA ($log_{10}$ IU/mL) | 6.5 | 6.5 |
| Mean MELD (range) | 7 (6-16) | 7 (6-12) |
| Varices, n (%) | 16 (21) | 25 (32) |
| Platelets <100 x $10^9$/L | 56 (39-74) | 57 (23-77) |
| Albumin < 35 g/L | 6 (8) | 14 (18) |

**Source: Bourliere M, et al. Lancet Infect Dis. 2015;15:397-404.**

Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis

# SIRIUS Trial: Baseline Characteristics (continued)

| | LDV-SOF + RBV 12 wks N = 77 | LDV-SOF x 24 wks N = 78 |
|---|---|---|
| HCV Genotype | | |
| 1a | 48 (62%) | 50 (64) |
| 1 | 28 (36%) | 27 (35%) |
| 1 (no confirmed subtype) | 1 (1%) | 1 (1%) |
| Prior Protease Inhibitor | | |
| Telaprevir | 43 (56%) | 49 (63%) |
| Boceprevir | 30 (39%) | 27 (35%) |
| Telaprevir and Boceprevir | 1 (1%) | 1 (1%) |
| Simeprevir | 1 (1%) | 2 (3%) |
| Faldaprevir | 2 (3%) | 0 |
| Patients with NS3A RAVs | 44 (57%) | 39 (50%) |
| Patients with NS5A RAVs | 12 (16%) | 12 (15%) |

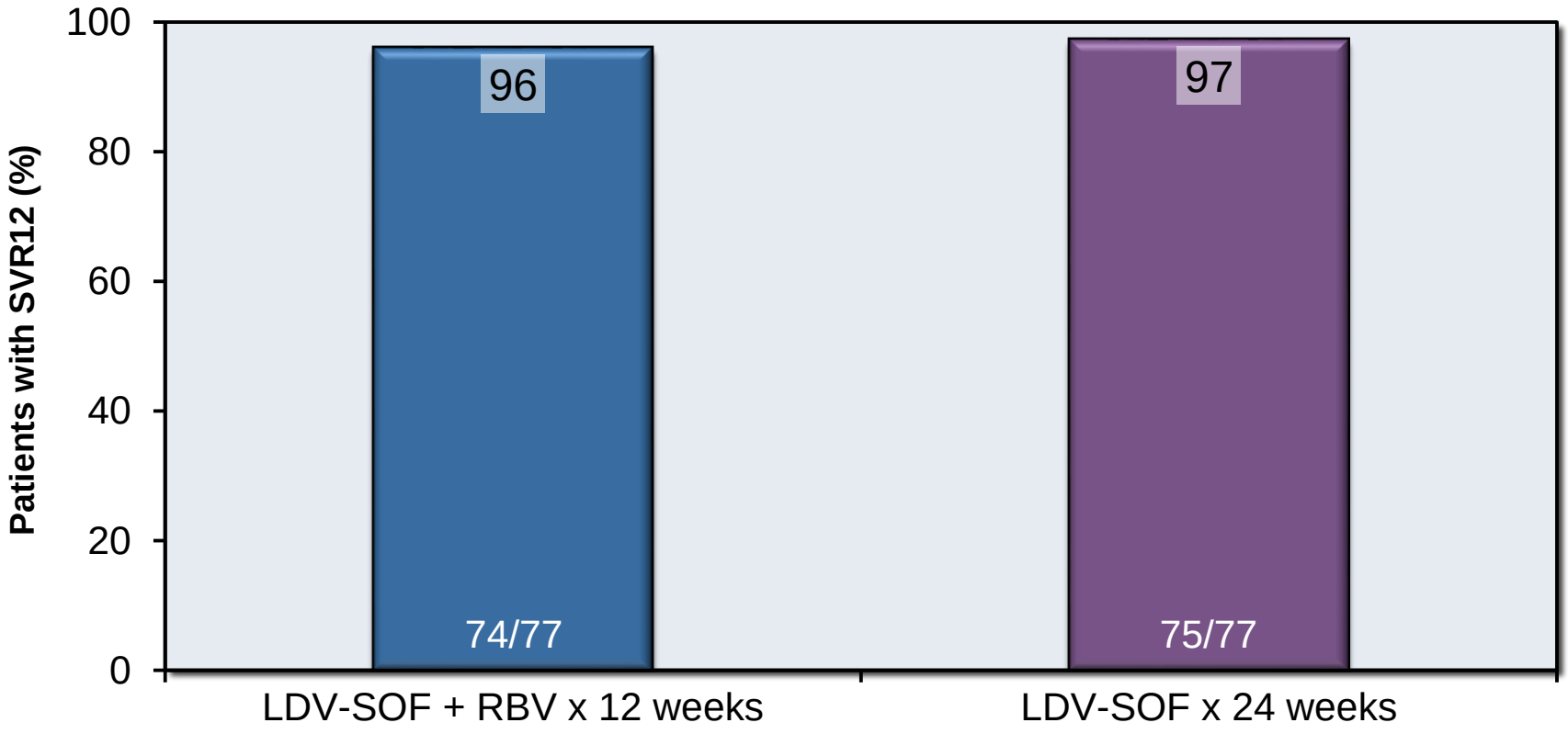
Abbreviations: RAVs = Resistant Associated Variants

**Source: Bourliere M, et al. Lancet Infect Dis. 2015;15:397-404.**

# Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis

# SIRIUS Trial: Results

## SIRIUS: SVR 12 by Treatment Duration and Regimen

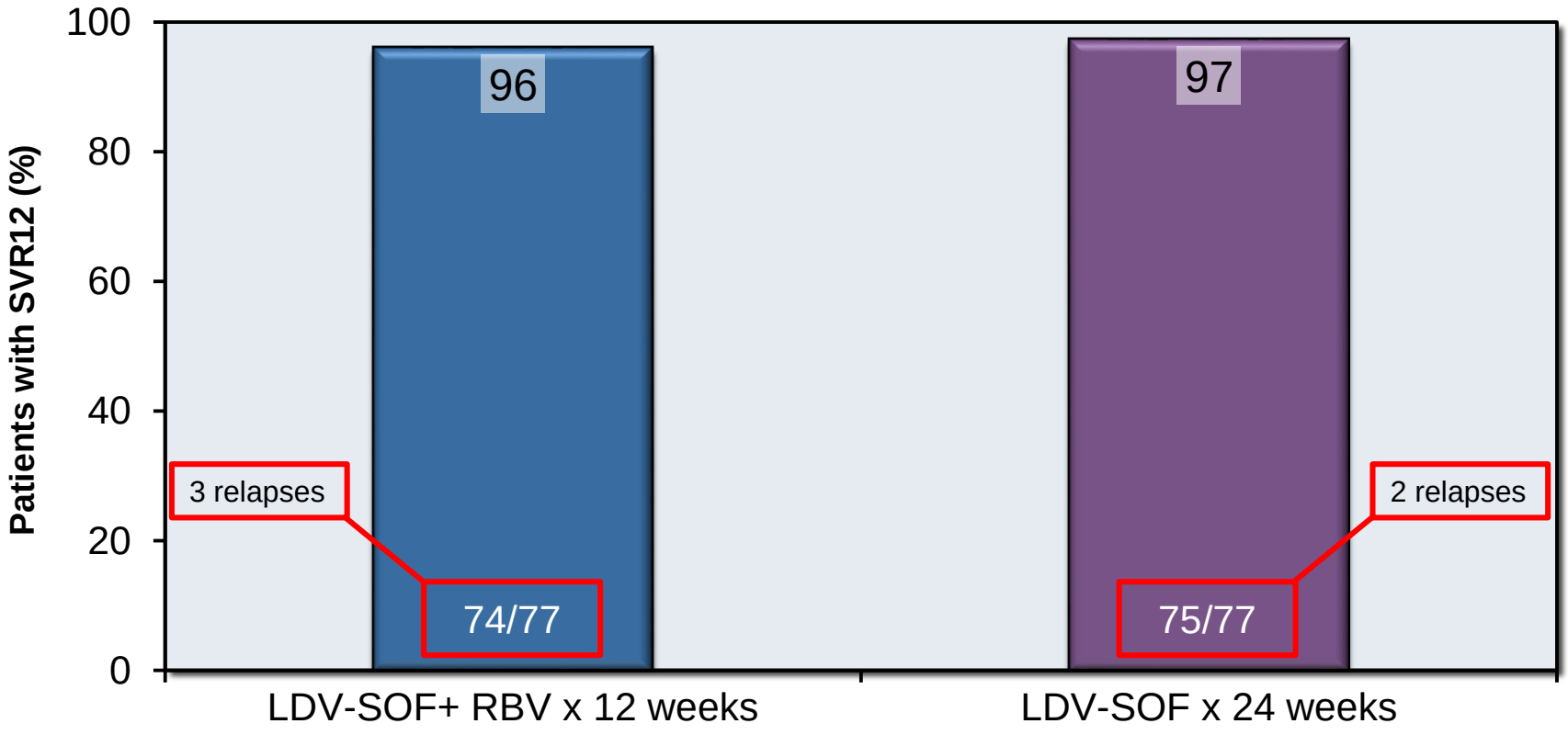



**Source: Bourliere M, et al. Lancet Infect Dis. 2015;15:397-404.**

# Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis

# SIRIUS Trial: Results

## SIRIUS: SVR 12 by Treatment Duration and Regimen

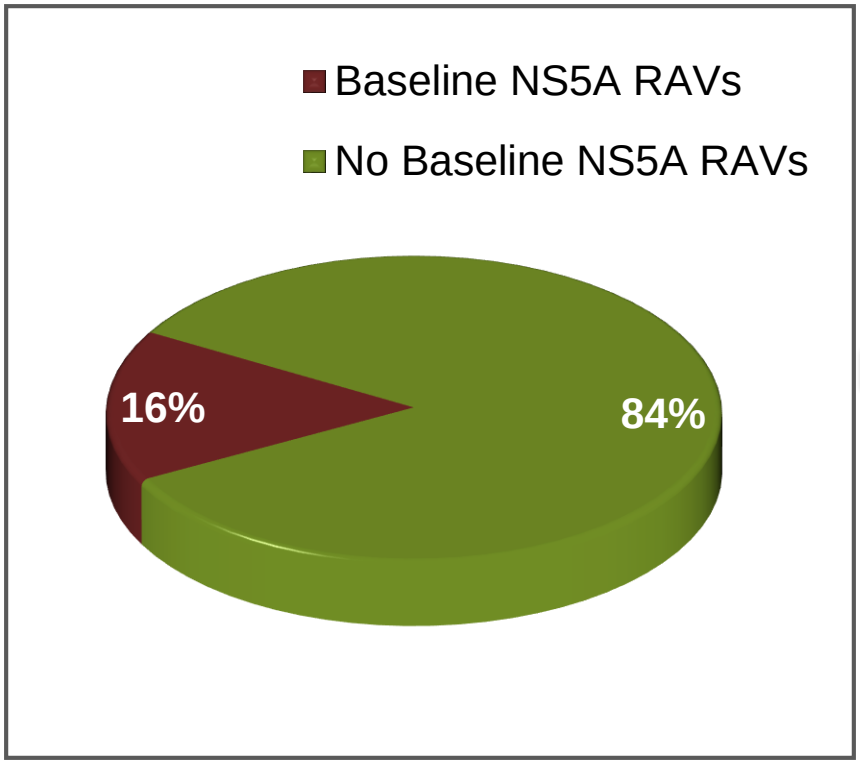


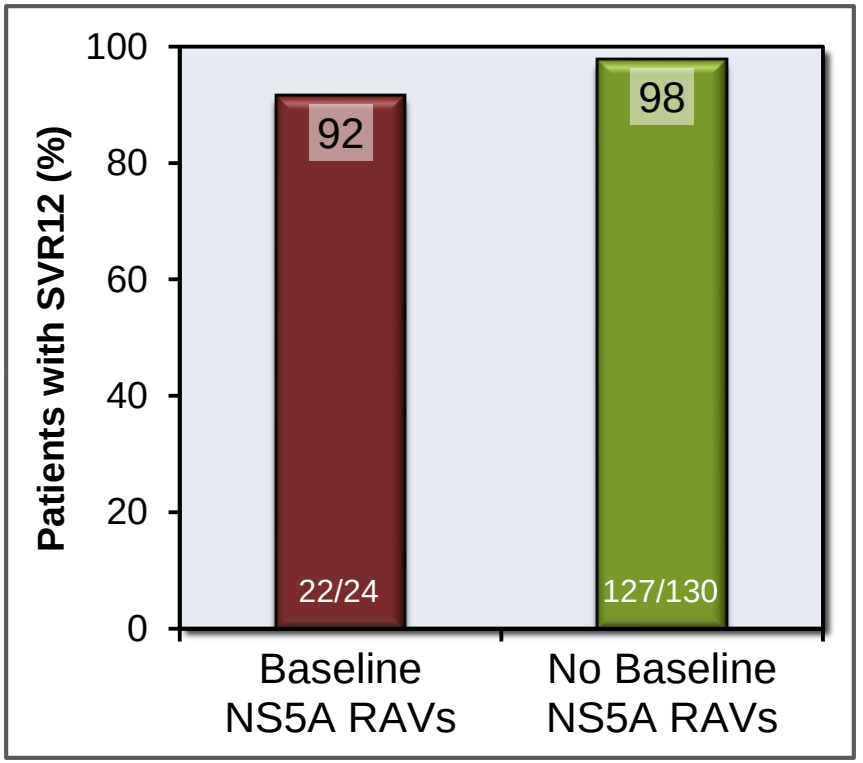

Source: Bourliere M, et al. Lancet Infect Dis. 2015;15:397-404.

# Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis

# SIRIUS Trial: Results HCV Sequence Analysis

## Correlation of Baseline NS5A RAVs and SVR12 Responses




No statistically significant difference in SVR12 based on baseline NS5A mutations

Abbreviations: RAVs = Resistant Associated Variants

**Source: Bourliere M, et al. Lancet Infect Dis. 2015;15:397-404.**

# Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis

## SIRIUS Trial: Safety Summary

| Patients, N (%) | LDV-SOF + RBV x 12 Weeks | | | LDV-SOF x 24 Weeks | |
|---|---|---|---|---|---|
| | Placebo 12 Wk N = 78 | LDV/SOF+ RBV 12 Wk N = 77 | Overall Period N = 78 | First 12 Wk N = 77 | Overall Period N = 77 |
| Any adverse event | 63 (81%) | 66 (86%) | 75 (96%) | 65 (84%) | 67 (87%) |
| Treatment D/C due to AEs | 1 (1%) | 0 | 1 (1%) | 0 | 0 |
| Serious adverse event | 1 (1%) | 3 (4%) | 4 (5%) | 3 (4%) | 8 (10%) |
| Grade 3-4 lab abnormalities | 18 (23) | 8 (11) | 24 (31) | 15 (19) | 11 (14) |
| Hemoglobin <100 g/L | 1 (1%) | 1 (1%) | 2 (3%) | 0 | 1 (1%) |
| Hemoglobin <85 g/L | 1 (1%) | 1 (1%) | 2 (3%) | 0 | 0 |

Abbreviations: LDV-SOF = Ledipasvir-sofosbuvir; AE = adverse event; D/C = discontinued

**Source: Bourliere M, et al. Lancet Infect Dis. 2015;15:397-404.**

# Ledipasvir-Sofosbuvir in Treatment-Experienced GT1 with Cirrhosis

## SIRIUS Trial: Adverse Events ≥10%

| Patients, N (%) | LDV-SOF + RBV x 12 Weeks | | | LDV-SOF x 24 Weeks | |
|---|---|---|---|---|---|
| | Placebo 12 Wk N = 78 | LDV/SOF+ RBV 12 Wk N = 77 | Overall Period N = 78 | First 12 Wk N = 77 | Overall Period N = 77 |
| Asthenia | 24 (31%) | 29 (38%) | 45 (58%) | 28 (36%) | 35 (45%) |
| Headache | 16 (21%) | 13 (17%) | 21 (27%) | 27 (35%) | 31 (40%) |
| Pruritus | 14 (18%) | 11 (14%) | 22 (28%) | 4 (5%) | 7 (9%) |
| Insomnia | 9 (12%) | 7 (9%) | 17 (22%) | 11 (14%) | 13 (17%) |
| Nausea | 8 (10%) | 8 (10%) | 14 (18%) | 7 (9%) | 8 (10%) |
| Fatigue | 3 (4%) | 5 (6%) | 7 (9%) | 13 (17%) | 15 (19%) |
| Dry skin | 6 (8%) | 4 (5%) | 11 (14%) | 4 (5%) | 4 (5%) |
| Arthralgia | 5 (6%) | 0 | 6 (8%) | 6 (8%) | 12 (16%) |
| Bronchitis | 1 (1%) | 4 (5%) | 4 (5%) | 4 (5%) | 13 (17%) |

Abbreviations: LDV-SOF = Ledipasvir-sofosbuvir; AE = adverse event; D/C = discontinued

**Source: Bourliere M, et al. Lancet Infect Dis. 2015;15:397-404.**

# SIRIUS Trial: Interpretation

**Interpretation**: “Ledipasvir-sofosbuvir plus ribavirin for 12 weeks and ledipasvir-sofosbuvir for 24 weeks provided similarly high SVR12 rates in previous non-responders with HCV genotype 1 and compensated cirrhosis. The shorter regimen, when given with ribavirin, might, therefore, be useful to treat treatment-experienced patients with cirrhosis if longer-term treatment is not possible.”

**Source: Bourliere M, et al. Lancet Infect Dis. 2015;15:397-404.**

# Ledipasvir-Sofosbuvir in Treatment-Naïve and Treatment-Experienced Patients

Hepatitis web study

Treatment Naïve and Treatment Experienced

# Sofosbuvir-Ledipasvir +/- Ribavirin in GT-1
# LONESTAR Trial

Lawitz E, et al. Lancet. 2014:383:515-23.

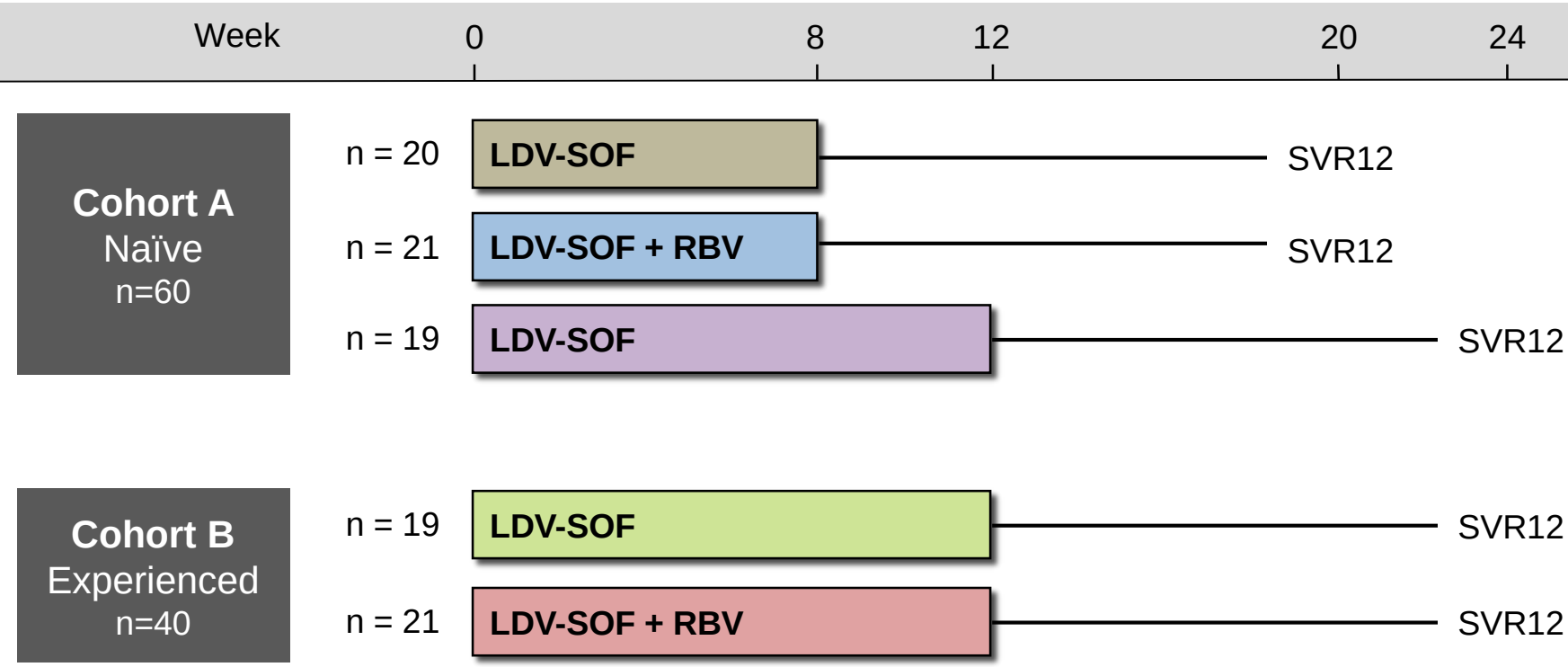
# Ledipasvir-Sofosbuvir +/- Ribavirin in Naïve & Experienced GT1
## LONESTAR Trial: Features

### LONESTAR Trial

- **Design**: Open-label, phase 2, using fixed dose combination of ledipasvir-sofosbuvir +/- ribavirin in treatment-naïve and treatment-experienced GT 1
- **Setting**: one center in USA (San Antonio, Texas)
- **Entry Criteria**
  - Chronic HCV Genotype 1
  - Cohort A: Treatment-naïve
  - Cohort B: Prior virologic failure with protease inhibitor regimen
- **Patient Characteristics (range in different treatment arms)**
  - N = 100 adult patients
  - Treatment-Naive: none with cirrhosis
  - Previously Treated: approximately 55% with cirrhosis
  - Previously Treated: approximately 2/3 non-responders and 1/3 relapsers
  - IL28B Genotype: non-CC (range of 67-95%)
- **End-Points**: Primary = SVR12; safety and tolerability

**Source: Lawitz E, et al. Lancet. 2014:383:515-23.**

# Ledipasvir-Sofosbuvir +/- Ribavirin in Naïve & Experienced GT1
# LONESTAR: Study Design




**Abbreviations**: LDV-SOF= ledipasvir-sofosbuvir; RBV = ribavirin

**Drug Dosing**

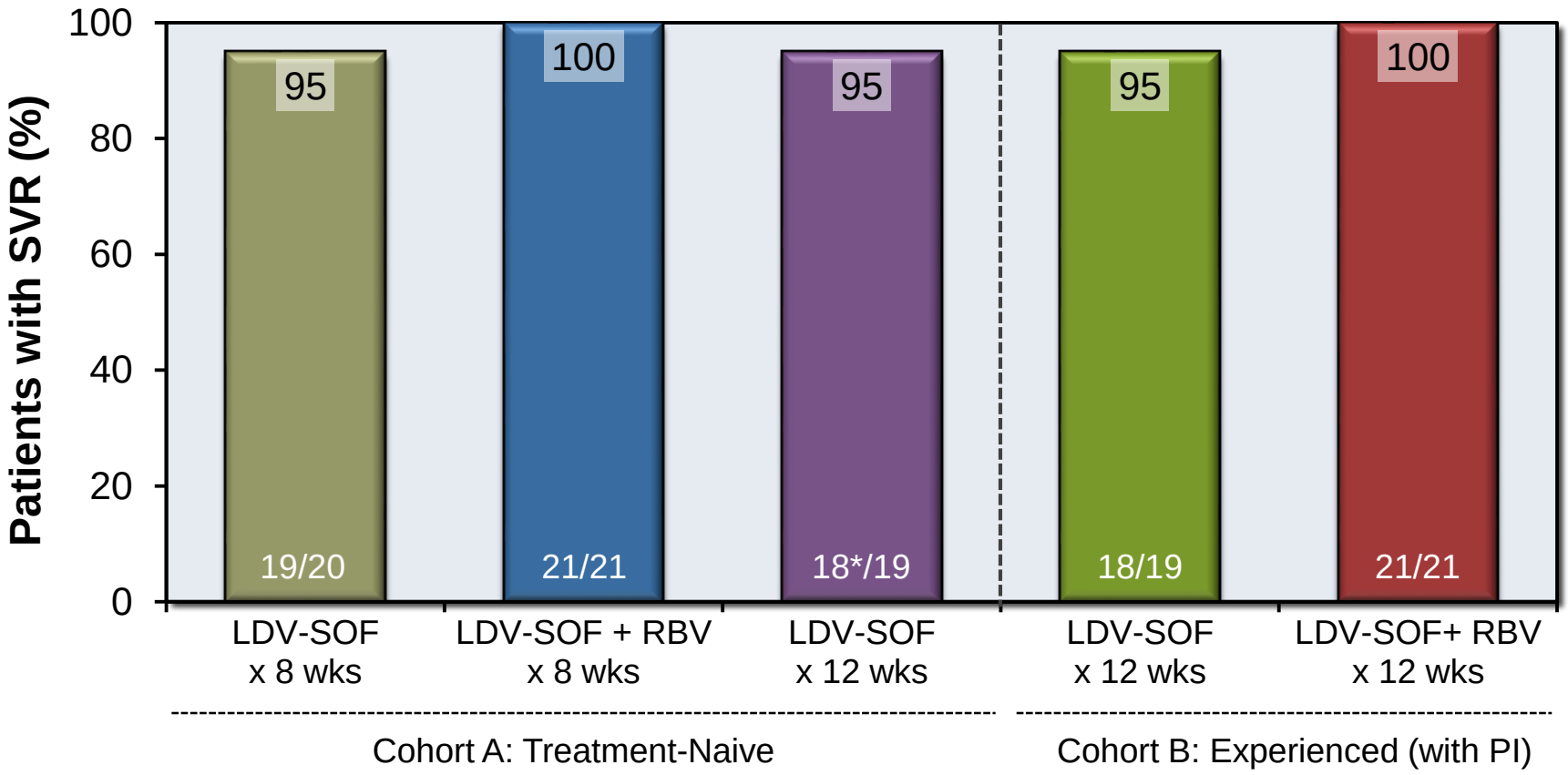
Ledipasvir-Sofosbuvir: 90/400 mg fixed dose combination one pill once daily

Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

**Source: Lawitz E, et al. Lancet. 2014:383:515-23.**

# Ledipasvir-Sofosbuvir +/- Ribavirin in Naïve & Experienced GT1 LONESTAR Trial: Results

## LONESTAR: SVR 12, by Cohort and Treatment Regimen




*One patient lost to follow-up; LDV-SOF = ledipasvir-sofosbuvir; RBV = ribavirin; PI = protease inhibitor

**Source: Lawitz E, et al. Lancet. 2014:383:515-23.**

# Ledipasvir-Sofosbuvir +/- Ribavirin in Naïve & Experienced GT1 LONESTAR Trial: Adverse Events

| Adverse Event (AE) | Cohort A | | | Cohort B | |
|---|---|---|---|---|---|
| | LDV-SOF x 8 weeks (n=20) | LDV-SOF + RBV x 8 weeks (n=21) | LDV-SOF x 12 weeks (n=19) | LDV-SOF x 12 weeks (n=19) | LDV-SOF + RBV x 12 weeks (n=21) |
| Serious AE | 0 (0%) | 1 (5%) | 1 (5%) | 1 (5%) | 1 (5%) |
| Nausea | 2 (10%) | 2 (10%) | 1 (5%) | 0 (0%) | 4 (19%) |
| Anemia | 0 (0%) | 2 (10%) | 0 (0%) | 0 (0%) | 6 (29%) |
| Upper RTI | 2 (10%) | 0 (0%) | 1 (5%) | 1 (5%) | 4 (19%) |
| Headache | 2 (10%) | 3 (14%) | 0 (0%) | 1 (5%) | 1 (5%) |
| Abdominal pain | 1 (5%) | 1 (5%) | 1 (5%) | 0 (0%) | 1 (5%) |
| Bronchitis | 1 (5%) | 1 (5%) | 0 (0%) | 1 (5%) | 1 (5%) |
| Back pain | 1 (5%) | 1 (5%) | 1 (5%) | 1 (5%) | 0 (0%) |
| Decreased appetite | 0 (0%) | 2 (10%) | 0 (0%) | 1 (5%) | 0 (0%) |
| Dermatitis | 1 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (10%) |
| Muscle spasms | 1 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (10%) |

**Source: Lawitz E, et al. Lancet. 2014:383:515-23.**

# Ledipasvir-Sofosbuvir +/- Ribavirin in Naïve & Experienced GT1 LONESTAR Trial: Conclusion

**Interpretation**: “These findings suggest that the fixed-dose combination of sofosbuvir-ledipasvir alone or with ribavirin has the potential to cure most patients with genotype-1 HCV, irrespective of treatment history or the presence of compensated cirrhosis. Further clinical trials are needed to establish the best treatment duration and to further assess the contribution of ribavirin.”

**Source: Lawitz E, et al. Lancet. 2014:383:515-23.**

Phase 2

Treatment Naïve and Treatment Experienced

# Ledipasvir-Sofosbuvir +/- Ribavirin in HCV Genotype 3 or 6

# New Zealand Genotype 3 and 6 Study

Gane EJ, et al. Gastroenterology. 2015 August 7. [Epub ahead of print]

Hepatitis web study

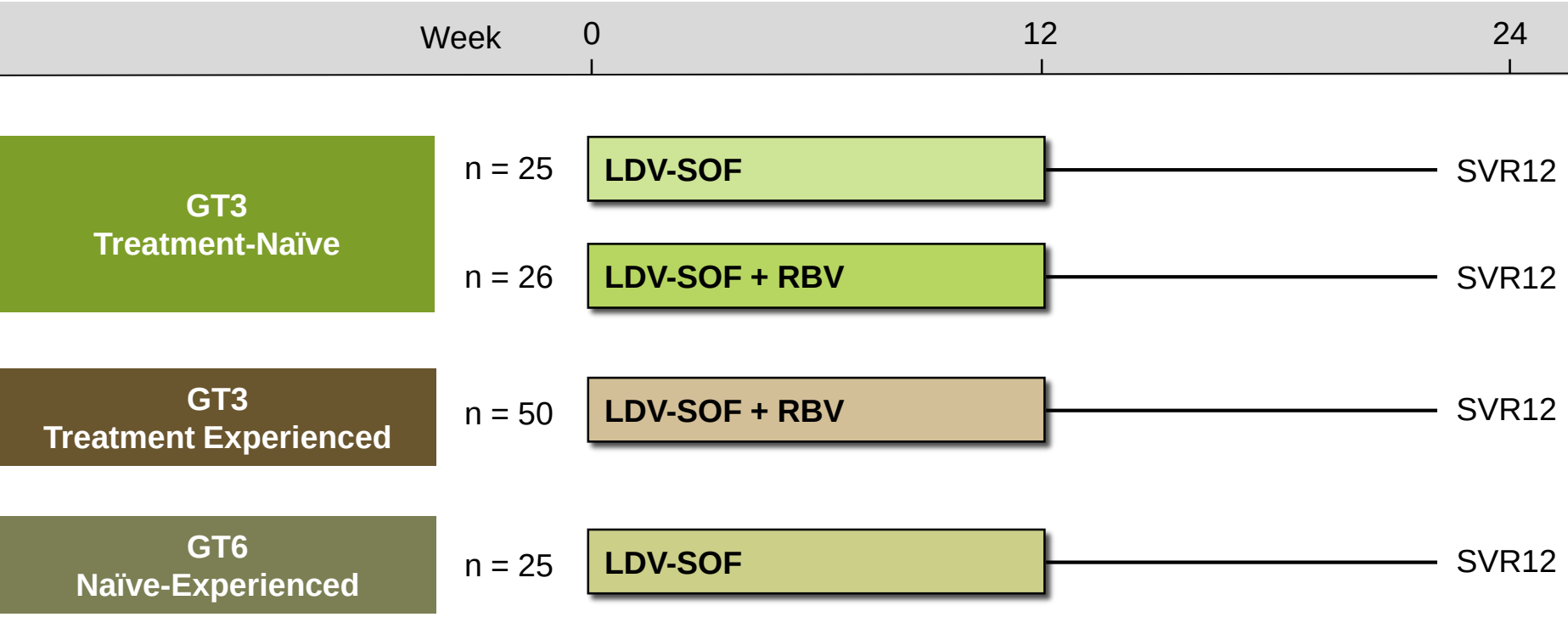
# Ledipasvir-Sofosbuvir +/- Ribavirin in HCV GT 3 or 6
# New Zealand GT 3 & 6 Study: Features

## ELECTRON 2 Trial

- **Design**: Open-label, phase 2, using fixed-dose combination of ledipasvir-sofosbuvir +/- ribavirin in treatment-naïve GT3, ledipasvir-sofosbuvir + ribavirin in treatment-experienced genotype 3, and ledipasvir-sofosbuvir in treatment-naïve or treatment-experienced patients with genotype 6
- **Setting**: Two hepatitis treatment centers in New Zealand
- **Entry Criteria**
  - Chronic HCV (n=126)
  - 18 years or older
  - HCV RNA > 10,000 IU/mL
  - Failed prior therapy with sequential PEG + RBV and PEG + RBV + PI
  - Compensated cirrhosis by: (a) biopsy, (b) FibroScan >12.5 kPa, or (c) FibroTest (FibroSURE) >0.75 and APRI >2
  - Excluded if evidence of hepatic decompensation, HCC, HIV, or HBV
- **Primary End-Point**: SVR12

Gane EJ, et al. Gastroenterology. 2015 August 7. [Epub ahead of print]

# Ledipasvir-Sofosbuvir +/- Ribavirin in HCV GT 3 or 6
# New Zealand GT 3 & 6 Study: Study Design




**Abbreviations**: LDV-SOF = ledipasvir-sofosbuvir; RBV = ribavirin

**Drug Dosing**

Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily

Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

**Source: Gane EJ, et al. Gastroenterology. 2015 August 7. [Epub ahead of print]**

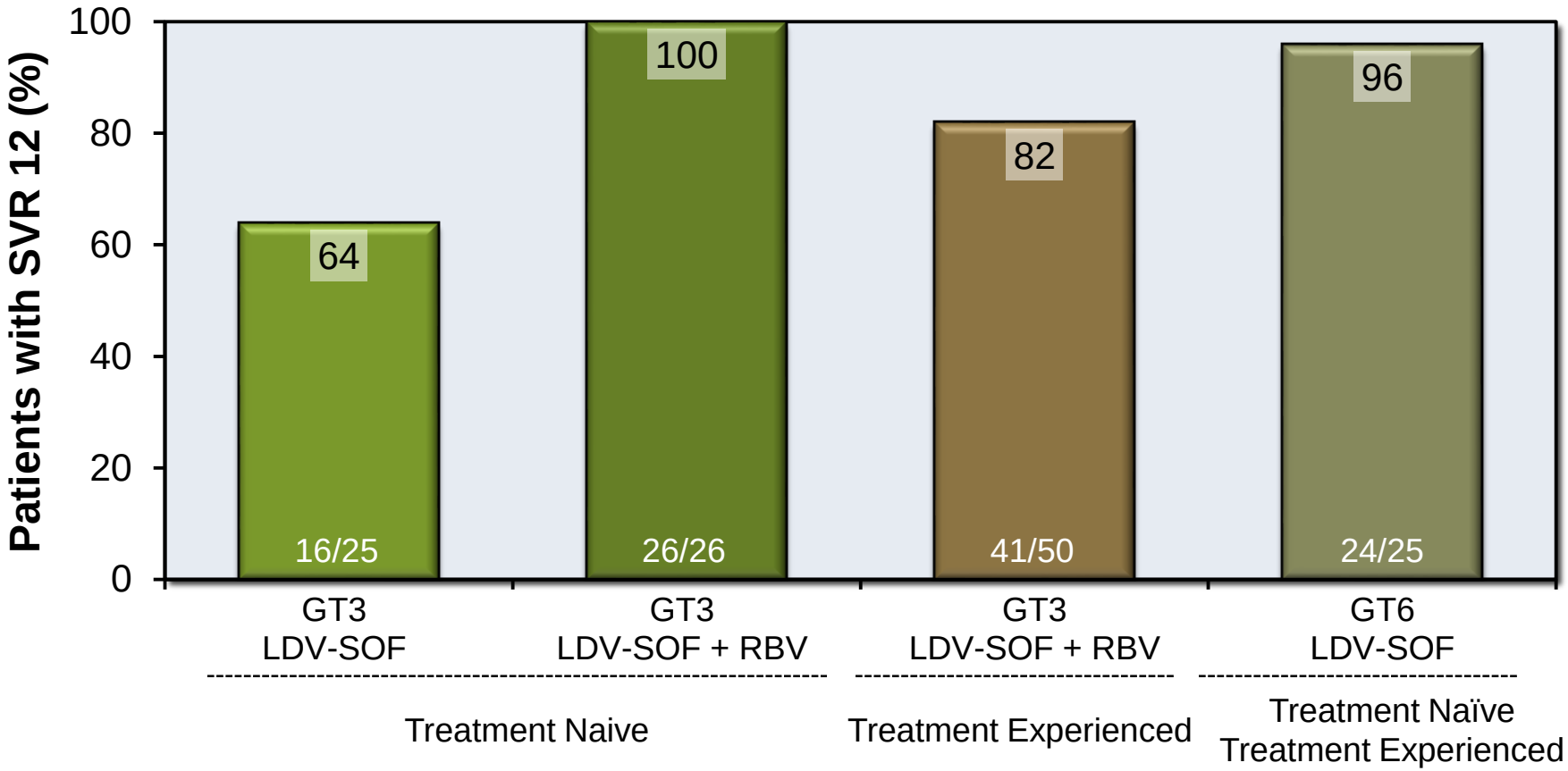
# Ledipasvir-Sofosbuvir +/- Ribavirin in HCV GT 3 or 6
# New Zealand GT 3 & 6 Study: Baseline Characteristics

| | GT 3 Naïve | | GT 3 Experienced | GT 6 Naïve/Experienced |
|---|---|---|---|---|
| | LDV-SOF n=25 | LDV-SOF + RBV n=26 | LDV-SOF + RBV n=50 | LDV-SOF n=25 |
| Mean age, years | 43 | 48 | 52 | 51 |
| Male, n (%) | 13 (52) | 11 (42) | 39 (78) | 16 (64) |
| White, n (%) | 22 (88) | 23 (88) | 40 (80) | 4 (16) |
| BMI <30 kg/m$^2$, n (%) | 19 (76) | 18 (69) | 42 (84) | 23 (92) |
| Cirrhosis, n (%) | 3 (12) | 5 (19) | 0 | 20 (100) |
| IL28B CC, n (%) | 9 (36) | 15 (58) | 4 (21) | 7 (35) |
| Prior Treatment, n (%) | 0 | 0 | 50 (100) | 2 (8) |
| Cirrhosis, n (%) | 4 (16) | 6 (23) | 22 (44) | 2 (8) |
| Mean HCV RNA, $\log_{10}$ IU/mL | 6.3 | 6.3 | 6.3 | 6.7 |

**Source: Gane EJ, et al. Gastroenterology. 2015 August 7. [Epub ahead of print]**

# Ledipasvir-Sofosbuvir +/- Ribavirin in HCV GT 3 or 6
# New Zealand GT 3 & 6 Study: Results

## SVR 12, by GT and Treatment Regimen




LDV-SOF = ledipasvir-sofosbuvir; RBV = ribavirin

**Source: Gane EJ, et al. Gastroenterology. 2015 August 7. [Epub ahead of print]**

# Ledipasvir-Sofosbuvir +/- Ribavirin in HCV GT 3 or 6
## New Zealand GT 3 & 6 Study: Conclusions

**Conclusions**: “In an uncontrolled, open-label trial, high rates of SVR12 were achieved by patients with HCV genotype 3 infection who received 12 weeks of ledipasvir-sofosbuvir plus ribavirin, and by patients with HCV genotype 6 infection who received 12 weeks of sofosbuvir-ledipasvir without ribavirin. Current guidelines do not recommend the use of ledipasvir-sofosbuvir, with or without ribavirin, in patients with HCV genotype 3 infection.”

**Source: Gane EJ, et al. Gastroenterology. 2015 August 7. [Epub ahead of print]**

Treatment Naïve and Treatment Experienced

# Sofosbuvir + (Ledipasvir or GS-9669) +/- Ribavirin in GT-1

# ELECTRON Trial (Arms 12-17 & 22)

Gane EJ, et al. Gastroenterogy. 2014:146:736-43.

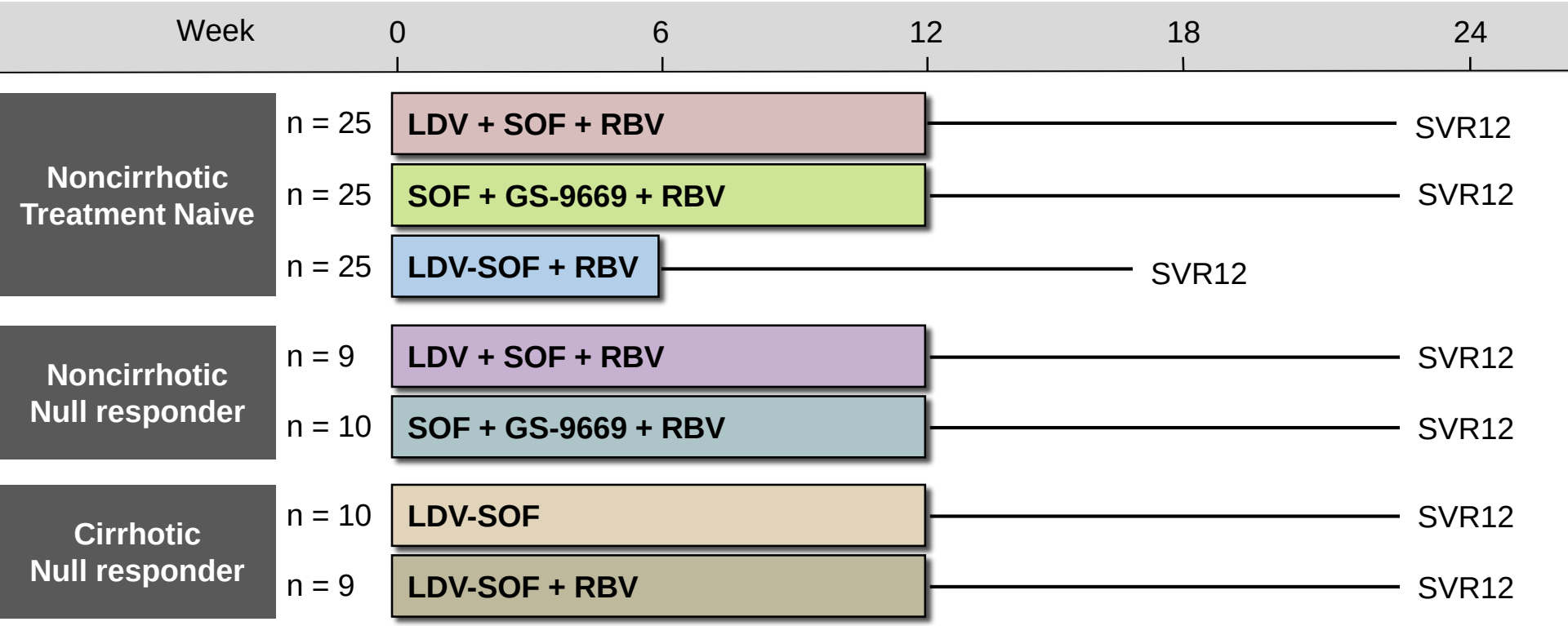
# Sofosbuvir + (Ledipasvir or GS-9669) +/- Ribavirin in GT1 ELECTRON Trial (Arms 12-17 & 22): Features

## ELECTRON Trial (Arms 12-17 & 22)

- **Design**: Open-label, phase 2, using sofosbuvir plus [ledipasvir or GS-9669] with or without ribavirin in treatment-naïve and treatment-experienced GT1
- **Setting**: two hepatitis treatment centers in New Zealand
- **Entry Criteria**
  - Chronic HCV Genotype 1
  - HCV RNA > 50,000 IU/mL
  - Age > 18
- **Patient Characteristics (range in different treatment arms)**
  - N = 113 patients enrolled
  - Three of seven groups were treatment naïve
  - Four of seven groups were treatment experienced with prior null response
  - Two groups of seven groups were treatment experienced and cirrhotic
  - Three treatment arms used fixed dose ledipasvir-sofosbuvir
- **Primary End-Point**: SVR12

**Source: Gane EJ, et al. Gastroenterogy. 2014:146:736-43.**

# Sofosbuvir + (Ledipasvir or GS-9669) +/- Ribavirin in GT1
# ELECTRON Trial Arms (12-17 & 22): Design




**Abbreviations**: LDV= ledipasvir; SOF = sofosbuvir; RBV = ribavirin

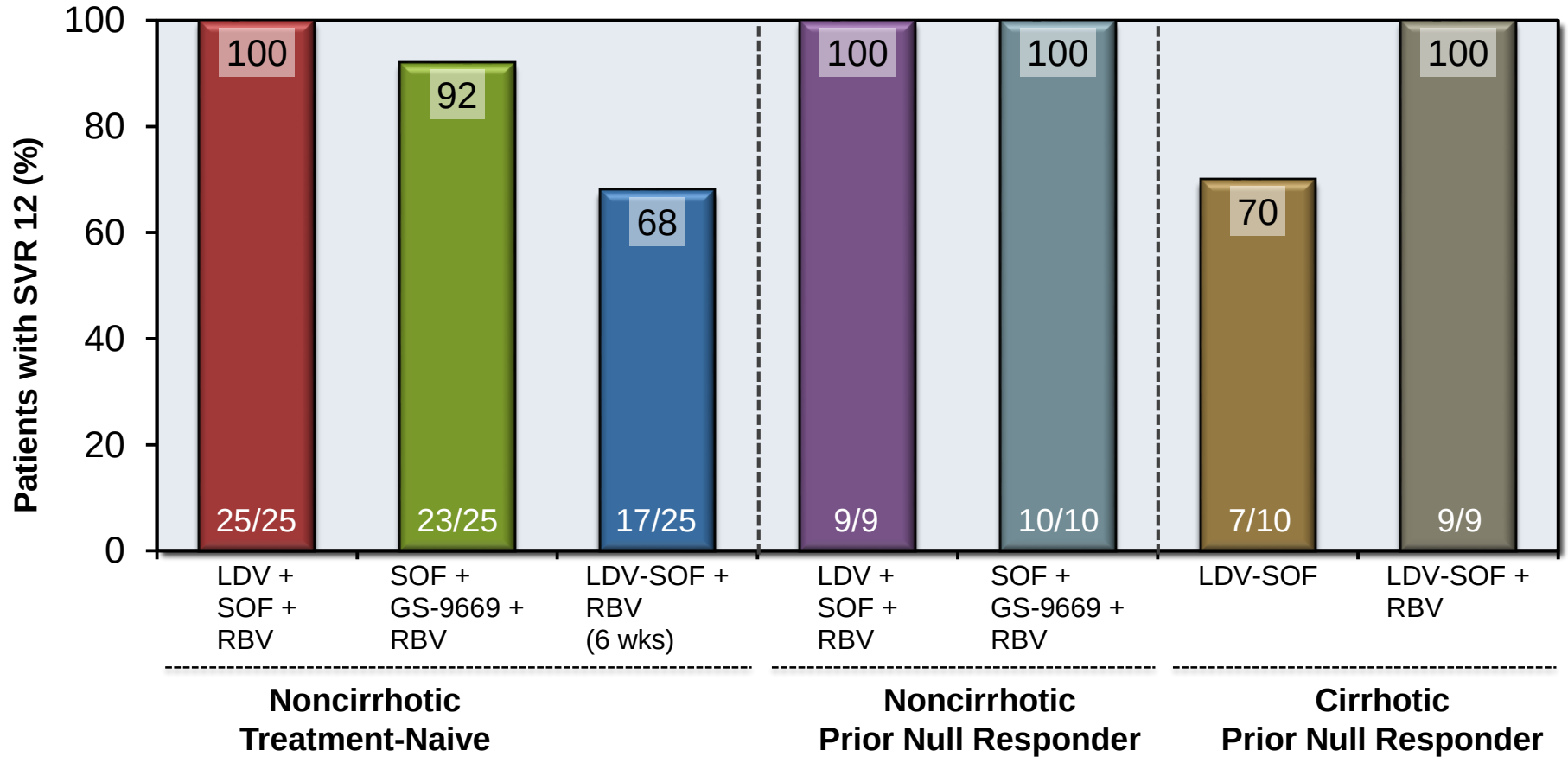
**Drug Dosing**

Sofosbuvir: 400 mg once daily; Ledipasvir: 90 mg once daily; GS-9669 = 500 mg once daily
Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination one pill once daily
Ribavirin (weight-based and divided bid): 1000 mg/day if < 75kg or 1200 mg/day if ≥ 75kg

**Source: Gane EJ, et al. Gastroenterogy. 2014:146:736-43.**

# Sofosbuvir + (Ledipasvir or GS-9669) +/- Ribavirin in GT1 ELECTRON Trial (Arms 12-17 & 22): Results

## ELECTRON TRIAL, SVR 12 by Treatment Regimen




*All regimens 12 weeks except treatment-naïve LDV-SOF + Ribavirin= 6 week regimen

**Source: Gane EJ, et al. Gastroenterogy. 2014:146:736-43.**

# Sofosbuvir + (Ledipasvir or GS-9669) +/- Ribavirin in GT1 ELECTRON Trial (Arms 12-17 & 22): Conclusion

**Conclusions**: “The combination of sofosbuvir and a second direct-acting antiviral agent is highly effective in treatment-naïve patients with HCV genotype 1 infection and in patients that did not respond to previous treatment.”

**Source: Gane EJ, et al. Gastroenterogy. 2014:146:736-43.**

NEW TO AL

Treatment Naïve and Treatment Experienced

# Ledipasvir-Sofosbuvir in HCV Genotype 4

# NIAID SYNERGY (Genotype 4)

Kohli A, et al. Lancet Infect Dis. 2015:15:1049-54.

# Ledipasvir-Sofosbuvir in Genotype 4
# NIAID SYNERGY (GT4) Trial: Features

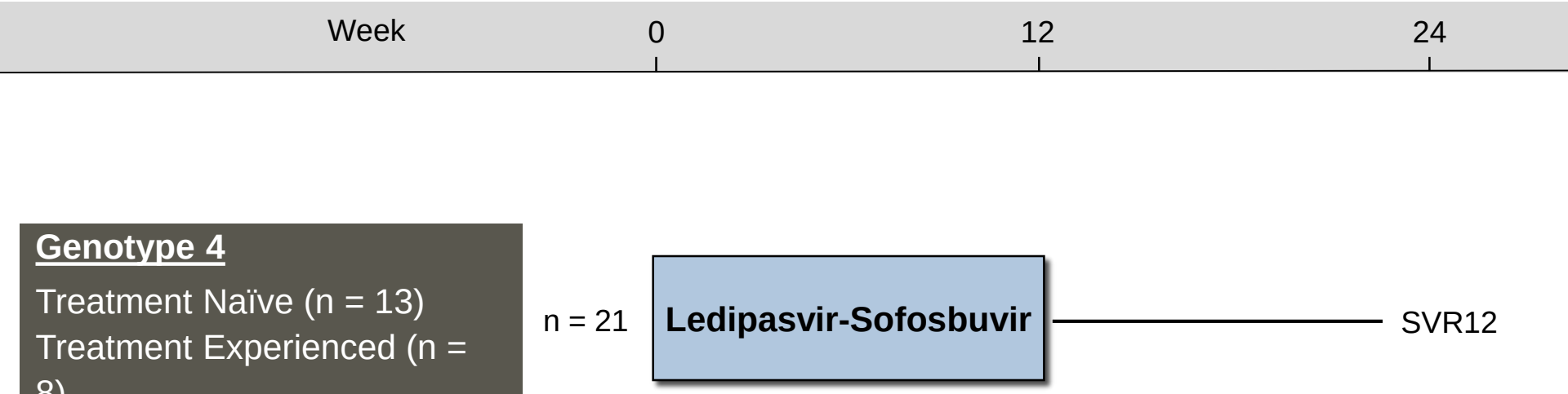
## NIAID SYNERGY Trial

- **Design**: Open-label, phase 2a trial using fixed dose ledipasvir-sofosbuvir for treatment-naïve and interferon treatment-experienced patients with chronic HCV genotype 4
- **Setting**: single center (Clinical Center at NIH, United States)
- **Entry Criteria**
  - 18 years of age or older
  - Chronic HCV Genotype 4
  - Treatment naïve or prior interferon treatment failure
  - HCV RNA ≥2,000 IU/mL
  - Exclusions: HBV, HIV, or decompensated liver disease
- **Primary End-Point**: SVR12

**Source: Kohli A, et al. Lancet Infect Dis. 2015:15:1049-54.**

Hepatitis web study

# Ledipasvir-Sofosbuvir in Genotype 4
# NIAID SYNERGY (GT4) Trial: Features




**Drug Dosing**
Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily

**Source: Kohli A, et al. Lancet Infect Dis. 2015:15:1049-54.**

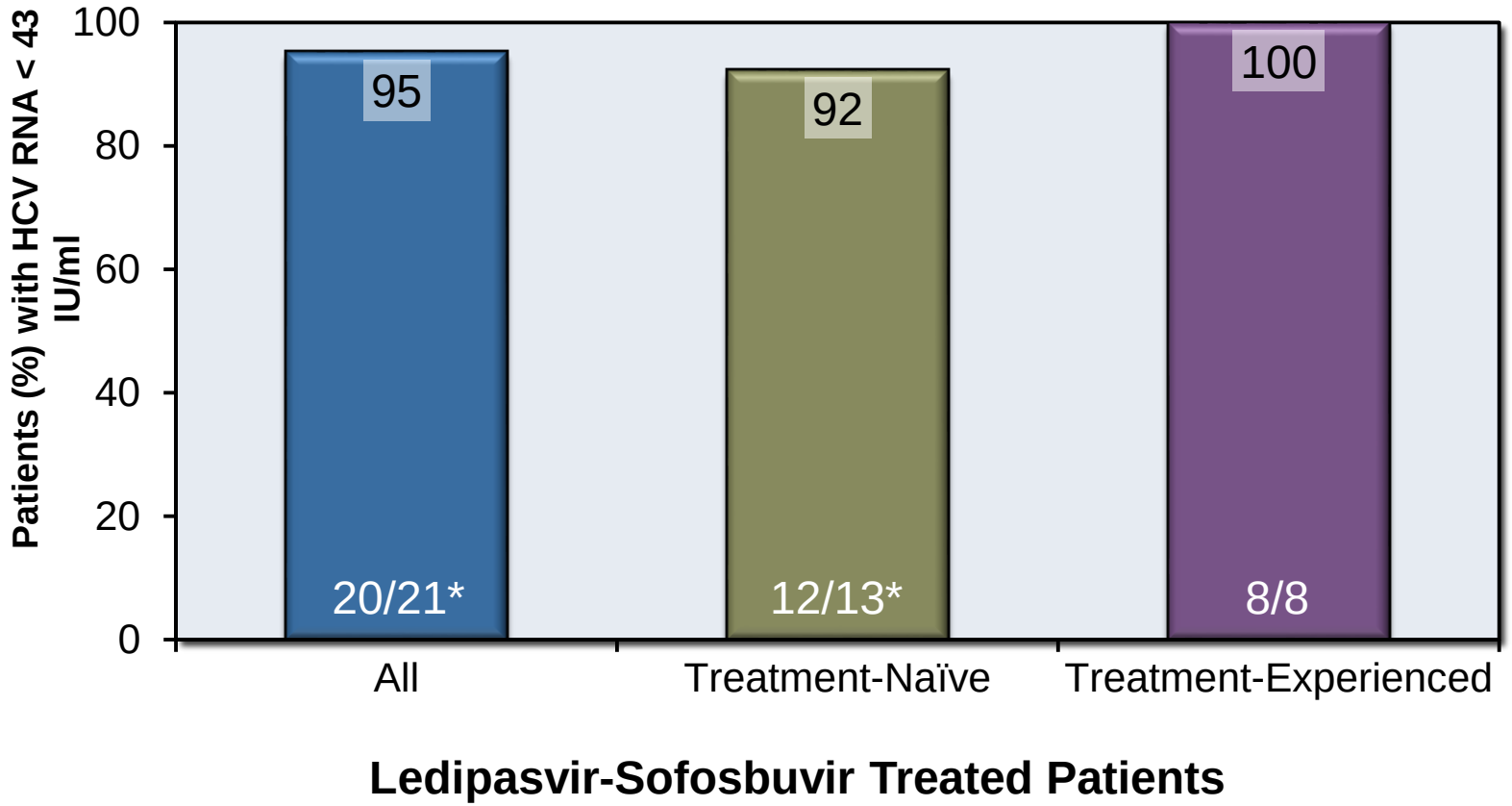
# Ledipasvir-Sofosbuvir in Genotype 4
## NIAID SYNERGY (GT4) Trial: Key Baseline Characteristics

- Sex: Male 67%
- Race: 43% Black; 52% White; 5% Native American
- Country of Origin: 29% Egypt; 24% United States
- Treatment Experience: 62% naïve; 38% experienced
- HCV RNA > 800,000 IU/mL: 62%

**Source: Kohli A, et al. Lancet Infect Dis. 2015:15:1049-54.**

# Ledipasvir-Sofosbuvir in Genotype 4
# NIAID SYNERGY (GT4) Trial: Results

## NIH SYNERGY: SVR 12, Intent to Treat Analysis




*1 patient did not complete 12 weeks of treatment due to drug non-adherence

**Source: Kohli A, et al. Lancet Infect Dis. 2015:15:1049-54.**

# Ledipasvir-Sofosbuvir in Genotype 4
# NIAID SYNERGY (GT4) Trial: Interpretation

**Interpretation**: “Ledipasvir and sofosbuvir treatment for 12 weeks was well tolerated by patients with HCV genotype 4 and resulted in 100% SVR for all patients who received all 12 weeks of study drugs, irrespective of previous treatment status and underlying liver fibrosis. This is the first report of a single-pill, all-oral, interferon-free, ribavirin-free treatment for patients with HCV genotype 4.”

**Source: Kohli A, et al. Lancet Infect Dis. 2015:15:1049-54.**

# Sofosbuvir in Patients Pre and Post Liver Transplant

Hepatitis
web study

Treatment Naïve and Treatment Experienced

# Ledipasvir-Sofosbuvir + RBV in HCV GT 1,4 and Advanced Liver Disease

# SOLAR-1 (Cohorts A and B)

Charlton M, al. Gastroenterology. 2015; 149:649-59.

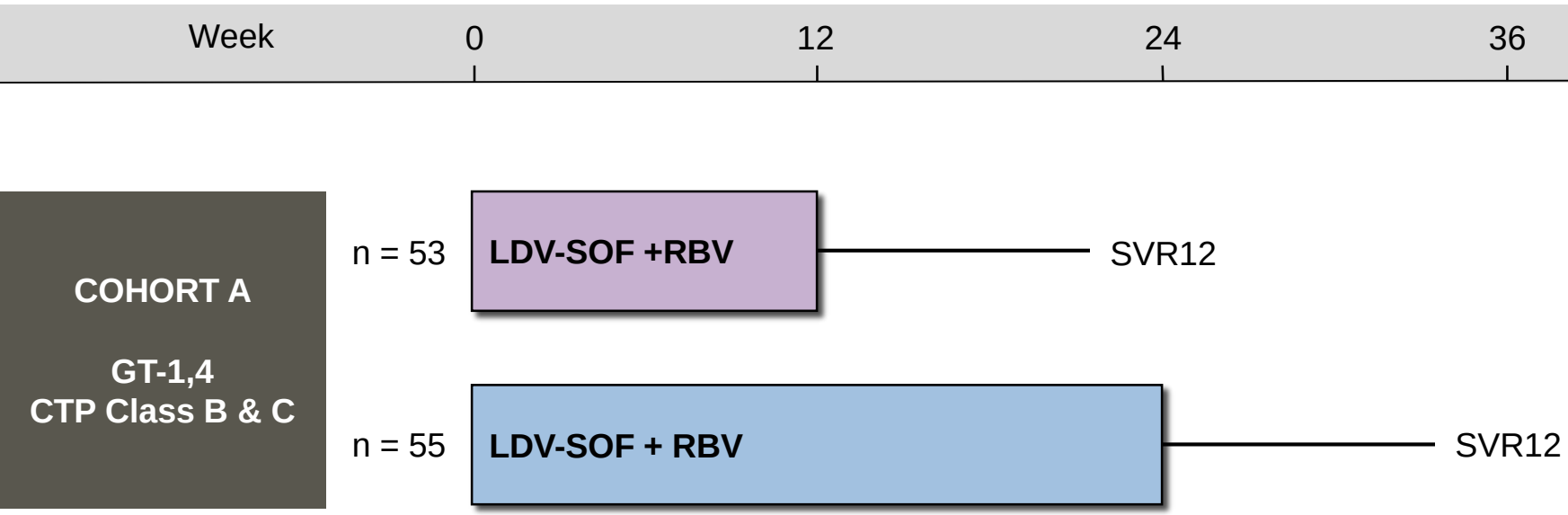
# Ledipasvir-Sofosbuvir + Ribavirin in Advanced Liver Disease
# SOLAR-1 (Cohorts A and B): Features

## SOLAR-1 (Cohorts A and B): Design

- **Design**: Phase 2, open label, randomized prospective, trial, using fixed-dose combination of ledipasvir-sofosbuvir plus ribavirin for 12 or 24 weeks in treatment-naïve and treatment-experienced patients with HCV GT 1 or 4.
- **Cohorts**
  Cohort A = cirrhosis and moderate to severe hepatic impairment who had not undergone liver transplantation
  Cohort B = post liver transplantation
- **Setting**: multicenter study in United States
- **Entry Criteria**
  - Adults with Chronic HCV Genotype 1 or 4
  - Treatment-naïve or treatment experienced
  - Total bilirubin ≤ 10 mg/dL; Creatinine clearance ≥ 40 mL/min
  - Hemoglobin ≥ 10 g/dL; Platelet count > 30,000/$mm^3$
  - Exclusion: hepatitis B or HIV coinfection or prior receipt of NS5a inhibitor
- **Primary End-Point**: SVR12

**Source: Charlton M, et al. Gastroenterology. 2015; 149:649-59.**

# Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4
# SOLAR-1 (Cohort A = Pre-transplantation): Study Design




**Abbreviations**: LDV= ledipasvir; SOF = sofosbuvir; RBV = ribavirin

**Drug Dosing**
Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily
Ribavirin: started at 600 mg/day and then escalated as tolerated up to maximum of 1200 mg/day

**Source: Charlton M, et al. Gastroenterology. 2015; 149:649-59.**

# Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4
# SOLAR-1 (Cohort A = Pre-transplantation): Baseline Characteristics

| *Cohort A* Characteristic | CTP B | | CTP C | |
|---|---|---|---|---|
| | **12-Weeks** n=30 | **24-Weeks** n=29 | **12-Weeks** n=23 | **24-Weeks** n=26 |
| Median age, years | 60 | 58 | 58 | 59 |
| Male, n (%) | 22 (73) | 18 (62) | 14 (61) | 18 (69) |
| White, n (%) | 29 (97) | 26 (90) | 21 (91) | 24 (92) |
| HCV RNA, $\log_{10}$ IU/mL | 5.9 | 5.8 | 5.6 | 5.8 |
| *IL28B* genotype CC, n (%) | 4 (13) | 5 (17) | 6 (26) | 7 (27) |
| HCV Genotype | | | | |
| 1a, n (%) | 19 (63) | 22 (76) | 15 (65) | 18 (69) |
| 1b, n (%) | 10 (33) | 7 (24) | 6 (26) | 8 (31) |
| 4, n (%) | 1 (3) | 0 | 2 (9) | 0 |
| Prior Treatment | 22 (73) | 19 (66) | 11 (48) | 18 (69) |

Abbreviations: CTP=Child-Turcotte-Pugh

**Source: Charlton M, et al. Gastroenterology. 2015; 149:649-59.**

# Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4
# SOLAR-1 (Cohort A = Pre-transplantation): Baseline Liver Status

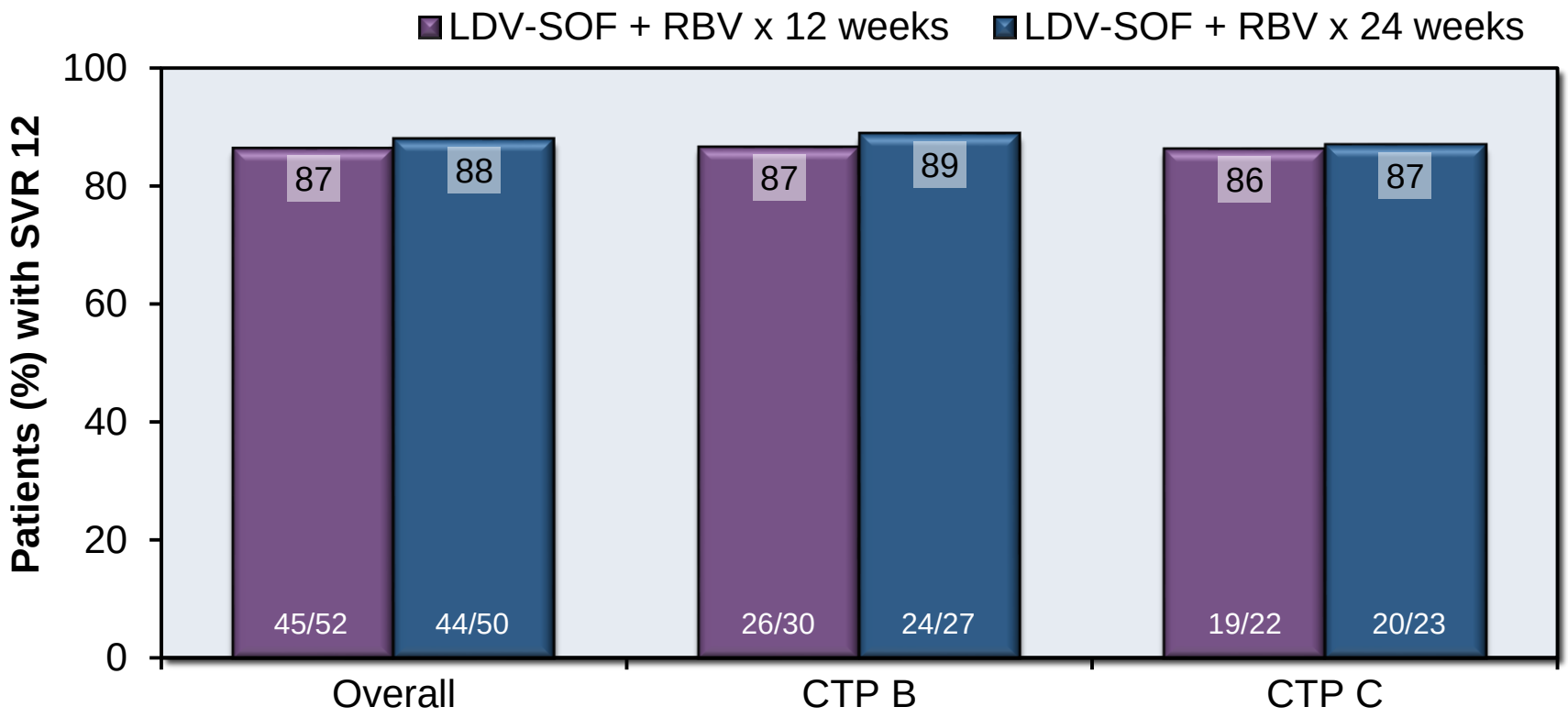
| *Cohort A* Characteristic | CTP B | | CTP C | |
|---|---|---|---|---|
| | 12-Weeks n=30 | 24-Weeks n=29 | 12-Weeks n=23 | 24-Weeks n=26 |
| Child-Turcotte-Pugh | | | | |
| Class A (5-6) | 0 | 1 (3) | 0 | 0 |
| Class B (7-9) | 27 (90) | 27 (93) | 7 (30) | 4 (15) |
| Class C (10-12) | 3 (10) | 1 (3) | 16 (70) | 22 (85) |
| MELD Score, n (%) | | | | |
| <10 | 6 (20) | 8 (28) | 0 | 0 |
| 10-15 | 21 (70) | 16 (55) | 16 (70) | 13 (50) |
| 16-20 | 3 (10) | 5 (17) | 7 (30) | 12 (46) |
| 21-25 | 0 | 0 | 0 | 1 (4) |
| Median eGFR, mL/min | 98 | 81 | 77 | 78 |
| Median platelets, x $10^3$ µL | 88 | 73 | 81 | 71 |

Abbreviations: CTP=Child-Turcotte-Pugh

**Source: Charlton M, et al. Gastroenterology. 2015; 149:649-59.**

# Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4
# SOLAR-1 (Cohort A= Pre-transplantation): Results

## SOLAR-1 Cohort A (Pre-Transplantation): SVR12 Results

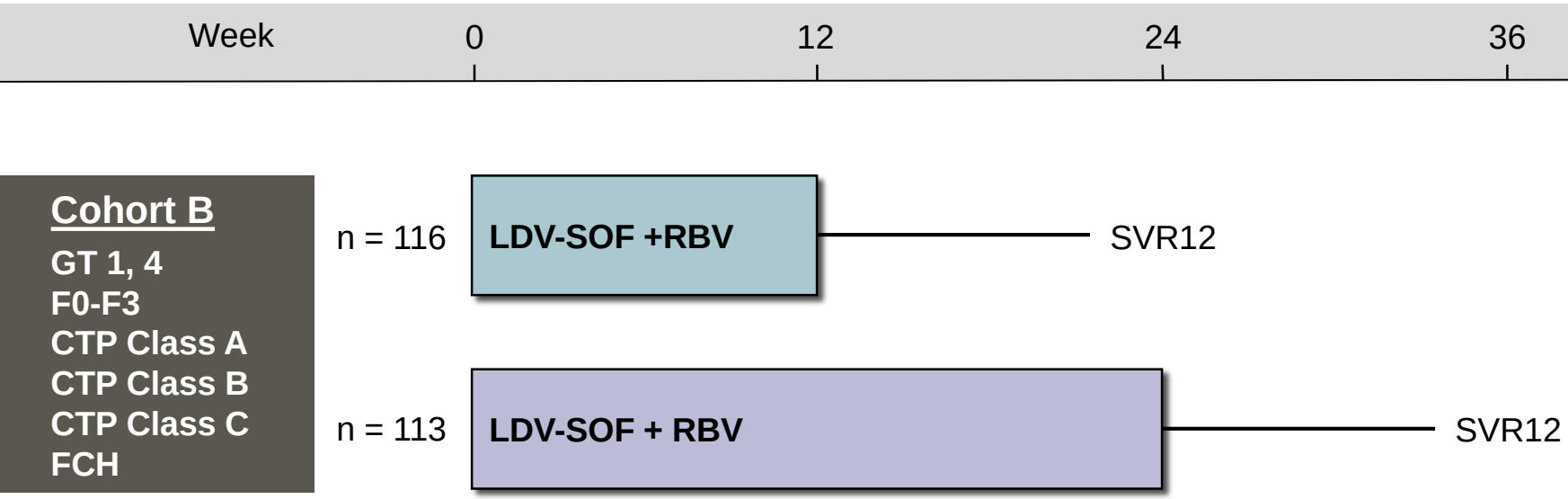



Abbreviations: CTP=Child-Turcotte-Pugh

6 subjects excluded because received transplant while on study: (2 CTP B/24 week; 1 CTP 2/12 week; 3 CTP C/24 week

**Source: Charlton M, et al. Gastroenterology. 2015; 149:649-59.**

# Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4
# SOLAR-1 (Cohort B = Post Transplant): Study Design




**Abbreviations**: CTP=Child-Turcotte-Pugh; FCH=fibrosing cholestatic hepatitis; LDV=ledipasvir; SOF=sofosbuvir; RBV=ribavirin

**Drug Dosing**

Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily

Ribavirin Dosing

- No cirrhosis; FCH: weight-based and divided bid (1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg)
- CTP B, C: started at 600 mg/day and escalated up to maximum of 1200 mg/day

**Source: Charlton M, et al. Gastroenterology. 2015; 149:649-59.**

# Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4
## SOLAR-1 (Cohort B = Post-transplantation): Baseline Characteristics

| *Cohort B* Characteristic | No Cirrhosis | | CTP A | | CTP B | | CTP C | | FCH | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 12w n=55 | 24w n=56 | 12w n=26 | 24w n=25 | 12w n=26 | 24w n=26 | 12w n=5 | 24w n=4 | 12w n=4 | 24w n=2 |
| Median age, years | 59 | 58 | 60 | 61 | 61 | 61 | 58 | 61 | 62 | 58 |
| Male, n (%) | 45 (82) | 46 (82) | 19 (73) | 22 (88) | 22 (85) | 23 (88) | 5 (100) | 4 (100) | 4 (100) | 2 (100) |
| White, n (%) | 50 (91) | 49 (88) | 21 (81) | 20 (80) | 21 (81) | 24 (92) | 4 (80) | 4 (100) | 4 (100) | 2 (100) |
| HCV RNA, $\log_{10}$ IU/mL | 6.5 | 6.4 | 6.2 | 6.7 | 6.3 | 6.2 | 6.4 | 6.3 | 6.5 | 7.1 |
| *IL28B* GT CC, n (%) | 11 (20) | 10 (18) | 7 (27) | 1 (4) | 3 (12) | 5 (19) | 12 (40) | 1 (25) | 0 | 0 |
| HCV Genotype | | | | | | | | | | |
| 1a, n (%) | 40 (73) | 40 (71) | 17 (65) | 17 (68) | 20 (77) | 18 (69) | 4 (80) | 3 (75) | 3 (75) | 2 (100) |
| 1b, n (%) | 14 (25) | 16 (29) | 9 (35) | 8 (32) | 6 (23) | 7 (27) | 1 (20) | 1 (25) | 1 (25) | 0 |
| 4, n (%) | 1 (2) | 0 | 0 | 0 | 0 | 1 (4) | 0 | 0 | 2 (9) | 0 |
| Prior Treatment | 39 (71) | 48 (86) | 22 (85) | 24 (96) | 22 (85) | 22 (85) | 4 (80) | 4 (100) | 4 (100) | 1 (50) |

Abbreviations: CTP=Child-Turcotte-Pugh

**Source: Charlton M, et al. Gastroenterology. 2015; 149:649-59.**

# Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4
## SOLAR-1 (Cohort B = Post-transplantation): Baseline Characteristics

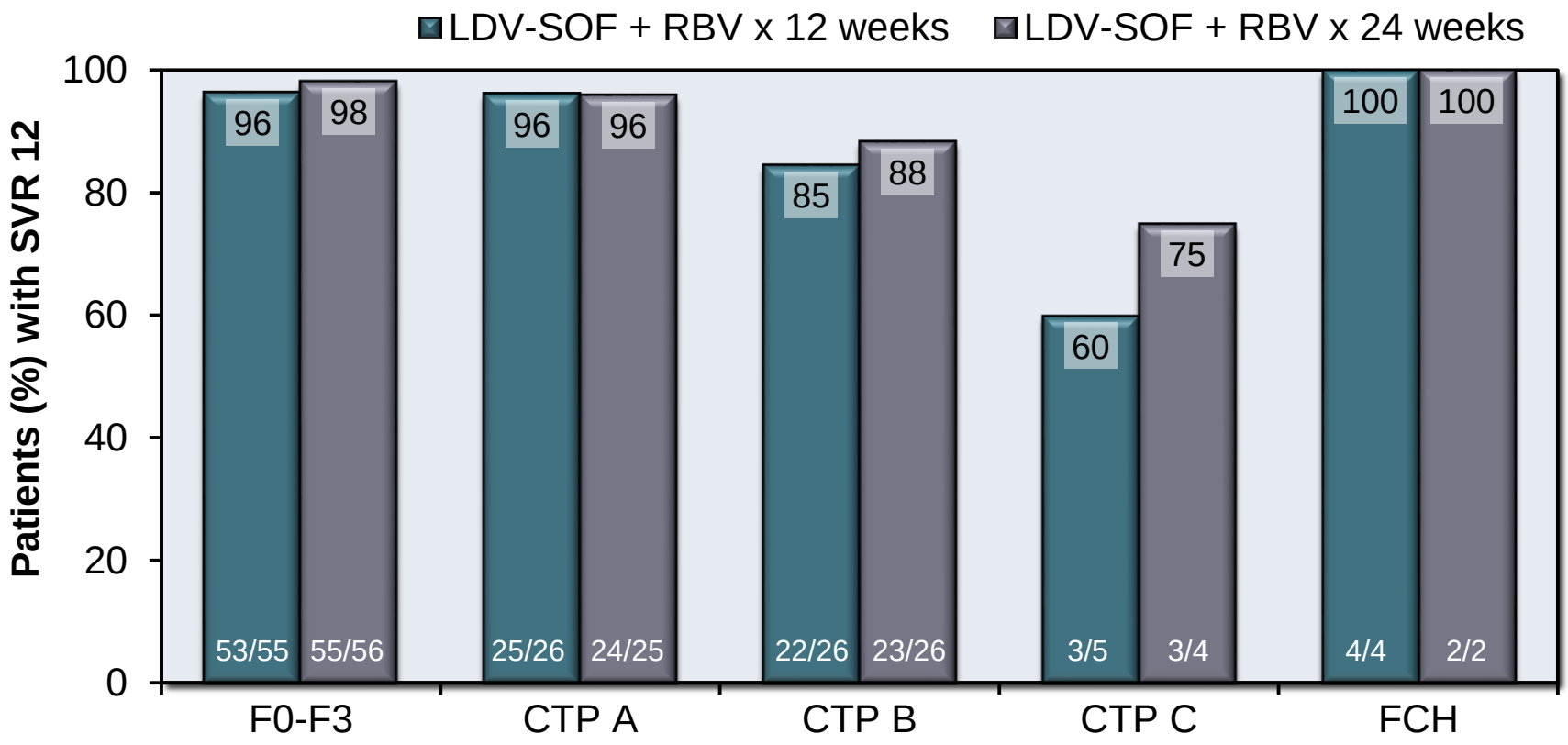
| *Cohort B* Characteristic | F0-F3 | | CTP A | | CTP B | | CTP C | | FCH | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 12w n=55 | 24w n=56 | 12w n=26 | 24w n=25 | 12w n=26 | 24w n=26 | 12w n=5 | 24w n=4 | 12w n=4 | 24w n=2 |
| Median yrs post transplant | 2.9 | 2.8 | 8.8 | 6.6 | 5.1 | 6.3 | 5.2 | 5.7 | 1.1 | 0.3 |
| Child-Turcotte-Pugh | | | | | | | | | | |
| Class A (5-6) | - | - | 25 (96) | 22 (88) | 0 | 2 (8) | 0 | 0 | - | - |
| Class B (7-9) | - | - | 1 (4) | 3 (12) | 24 (92) | 24 (92) | 2 (40) | 1 (25) | - | - |
| Class C (10-12) | - | - | 0 | 0 | 2 (8) | 0 | 3 (60) | 3 (75) | - | - |
| Meld Score, n (%) | | | | | | | | | | |
| <10 | - | - | 15 (58) | 13 (52) | 8 (31) | 5 (19) | 1 (20) | 0 | - | - |
| 10-15 | - | - | 10 (38) | 10 (40) | 14 (54) | 19 (73) | 3 (60) | 2 (50) | - | - |
| 16-20 | - | - | 1 (4) | 2 (8) | 2 (8) | 2 (8) | 1 (20) | 1 (25) | - | - |
| 21-25 | - | - | 0 | 0 | 2 (8) | 0 | 0 | 1 (25) | - | - |
| Median eGFR, mL/min | 61 | 71 | 59 | 68 | 68 | 56 | 67 | 62 | 90 | 69 |
| Median platelets x $10^3$ µL | 143 | 152 | 106 | 112 | 93 | 97 | 106 | 65 | 45 | 196 |

Abbreviations: CTP=Child-Turcotte-Pugh

**Source: Charlton M, et al. Gastroenterology. 2015; 149:649-59.**

# Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4
# SOLAR-1 (Cohort B = Post-transplantation): Results

## SOLAR-1 Cohort B (Post-Transplantation): SVR12 Results




CTP = Child-Turcotte-Pugh; FCH = fibrosing cholestatic hepatitis; 8 subjects CPT B 24 weeks

**Source: Charlton M, et al. Gastroenterology. 2015; 149:649-59.**

Hepatitis web study

# Ledipasvir-Sofosbuvir + RBV in Advanced Liver Disease SOLAR-1 (Cohorts A and B): Conclusion

**Conclusions**: “The combination of ledipasvir, sofosbuvir, and ribavirin for 12 weeks produced high rates of SVR12 in patients with advanced liver disease, including those with decompensated cirrhosis before and after liver transplantation.”

**Source: Charlton M, et al. Gastroenterology. 2015; 149:649-59.**

# Ledipasvir-Sofosbuvir in Prior Failure with Sofosbuvir-Based Regimen

Hepatitis web study

Treatment Experienced

Prior Sofosbuvir Failure

# Ledipasvir-Sofosbuvir Retreatment with HCV Genotype 1

# NIAID Retreatment

Osinusi A, et al. Ann Intern Med. 2014;161:634-8.

# Ledipasvir-Sofosbuvir Retreatment of SOF + RBV Failure in HCV GT 1

## NIAID Retreatment Study: Features

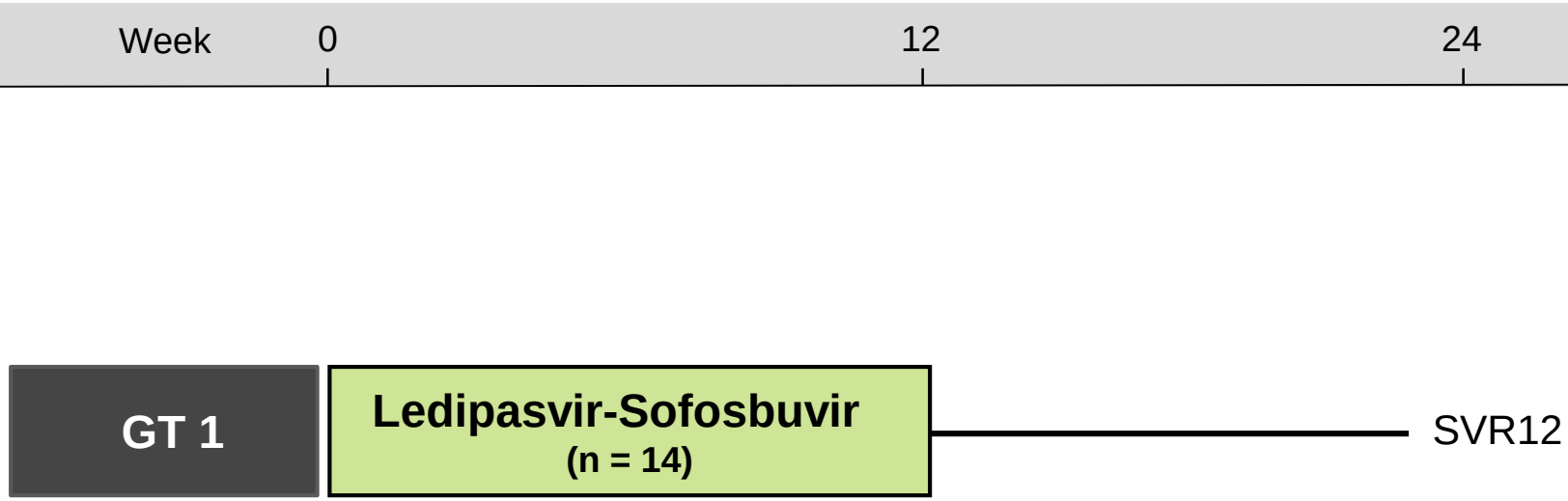
**NIAID Retreatment Trial**

- **Design**: Open-label, phase 2a, using fixed-dose combination of ledipasvir-sofosbuvir for 12 weeks in patients with GT1 HCV who previously had failed a 24-week treatment course of sofosbuvir plus ribavirin
- **Setting**: single site in United States (NIH and community clinics in DC)
- **Entry Criteria**
  - Chronic HCV Genotype 1 (n=14)
  - 18 years or older
  - Prior relapse after a 24-week treatment course of sofosbuvir plus ribavirin
- **Primary End-Point**: SVR12

**Source: Osinusi A, et al. Ann Intern Med. 2014;161:634-8.**

# Ledipasvir-Sofosbuvir Retreatment of SOF + RBV Failure in HCV GT 1

## NIAID Retreatment Study: Design




**Drug Dosing**

Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily

**Source: Osinusi A, et al. Ann Intern Med. 2014;161:634-8.**

# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Experienced HCV GT 1
## NIAID Retreatment Study: Baseline Characteristics

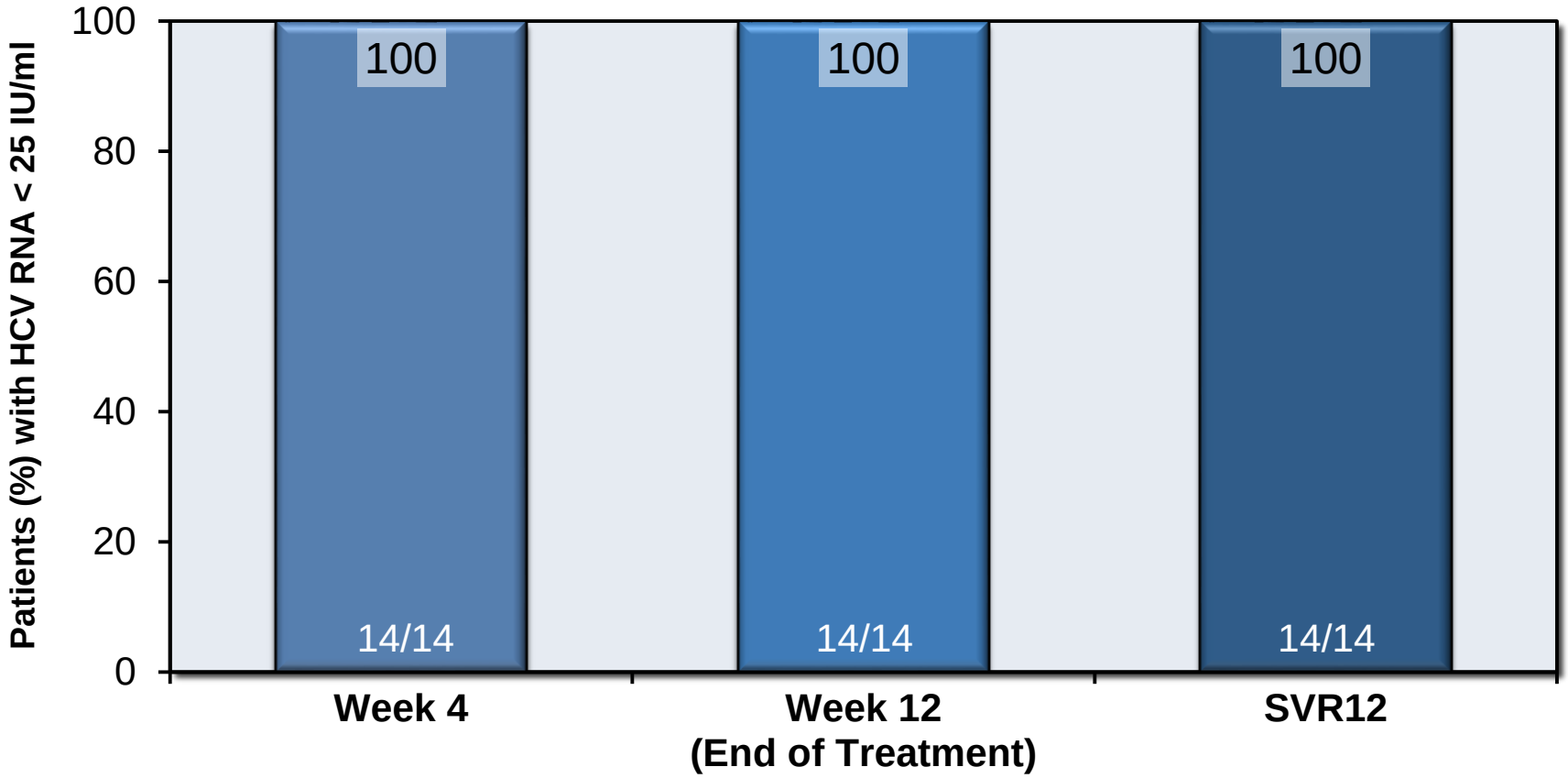
| Baseline Characteristic | Ledipasvir-Sofosbuvir (n=14) |
|---|---|
| Age, median (range) | 59 (48-72) |
| Male, n (%) | 13 (93) |
| Black race, n (%) | 13 (93) |
| Body Mass Index (BMI) ≥30 kg/m$^2$, n (%) | 5 (36) |
| IL28B genotype CC, n (%) | 2 (14) |
| Knodell Histology Activity Index score, n (%)<br>0-1<br>3-4 | <br>7 (50)<br>7 (50) |
| HCV GT-1 Subtype<br>1a<br>1b | <br>8 (57)<br>6 (43) |
| NS5B S282T Mutation | 1 (7) |
| Median baseline HCV RNA, $\log_{10}$ IU/ml (range) | 6.31 (5.50-6.76) |

**Source: Osinusi A, et al. Ann Intern Med. 2014;161:634-8.**

Hepatitis web study

# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-experienced HCV GT 1
# NIAID Retreatment Study: Results

## NIAID Retreatment: Virologic Response




Source: Osinusi A, et al. Ann Intern Med. 2014;161:634-8.

# Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-experienced HCV GT 1
## NIAID Retreatment Study: Conclusions

**Conclusions**: “The fixed-dose combination of sofosbuvir plus ledipasvir was efficacious in a small cohort of patients with HCV GT-1 that relapsed after sofosbuvir plus ribavirin therapy, even in the setting of advanced liver disease. Larger studies are needed to confirm these preliminary efficacy results.”

**Source: Osinusi A, et al. Ann Intern Med. 2014;161:634-8.**

Treatment Experienced

Prior Sofosbuvir Failure

# Ledipasvir-Sofosbuvir + RBV in Sofosbuvir-Experienced HCV GT1

# Retreatment of Sofosbuvir Failures

Wyles D, et al. Hepatology. 2015;61:1793-7.

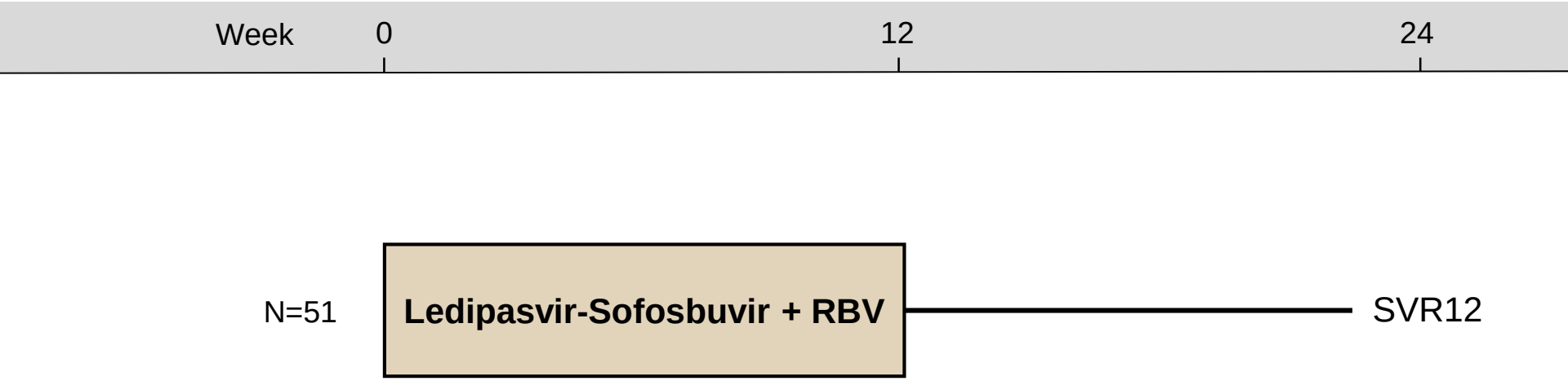
# LDV-SOF + RBV in Sofosbuvir-Experienced GT 1 HCV
## Study Features

- **Design**: Open-label, phase 2 retreatment study examining the efficacy of ledipasvir-sofosbuvir plus ribavirin in patients who did not achieve SVR with sofosbuvir-based therapy in one of 5 clinical trials.
- **Setting**: 24 study locations in United States
- **Entry Criteria**
  - Chronic HCV Genotype 1
  - Failed prior combination therapy with sofosbuvir in phase 2/3 clinical trials
  - Compensated cirrhosis allowed
  - Cirrhosis defined as FibroTest >0.75 and APRI > 2
- **Primary End-Point**: SVR12
- **Secondary End-Points**: Treatment discontinuation, adverse events, laboratory abnormalities

**Source: Wyles D, et al. Hepatology. 2015;61:1793-7.**

# LDV-SOF + RBV in Sofosbuvir-Experienced GT 1 HCV

## Study Features




**Abbreviations**: LDV = ledipasvir; SOF = sofosbuvir; PEG = peginterferon; RBV = ribavirin

**Drug Dosing**

Ledipasvir-sofosbuvir (90/400 mg): fixed-dose combination; one pill once daily

Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

**Source: Wyles D, et al. Hepatology. 2015;61:1793-7.**

# LDV-SOF + RBV in Sofosbuvir-Experienced GT 1 HCV
## Baseline Characteristics

| Patient Characteristics | Ledipasvir-Sofosbuvir + RBV x 12 wks N = 51 |
|---|---|
| Mean age, years (SD) | 54 (8.7) |
| Male sex, n (%) | 31 (61) |
| Race, n (%)<br>White<br>Black | <br>43 (84)<br>8 (16) |
| Mean body mass index, kg/m$^2$ (SD) | 30.4 (5.4) |
| Cirrhosis | 14 (27) |
| Genotype, n (%)<br>1a<br>1b<br>3a | <br>30 (59)<br>20 (39)<br>1 (2) |
| IL28b, n (%)<br>CC<br>CT<br>TT | <br>4 (8)<br>33 (65)<br>14 (27) |

Abbreviation: SD, standard deviation

**Source: Wyles D, et al. Hepatology. 2015;61:1793-7.**

Hepatitis web study

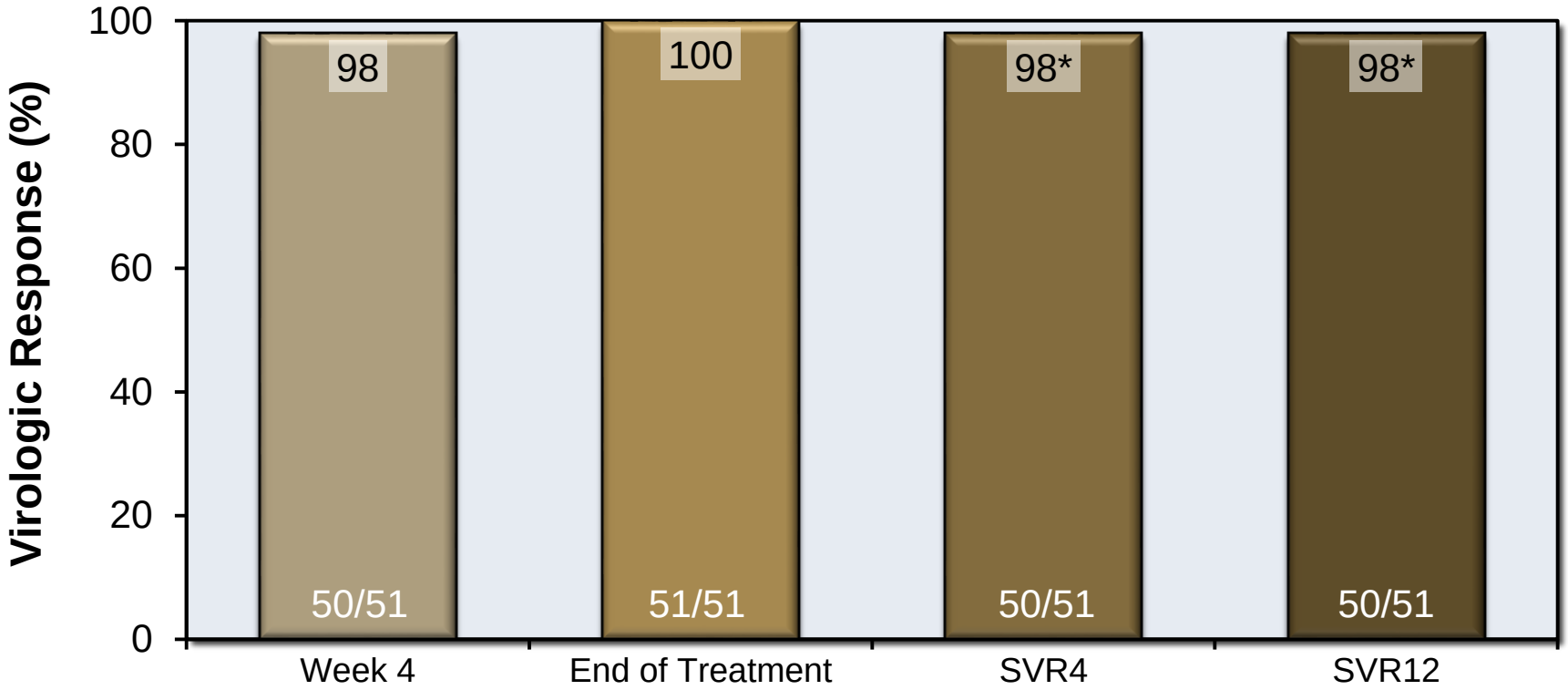
# LDV-SOF + RBV in Sofosbuvir-Experienced GT 1 HCV
# Baseline Characteristics

| Patient Characteristics | Ledipasvir-Sofosbuvir + RBV x 12 wks<br>N = 51 |
|---|---|
| **Previous HCV treatment regimen (by Sofosbuvir exposure in weeks), n (%)** | |
| Sofosbuvir + Peginterferon + Ribavirin | |
| For 4 weeks | 1 (2) |
| For 12 weeks | 22 (43) |
| For 24 weeks | 2 (4) |
| Sofosbuvir + Ribavirin | |
| For 12 weeks | 6 (12) |
| For 24 weeks | 14 (27) |
| Without Sofosbuvir | 6 (12) |
| **Outcome with previous treatment** | |
| Virologic Failure | 47 (92) |
| Discontinuation from Adverse Events | 2 (4) |
| Study terminated by sponsor | 2 (4) |

**Source: Wyles D, et al. Hepatology. 2015;61:1793-7.**

# LDV-SOF + RBV in Sofosbuvir-Experienced GT 1 HCV
# Study Results

## Virologic Response at Week 4, End-of-Treatment and SVR12, 24




Abbreviations: LDV= ledipasvir; SOF = sofosbuvir; RBV = ribavirin

* The one patient who relapsed found to have genotype 3a infection and was enrolled erroneously.

**Source: Wyles D, et al. Hepatology. 2015;61:1793-7.**

Hepatitis web study

# LDV-SOF + RBV in Sofosbuvir-Experienced GT 1 HCV
## Adverse Events

| Event | **Ledipasvir-Sofosbuvir + Ribavirin** (n=51) |
|---|---|
| Discontinuation due to adverse event | 1 (2%) |
| Serious adverse event | 2 (4%) |
| Fatigue | 13 (25%) |
| Headache | 11 (22%) |
| Diarrhea | 7 (14%) |
| Rash | 6 (12%) |
| Insomnia | 6 (12%) |
| Nausea | 5 (10%) |
| Constipation | 4 (8%) |

**Source: Wyles D, et al. Hepatology. 2015;61:1793-7.**

# LDV-SOF + RBV in Sofosbuvir-Experienced GT 1 HCV
## Conclusions

**Conclusions**: “Twelve weeks of ledipasvir-sofosbuvir plus ribavirin was an effective and safe treatment for patients who have not achieved SVR with earlier regimens that included sofosbuvir.”

**Source: Wyles D, et al. Hepatology. 2015;61:1793-7.**

# Ledipasvir-Sofosbuvir in Patients with HCV-HIV Coinfection

Hepatitis web study

Treatment Naïve and Treatment Experienced

HIV Coinfection

# Ledipasvir-Sofosbuvir in GT-1 and HIV Coinfection
# NIAID ERADICATE Trial

Osinusi A, et al. JAMA. 2015;313:1232-9.

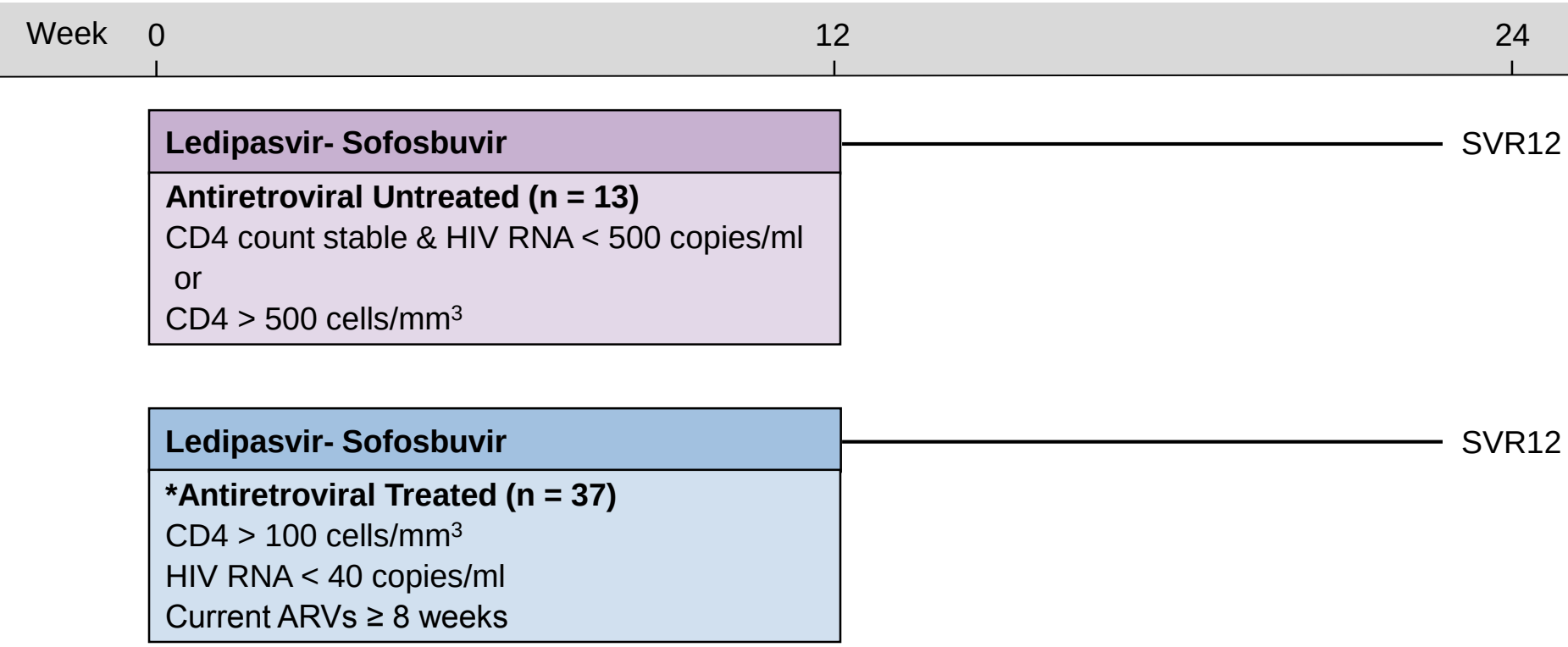
# Ledipasvir-Sofosbuvir in GT1 with HIV Coinfection
## NIAID ERADICATE Trial: Features

**NIAID ERADICATE Trial**

- **Design**: Open-label, phase 2, using fixed dose combination of ledipasvir-sofosbuvir for 12 or weeks in treatment-naïve GT 1 and HIV coinfection
- **Setting**: one center in United States
- **Entry Criteria**
  - Chronic HCV Genotype 1
  - HCV Treatment Naïve
- **Patient Characteristics (range in different treatment arms)**
  - N = 50 adult patients
  - Cohort A: Antiretroviral Untreated
  - Cohort B: Antiretroviral Treated
  - Fibrosis stage 0-3 (patients with cirrhosis excluded)
- **End-Points**: Primary = SVR12; safety and tolerability

**Source: Osinusi A, et al. JAMA. 2015;313:1232-9.**

# Ledipasvir-Sofosbuvir in GT1 with HIV Coinfection
## NIAID ERADICATE Trial: Study Design




**Drug Dosing**: Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily

***Antiretrovirals**: tenofovir-emtricitabine with one or more of following: efavirenz, rilpivirine, or raltegravir

**Source: Osinusi A, et al. JAMA. 2015;313:1232-9.**

# Ledipasvir-Sofosbuvir in GT1 with HIV Coinfection
# NIAID ERADICATE Trial: Baseline Characteristics

| Baseline Characteristic | Ledipasvir-Sofosbuvir | |
|---|---|---|
| | ARV Untreated (n = 13) | ARV Treated (n = 37) |
| Mean age, years | 59 | 58 |
| Male, n (%) | 7 (54) | 30 (81) |
| African American, n (%) | 10 (77) | 23 (88) |
| Mean BMI, $kg/m^2$ | 26 | 26 |
| GT 1a, n (%) | 9 (75) | 30 (81) |
| HAI Fibrosis Stage 3, n (%) | 5 (38) | 8 (22) |
| Mean HCV RNA, $log_{10}$ IU/mL | 6.07 | 5.97 |
| Median CD4 Count (cells/$mm^3$) | 687 | 576 |

**Source: Osinusi A, et al. JAMA. 2015;313:1232-9.**

# Ledipasvir-Sofosbuvir in GT1 with HIV Coinfection
# NIAID ERADICATE Trial: Antiretroviral Regimens

| Antiretroviral Agent | Antiretroviral Received (n = 37) |
|---|---|
| Tenofovir-emtricitabine | 37 (100) |
| Efavirenz | 15 (41) |
| Raltegravir | 10 (27) |
| Rilpivirine | 8 (21) |
| Rilpivirine + Raltegravir | 3 (8) |
| Efavirenz + Raltegravir | 1 (3) |

**Source: Osinusi A, et al. JAMA. 2015;313:1232-9.**

# Sofosbuvir-Ledipasvir in GT1 with HIV Coinfection
# NIAID ERADICATE Trial: Results

| HCV RNA < LLOQ, % | ARV Untreated (n=13) | ARV Treated (n=37) |
|---|---|---|
| Week 4 | 100 (n =13) | 100 (n=37) |
| Week 8 | 100 (n =13) | 100 (n=37)) |
| Week 12 (EOT) | 100 (n =13) | 100 (n=37) |
| SVR 4 | 100 (n =13) | 97 (n=36) |
| SVR 8 | 100 (n =13) | 97 (n=36) |
| SVR 12 | 100 (n =13) | 97 (n=36) |

**Source: Osinusi A, et al. JAMA. 2015;313:1232-9.**

# Sofosbuvir-Ledipasvir in GT1 with HIV Coinfection
# NIAID ERADICATE Trial: Conclusions

**Conclusions and Relevance**: “In this open-label, uncontrolled, pilot study enrolling patients co-infected with HCV genotype 1 and HIV, administration of an oral combination of ledipasvir and sofosbuvir for 12 weeks was associated with high rates of SVR after treatment completion. Larger studies that also include patients with cirrhosis and lower CD4 T-cell counts are required to understand if the results of this study generalize to all patients co-infected with HCV and HIV.”

**Source: Osinusi A, et al. JAMA. 2015;313:1232-9.**

# Ledipasvir-Sofosbuvir in GT1 or GT4 and HIV Coinfection

# ION-4

Naggie S, et al. N Engl J Med 2015;378:705-13.

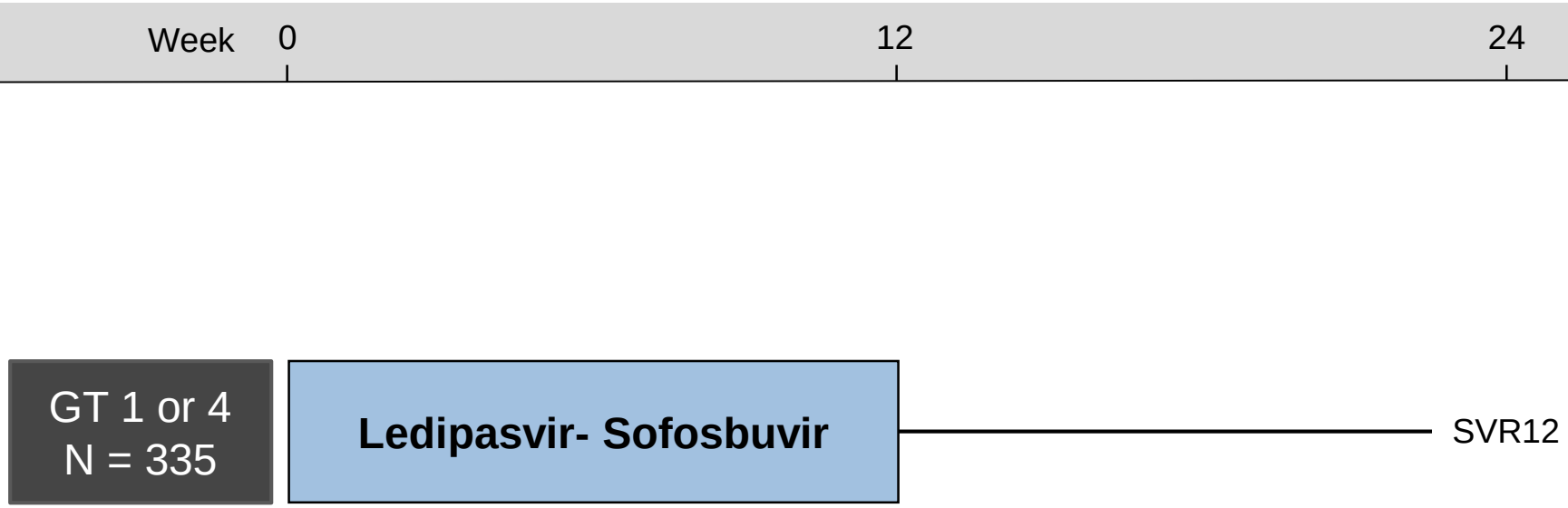
# Ledipasvir-Sofosbuvir in GT1 or GT4 with HIV Coinfection
# ION-4 Trial: Features

## ION-4 Trial

- **Design**: Open-label, single group, phase 3 trial, using ledipasvir-sofosbuvir for 12 weeks in treatment-naïve or treatment-experienced patients with GT 1 or 4 and HIV coinfection
- **Setting**: multicenter in United States, Canada, New Zealand
- **Entry Criteria**
  - Chronic HCV Genotype 1 or 4
  - Treatment-naïve or treatment experienced
  - Noncirrhotic or compensated cirrhosis
  - Platelet count > 50,000/$mm^3$, hemoglobin ≥10 mg/dL, CrCl≥60 mL/min
  - Stable ARV with HIV RNA < 50 copies/ml and CD4 count > 100 cells/$mm^3$
  - ARV regimens: tenofovir-emtricitabine plus either efavirenz, rilpivirine, or raltegravir
- **End-Points**: Primary = SVR12; safety and tolerability

**Source: Naggie S, et al. N Engl J Med 2015;378:705-13.**

# Ledipasvir-Sofosbuvir in GT1 or GT4 with HIV Coinfection
# ION-4 Trial: Study Design




**Drug Dosing**: Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily

**Antiretrovirals allowed**: tenofovir-emtricitabine plus either efavirenz, rilpivirine, or raltegravir

**Source: Naggie S, et al. N Engl J Med 2015;378:705-13.**

# Ledipasvir-Sofosbuvir in GT1 or GT4 with HIV Coinfection ION-4 Trial: Baseline Characteristics

| Baseline Characteristic | Ledipasvir-Sofosbuvir (n = 335) |
|---|---|
| Mean age, years | 52 |
| Male, n (%) | 276 (82) |
| African American, n (%) | 115 (34) |
| Hispanic or Latino, n (%) | 56 (17) |
| Mean BMI, $kg/m^2$ | 26 |
| IL28B CC, n (%) | 81 (24) |
| GT 1 (%) | 327 (98) |
| HCV treatment experienced, n (%) | 185 (55) |
| Cirrhosis, n (%) | 67 (20) |
| Mean HCV RNA, $log_{10}$ IU/mL | 6.7 ± 0.6 |
| Median CD4 Count, cells/$mm^3$ (range) | 628 (100-2069) |

**Source: Naggie S, et al. N Engl J Med 2015;378:705-13.**

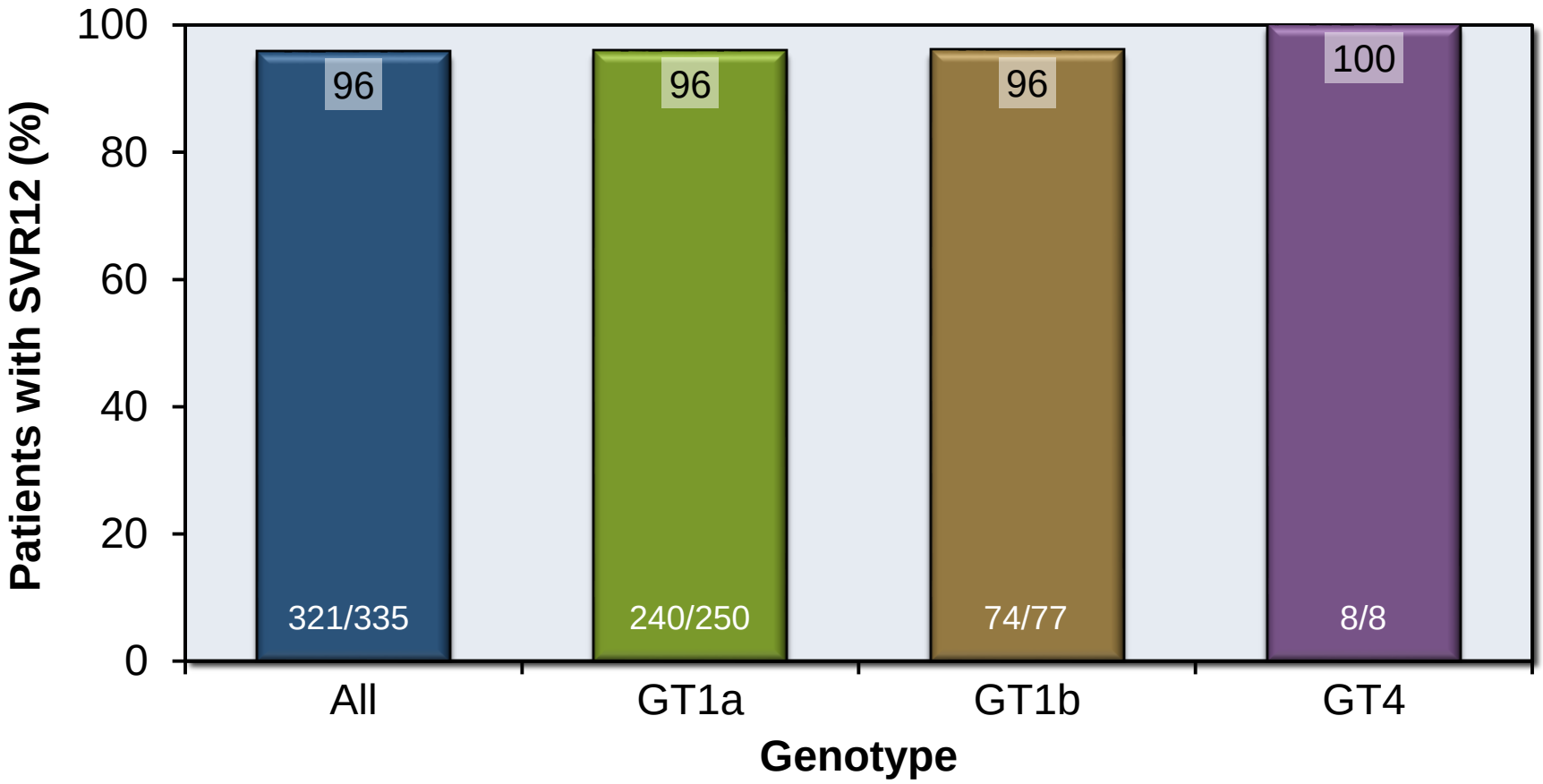
# Ledipasvir-Sofosbuvir in GT1 or GT4 with HIV Coinfection
# ION-4 Trial: Antiretroviral Regimens

| ION-4: HIV Antiretroviral Regimen | |
|---|---|
| **Antiretroviral Agent** | **Antiretroviral Received** (n = 335) |
| Tenofovir-emtricitabine-efavirenz | 160 (48) |
| Tenofovir-emtricitabine-rilpivirine | 29 (9) |
| Tenofovir-emtricitabine + Raltegravir | 146 (44) |

**Source: Naggie S, et al. N Engl J Med 2015;378:705-13.**

# Ledipasvir-Sofosbuvir in GT1 or GT4 with HIV Coinfection
# ION-4 Trial: Results

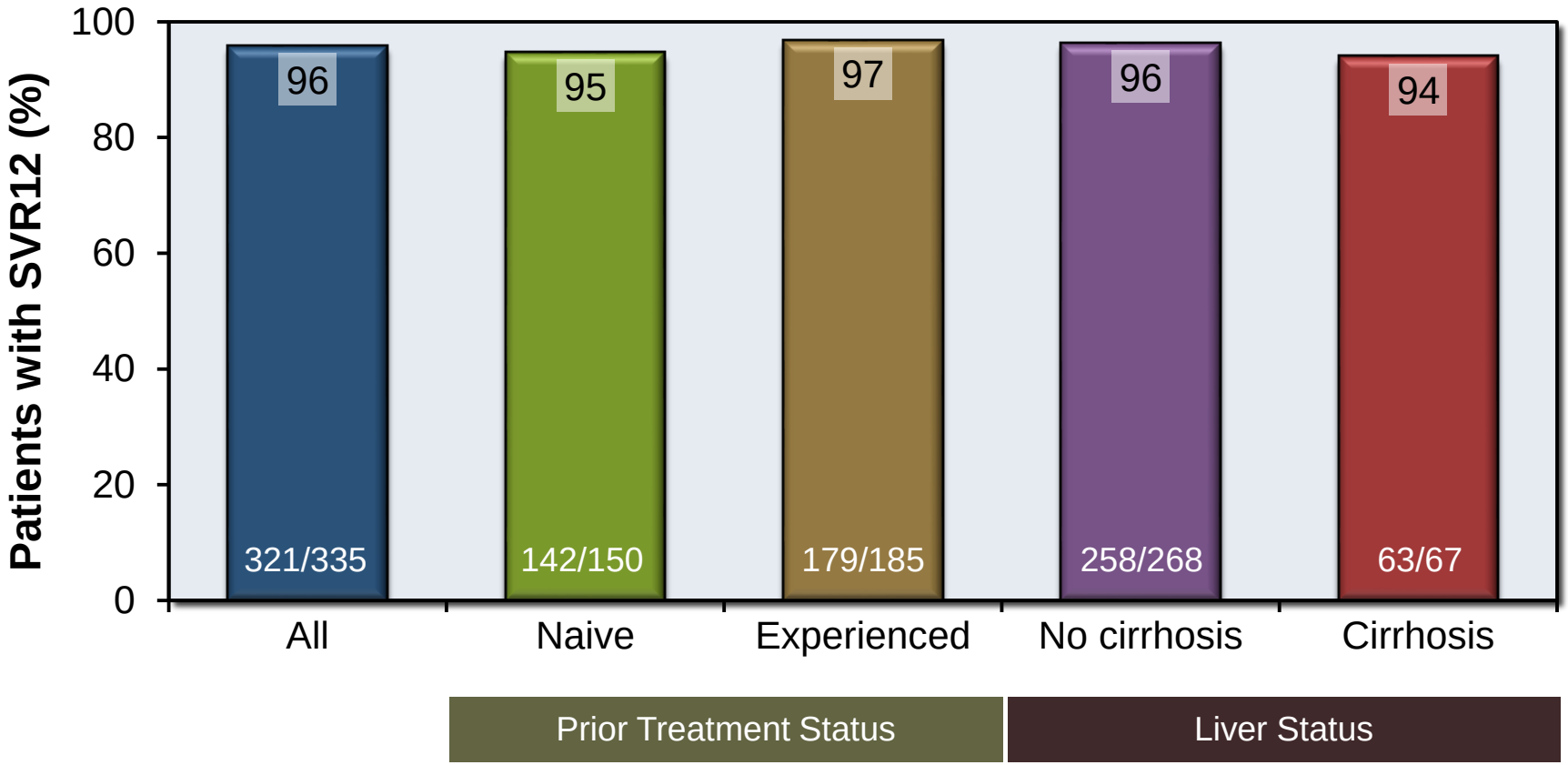
## ION-4: SVR12 Results by Genotype




Source: Naggie S, et al. N Engl J Med 2015;378:705-13.

# Ledipasvir-Sofosbuvir in GT1 or GT4 with HIV Coinfection
# ION-4 Trial: Results

## ION-4: SVR12 Results by Prior Treatment Status and Liver Status




Source: Naggie S, et al. N Engl J Med 2015;378:705-13.

Hepatitis web study

# Ledipasvir-Sofosbuvir in GT1 or GT4 with HIV Coinfection ION-4 Trial: Adverse Effects

| Event | Ledipasvir-Sofosbuvir (n = 335) |
|---|---|
| Discontinuation due to adverse event | 0 |
| Grade 3-4 Adverse Event | 14 (4%) |
| Serious Adverse Event | 8 (2%) |
| Headache | 83 (25%) |
| Fatigue | 71 (21%) |
| Diarrhea | 36 (11%) |
| Nausea | 33 (10%) |
| Arthralgia | 22 (7%) |
| Upper respiratory tract infection | 18 (5%) |
| Vomiting | 14 (4%) |
| Muscle spasms | 11 (3%) |

**Source: Naggie S, et al. N Engl J Med 2015;378:705-13.**

# Ledipasvir-Sofosbuvir in GT1 or GT4 with HIV Coinfection ION-4 Trial: Conclusions

**Conclusions**: “Ledipasvir and sofosbuvir for 12 weeks provided high rates of sustained virologic response in patients coinfected with HIV-1 and HCV genotype 1 or 4.”

**Source: Naggie S, et al. N Engl J Med 2015;378:705-13.**

This slide deck is from the University of Washington's *Hepatitis C Online* and *Hepatitis Web Study* projects.

Hepatitis C Online

www.hepatitisc.uw.edu

Hepatitis Web Study

http://depts.washington.edu/hepstudy/

Funded by a grant from the Centers for Disease Control and Prevention.

Hepatitis web study