HEPATITIS WEB STUDY HEPATITIS C ONLINE

# Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir (*Viekira Pak*)

Prepared by: Sophie Woolston, MD and David H. Spach, MD
Last Updated: August 24, 2017

Hepatitis web study

## OMBITASVIR-PARITAPREVIR-RITONAVIR + DASABUVIR

# Background and Dosing

# Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir (*Viekira Pak*)

- **Approval Status**: FDA approval on December 19, 2014
- **Indication:** Genotype 1 chronic HCV infection, including compensated cirrhosis
- **Class & Mechanism**
  - Ombitasvir (ABT-267): NS5A inhibitor
  - Paritaprevir (ABT-450): NS3/4A serine protease inhibitor
  - Ritonavir: HIV protease inhibitor used as pharmacologic booster
  - Dasabuvir (ABT-333): Non-nucleoside NS5B polymerase inhibitor
- **Tablets:** Ombitasvir-Paritaprevir-Ritonavir (fixed dose 12.5/75/50 mg)
  Dasabuvir: 250 mg
- **Dose**: 2 tablets Ombitasvir-Paritaprevir-Ritonavir once daily (am) with food plus Dasabuvir 1 tablet twice daily with food
- **Adverse Effects (AE)**: fatigue, pruritus, and insomnia
- **Cost:** **$**83,319 for 12-week course

**Source: *Viekira Pak* Prescribing Information. AbbVie Inc.**

# Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir (*Viekira Pak*)
## Indications and Usage

| Patient Populations | Treatment* | Duration |
|---|---|---|
| GT1a, without cirrhosis | Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir + Ribavirin | 12 weeks |
| GT1a, with cirrhosis | Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir + Ribavirin | 24 weeks** |
| GT1b, without cirrhosis | Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir | 12 weeks |
| GT1b, with cirrhosis | Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir + Ribavirin | 12 weeks |

*Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.

**Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir + ribavirin for 12 weeks may be considered for some patients based on prior treatment history

**Source: *Viekira Pak* Prescribing Information. AbbVie Inc.**

# Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir (*Viekira Pak*) Contraindications

- Decompensated cirrhosis
- Concomitantly taking medications that are:
  - highly dependent on CYP3A for clearance,
  - strong inducers of CYP3A and CYP2C8, or
  - strong inhibitors of CYP2C8
- Known hypersensitivity to ritonavir

**Source: *Viekira Pak* Prescribing Information. AbbVie Inc.**

# Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir (*Viekira Pak*) Estimated Medication Cost for Therapy

| Estimated Cost of Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir | |
|---|---|
| **Duration of Treatment** | **Estimated Cost*** |
| 12 Weeks (without ribavirin) | $83,319 |
| 24 Weeks (without ribavirin) | Unknown |

*Estimated cost based on Wholesaler Acquisition Cost in United States

| Drugs Contraindicated for Use with Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir | |
|---|---|
| **Drug Class** | **Drug(s) within Class that are Contraindicated** |
| Alpha1-adrenoreceptor antagonist | Alfuzosin HCL |
| Anticonvulsants | Carbamazepine, phenytoin, phenobarbital |
| Antihyperlipidemic agent | Gemfibrozil |
| Antimycobacterial | Rifampin |
| Ergot derivatives | Ergotamine, dihydroergotamine, ergonovine, methylergonovine |
| Ethinyl estradiol-containing products | Ethinyl estradiol-containing medications such as combined oral contraceptives |
| Herbal Product | St. John's Wort *(Hypericum perforatum)* |
| HMG-CoA Reductase | Lovastatin, simvastatin |
| Neuroleptics | Pimozide |
| Non-nucleoside reverse transcriptase inhibitor | Efavirenz |
| Phosphodiesterase-5 (PDE5) inhibitor | Sildenafil when dosed as *Revatio* for the treatment of pulmonary arterial hypertension (PAH) |
| Sedatives/hypnotics | Triazolam; Orally administered midazolam |

**Source: *Viekira Pak* Prescribing Information. AbbVie Inc.**

| Drugs Contraindicated for Use with Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir | | |
|---|---|---|
| **Drug Class** | **Drug(s) within Contraindicated Class** | **Clinical Comments** |
| Alpha1-adrenoreceptor antagonist | Alfuzosin HCL | Potential for hypotension. |
| Anticonvulsants | Carbamazepine, phenytoin, phenobarbital | Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of activity for HCV therapy |
| Antihyperlipidemic agent | Gemfibrozil | Increase in dasabuvir exposures by 10-fold which may increase the risk of QT prolongation. |
| Antimycobacterial | Rifampin | Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of HCV therapeutic activity. |
| Ergot derivatives | Ergotamine, dihydroergotamine, ergonovine, methylergonovine | Acute ergot toxicity characterized by vasospasm and tissue ischemia has been associated with co-administration of ritonavir and ergonovine, ergotamine, dihydroergotamine, or methylergonovine. |
| Ethinyl estradiol-containing products | Ethinyl estradiol-containing medications such as combined oral contraceptives | Potential for ALT elevations |
| Herbal Product | St. John's Wort *(Hypericum perforatum)* | Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of HCV therapeutic activity. |
| HMG-CoA Reductase | Lovastatin, simvastatin | Potential for myopathy including rhabdomyolysis. |
| Neuroleptics | Pimozide | Potential for cardiac arrhythmias. |
| Non-nucleoside reverse transcriptase inhibitor | Efavirenz | Co-administration of efavirenz based regimens with paritaprevir, ritonavir plus dasabuvir was poorly tolerated and resulted in liver enzyme elevations. |
| Phosphodiesterase-5 (PDE5) inhibitor | Sildenafil when dosed as REVATIO for the treatment of pulmonary arterial hypertension (PAH) | There is increased potential for sildenafil-associated adverse events such as visual disturbances, hypotension, priapism, and syncope. |
| Sedatives/hypnotics | Triazolam<br>Orally administered midazolam | Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with VIEKIRA PAK may cause large increases in the concentration of these benzodiazepines. The potential exists for serious and/or life threatening events such as prolonged or increased sedation or respiratory depression. |

**Source: *Viekira Pak* Prescribing Information. AbbVie Inc.**

# Summary of Key Phase 3 Studies

- **SAPPHIRE-I**: GT1 (a & b), Treatment-Naïve, without cirrhosis
  - Ombitasvir-paritaprevir-ritonavir + dasabuvir + RBV x 12 weeks
- **PEARL-III:** GT1b, Treatment-Naïve, without cirrhosis
  - Ombitasvir-paritaprevir-ritonavir + dasabuvir +/- RBV x 12 weeks
- **PEARL-IV:** GT1a, Treatment-Naïve, without cirrhosis
  - Ombitasvir-paritaprevir-ritonavir + dasabuvir +/- RBV x 12 weeks
- **SAPPHIRE-II**: GT1 (a & b), Treatment-Experienced, without cirrhosis
  - Ombitasvir-paritaprevir-ritonavir + dasabuvir + RBV x 12 weeks
- **PEARL-II:** GT1b, Treatment-Experienced, without cirrhosis
  - Ombitasvir-paritaprevir-ritonavir + dasabuvir +/- RBV x 12 week
- **TURQUOISE II:** GT1 (a & b), Treatment-Naïve & Experienced, with cirrhosis
  - Ombitasvir-paritaprevir-ritonavir + dasabuvir + RBV x 12 or 24 weeks
- **UOISE II:** GT1b, Treatment-Naïve & Experienced, with cirrhosis
  - Ombitasvir-paritaprevir-ritonavir + dasabuvir x 12 weeks

# Summary of Key Studies in Special Populations

- **TURQUOISE-I:** GT1 (a & b), HIV Coinfection, Treatment Naïve/Experienced
  - Ombitasvir-paritaprevir-ritonavir + dasabuvir + RBV x 12 or 24 weeks
- **CORAL-I:** GT1 (a & b), Post-Liver Transplantation Recipients
  - Ombitasvir-paritaprevir-ritonavir + dasabuvir + RBV x 24 weeks

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir in Treatment-Naïve Patients

Treatment Naïve

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir + RBV in GT1

# SAPPHIRE-I

Feld JJ, et al. N Engl J Med. 2014;370:1594-1603.

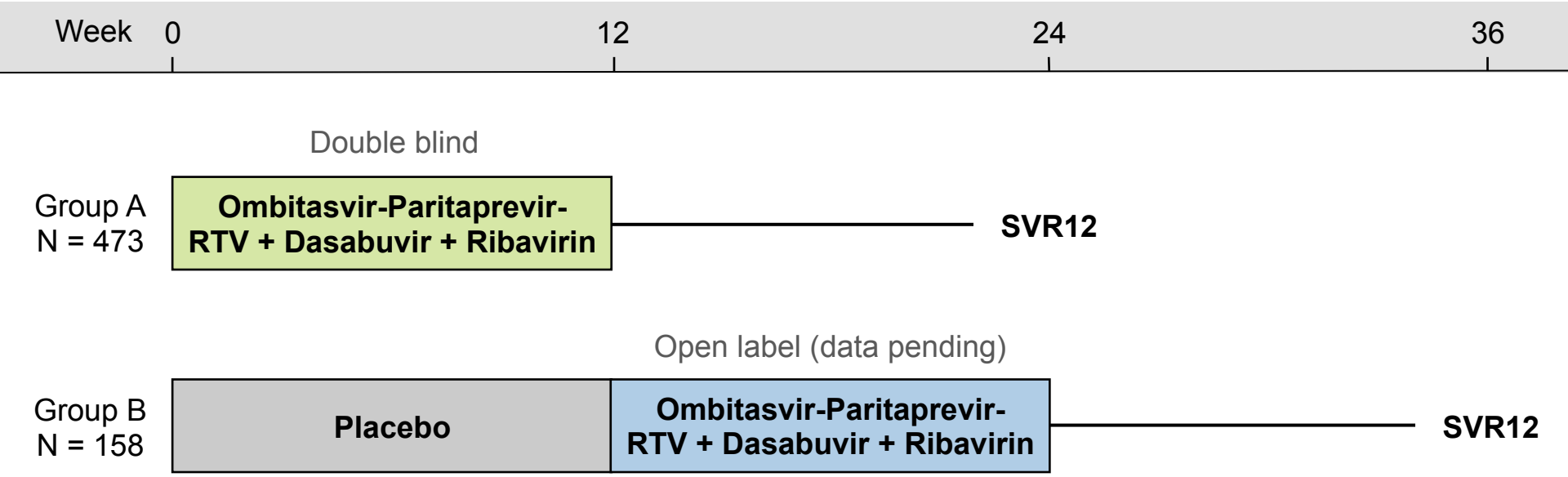
# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir + Ribavirin in GT1
# SAPPHIRE-I Study: Design

## SAPPHIRE-I: Features

- **Design**: Phase 3, randomized, double-blind, placebo-controlled trial evaluating safety and efficacy of ombitasvir-paritaprevir-ritonavir and dasabuvir + ribavirin for 12 weeks in treatment-naïve patients with chronic hepatitis C virus genotype 1
- **Setting**: International at 79 sites in North America, Europe, and Australia
- **Entry Criteria**
  - Chronic HCV infection with genotype 1a or 1b
  - Treatment-naïve
  - Age 18-70
  - Plasma HCV RNA greater than 10,000 IU/mL
  - Absence of cirrhosis
  - Absence of coinfection with HBV or HIV
- **Primary End-Point**: SVR12

**Source: Feld JJ, et al. N Engl J Med. 2014;370:1594-1603.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir + Ribavirin in GT1
## SAPPHIRE-I Study: Study Regimens




**RTV** = Ritonavir

**Drug Dosing**

Ombitasvir-Paritaprevir-Ritonavir (25/150/100 mg once daily) + Dasabuvir: 250 mg twice daily

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

**Source: Feld JJ, et al. N Engl J Med. 2014;370:1594-1603.**

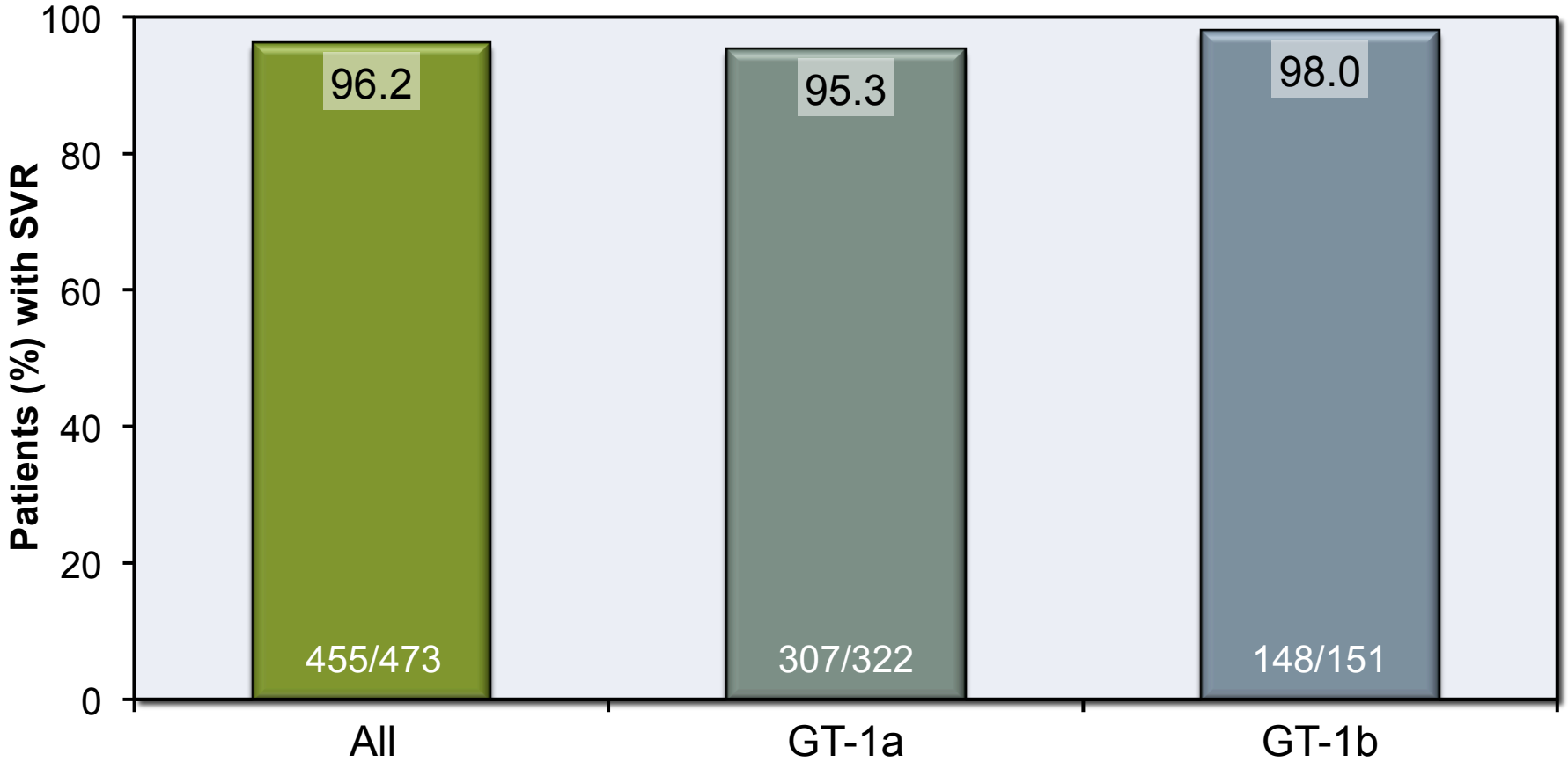
# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir + Ribavirin in GT1
## SAPPHIRE-I Study: Baseline Characteristics

| Baseline Characteristic | Group A (N=473) | Group B (N=158) |
|---|---|---|
| Age (years), Mean | 49.4 | 51.2 |
| Male sex % | 57.3 | 46.2 |
| Race (%) | | |
| White | 90.5 | 91.1 |
| Black | 5.5 | 5.1 |
| Other | 4.0 | 3.8 |
| Body Mass Index (Mean) | 25.7 | 26.2 |
| HCV genotype (%) | | |
| 1a | 68.1 | 66.5 |
| 1b | 31.9 | 33.5 |
| IL28B CC genotype, (%) | 30.4 | 31.6 |
| HCV RNA, $\log_{10}$ IU/ml | 6.40 | 6.47 |
| Fibrosis score ≥ F2 | 23.3 | 26.6 |

**Source: Feld JJ, et al. N Engl J Med. 2014;370:1594-1603.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir + Ribavirin in GT1
# SAPPHIRE-I Study: Results

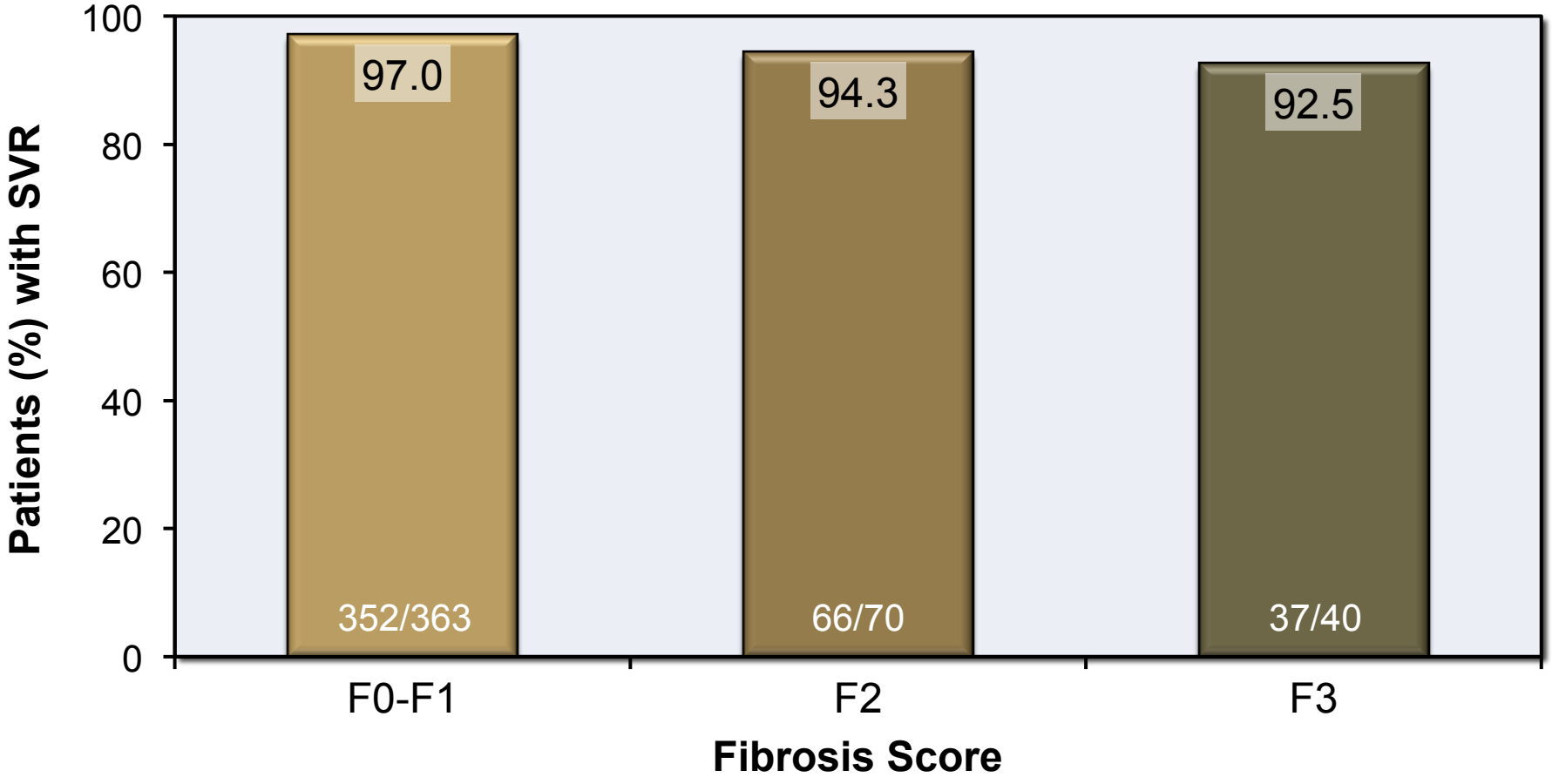
## SAPPHIRE-I: SVR12 in Group A, by Genotype 1 Subtype




Source: Feld JJ, et al. N Engl J Med. 2014;370:1594-1603.

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir + Ribavirin in GT1
# SAPPHIRE-I Study: Results

## SAPPHIRE-I: SVR12 in Group A, Fibrosis Score




Source: Feld JJ, et al. N Engl J Med. 2014;370:1594-1603.

Hepatitis web study

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir + Ribavirin in GT1
## SAPPHIRE-I Study: Adverse Events During Double-Blind Phase

| Event | Group A = 3D + RBV (N=473) | Group B = Placebo (N=158) |
|---|---|---|
| Any adverse event (%) | 87.5 | 73.4 |
| Any adverse event leading to discontinuation of study drug (%) | 0.6 | 0.6 |
| Any serious adverse event (%) | 2.1 | 0 |
| Grade 3 or 4 lab abnormality (%) | | |
| Alanine aminotransferase | 0.9 | 4.4 |
| Aspartate aminotransferase | 0.6 | 1.9 |
| Alkaline phosphatase | 0 | 0 |
| Total bilirubin | 2.8 | 0 |
| Hemoglobin | 0 | 0 |

**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = Ribavirin

**Source: Feld JJ, et al. N Engl J Med. 2014;370:1594-1603.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir + Ribavirin in GT1 SAPPHIRE-I Study: Conclusions

**Conclusions**: “In previously untreated patients with HCV genotype 1 infection and no cirrhosis, a 12-week multitargeted regimen of ABT-450/r–ombitasvir and dasabuvir with ribavirin was highly effective and was associated with a low rate of treatment discontinuation.”

**Note:** ABT-450/r = Paritaprevir-Ritonavir

**Source: Feld JJ, et al. N Engl J Med. 2014;370:1594-1603.**

Treatment Naïve

## Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir +/- RBV in GT1

# PEARL-III and PEARL-IV

Ferenci P, et al. N Engl J Med. 2014;370:1983-92.

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir +/- RBV in GT1
# PEARL-III and PEARL-IV: Study Design

## PEARL-III and PEARL-IV: Features

- **Design**: Two phase 3, randomized, open-label trials evaluating safety and efficacy of ombitasvir-paritaprevir-ritonavir + dasabuvir +/- ribavirin for 12 weeks in treatment-naïve patients with chronic HCV GT 1b (PEARL-III) or 1a (PEARL-IV)

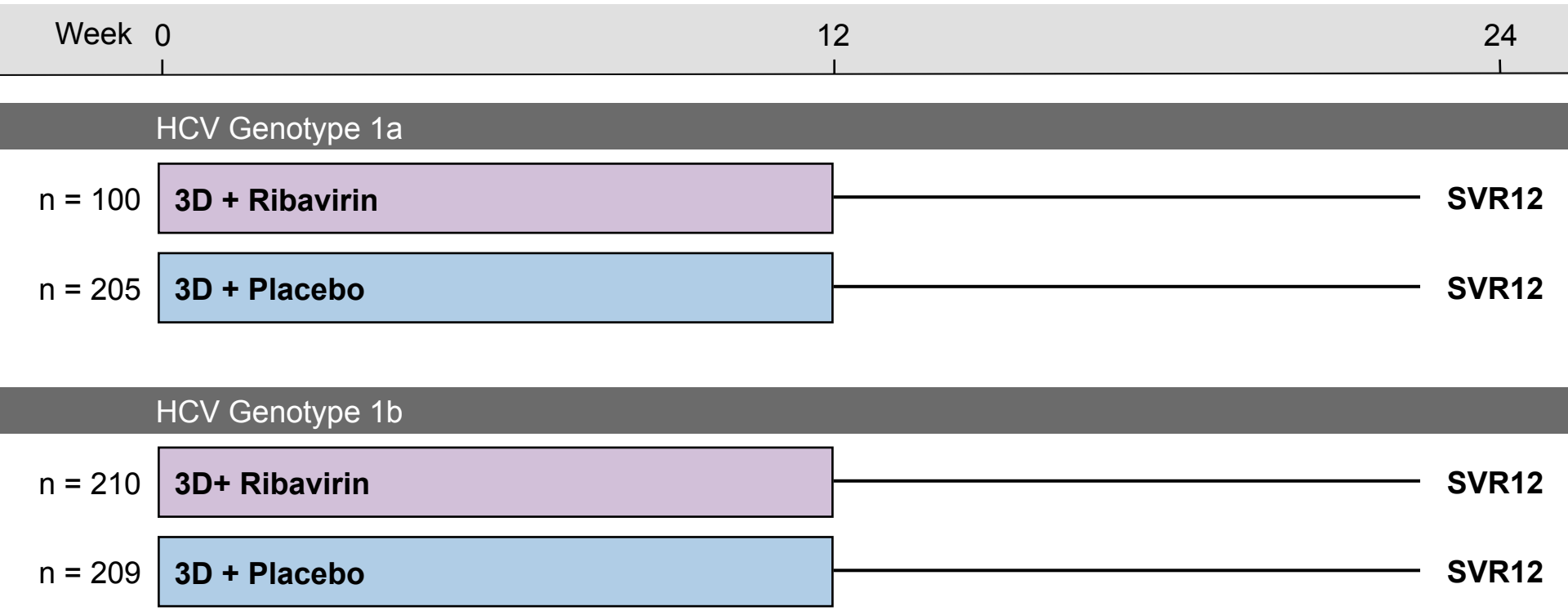
- **Setting**: International (PEARL-III at 53 sites and PEARL-IV at 50 sites)

- **Entry Criteria**
  - Chronic HCV infection with genotype 1a or 1b
  - Treatment-naïve
  - Age 18-70
  - Plasma HCV RNA greater than 10,000 IU/mL
  - Absence of cirrhosis
  - Absence of coinfection with HBV or HIV

- **Primary End-Point**: SVR12

Source: Ferenci P, et al. N Engl J Med. 2014;370:1983-92.

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir +/- RBV in GT1
# PEARL-III and PEARL-IV: Study Regimens




**3D** = Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir

**Drug Dosing**

3D = Ombitasvir-Paritaprevir-Ritonavir (25/150/100 mg once daily) + Dasabuvir: 250 mg twice daily
Ribavirin (RBV): weight-based and divided bid (1000 mg/day if < 75kg or 1200 mg/day if ≥ 75kg)

**Source: Ferenci P, et al. N Engl J Med. 2014;370:1983-92.**

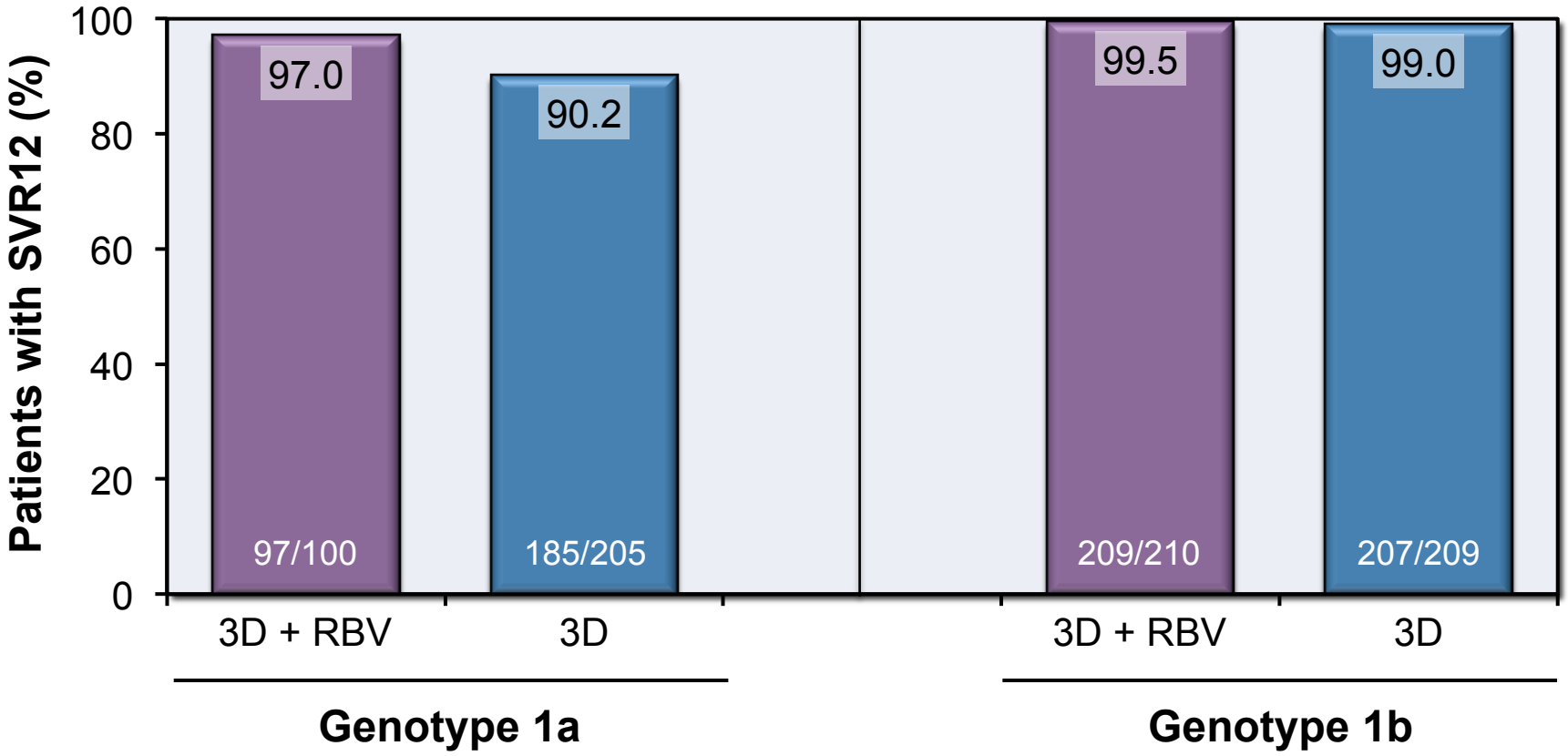
# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir +/- RBV in GT1
# PEARL-III and PEARL-IV: Baseline Characteristics

| Baseline Characteristic | Genotype 1a | | Genotype 1b | |
|---|---|---|---|---|
| | 3D + RBV (n=100) | 3D (n=205) | 3D + RBV (n=210) | 3D (n=209) |
| Age, years | 51.6 | 51.4 | 48.4 | 49.2 |
| Male sex (%) | 70.0 | 62.9 | 50.5 | 41.2 |
| BMI kg/$m^2$ | 26.9 | 26.7 | 25.8 | 26.1 |
| Race (%) | | | | |
| White | 86.0 | 83.4 | 94.3 | 94.2 |
| Black | 10.0 | 12.7 | 4.8 | 4.8 |
| Other | 4.0 | 3.9 | 1.0 | 1.0 |
| IL28B CC (%) | 31.0 | 30.7 | 21.0 | 21.1 |
| Metavir F3 (%) | 16.0% | 18.5% | 10.5% | 9.6% |
| HCV RNA $\log_{10}$ IU/ml | 6.64 | 6.53 | 6.29 | 6.33 |

**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = Ribavirin

**Source: Ferenci P, et al. N Engl J Med. 2014;370:1983-92.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir +/- RBV in GT1
## PEARL-III and PEARL-IV: Results




**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir
**RBV** = Ribavirin

**Source: Ferenci P, et al. N Engl J Med. 2014;370:1983-92.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir +/- RBV in GT1
# PEARL-III and PEARL-IV: Adverse Events

| Event | GT1a | | GT1b | |
|---|---|---|---|---|
| | 3D + RBV (n=100) | 3D (n=205) | 3D + RBV (n=210) | 3D (n=209) |
| Any adverse event % | 92.0 | 82.4 | 80.0 | 67 |
| Any serious adverse event % | 3.0 | 0.5 | 1.9 | 1.9 |
| Common adverse events: | | | | |
| Headache % | 25.0 | 28.3 | 24.3 | 23.4 |
| Fatigue % | 46.0 | 35.1 | 21.4 | 23.0 |
| Pruritus % | 10.0 | 5.9 | 11.9 | 5.3 |
| Nausea % | 21.0 | 13.7 | 11.0 | 4.3 |
| Insomnia % | 17.0 | 7.8 | 9.0 | 3.3 |
| Diarrhea % | 14.0 | 16.1 | 4.3 | 6.2 |
| Laboratory abnormalities (%): | | | | |
| Hemoglobin < 10 g/dl | 4.0 | 0 | 9.0 | 0 |
| Total bilirubin > 3x ULN | 3.0 | 0.5 | 5.7 | 0.5 |

**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = Ribavirin

**Source: Ferenci P, et al. N Engl J Med. 2014;370:1983-92.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir +/- RBV in GT1
# PEARL-III and PEARL-IV: Adverse Events

| Event | GT1a | | GT1b | |
|---|---|---|---|---|
| | 3D + RBV (n=100) | 3D (n=205) | 3D + RBV (n=210) | 3D (n=209) |
| Any adverse event % | 92.0 | 82.4 | 80.0 | 67 |
| Any serious adverse event % | 3.0 | 0.5 | 1.9 | 1.9 |
| Common adverse events: | | | | |
| Headache % | 25.0 | 28.3 | 24.3 | 23.4 |
| Fatigue % | 46.0 | 35.1 | 21.4 | 23.0 |
| Pruritus % | 10.0 | 5.9 | 11.9 | 5.3 |
| Nausea % | 21.0 | 13.7 | 11.0 | 4.3 |
| Insomnia % | 17.0 | 7.8 | 9.0 | 3.3 |
| Diarrhea % | 14.0 | 16.1 | 4.3 | 6.2 |
| Laboratory abnormalities (%): | | | | |
| Hemoglobin < 10 g/dl | 4.0 | 0 | 9.0 | 0 |
| Total bilirubin > 3x ULN | 3.0 | 0.5 | 5.7 | 0.5 |

**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = ribavirin

**Source: Ferenci P, et al. N Engl J Med. 2014;370:1983-92.**

# PEARL-III and PEARL-IV: Conclusions

**Conclusions**: "Twelve weeks of treatment with ABT-450/r–ombitasvir and dasabuvir without ribavirin was associated with high rates of sustained virologic response among previously untreated patients with HCV genotype 1 infection. Rates of virologic failure were higher without ribavirin than with ribavirin among patients with genotype 1a infection but not among those with genotype 1b infection."

**Note:** ABT-450/r = Paritaprevir-Ritonavir

**Source: Ferenci P, et al. N Engl J Med. 2014;370:1983-92.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir in Treatment-Experienced Patients

Treatment Experienced

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir + RBV in GT1

# SAPPHIRE-II

Zeuzem S, et al. N Engl J Med. 2014;370:1604-14.

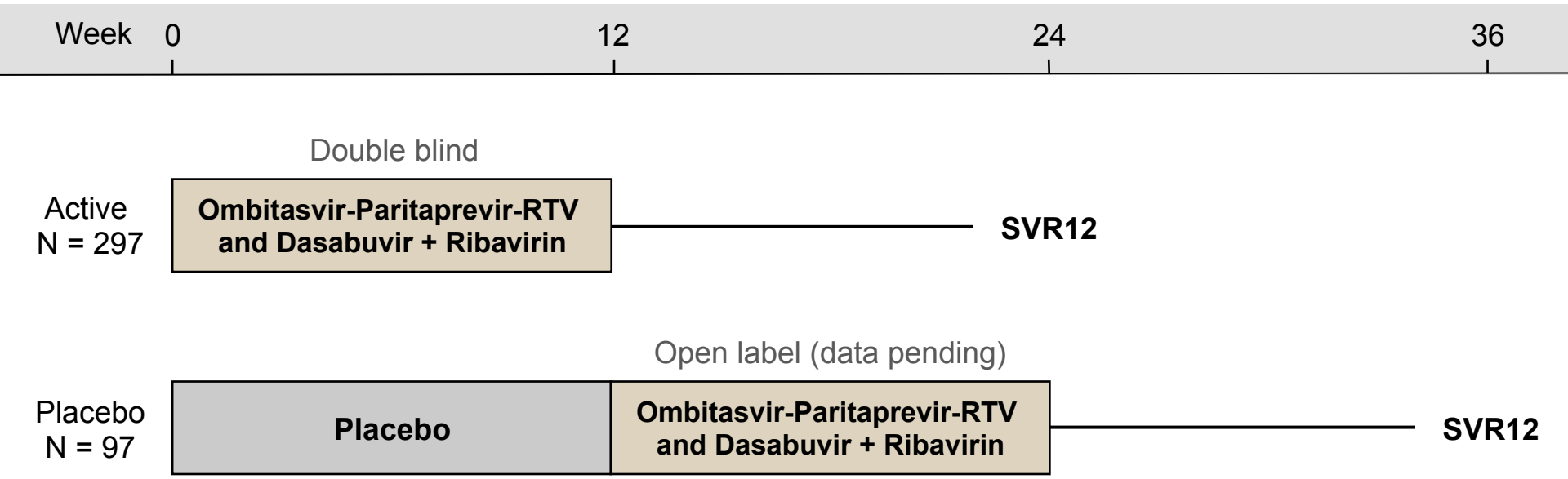
# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir + RBV in GT1 SAPPHIRE-II: Study Design

## SAPPHIRE-II: Features

- **Design**: Phase 3, randomized, open-label trial evaluating safety and efficacy of ombitasvir-paritaprevir-ritonavir and dasabuvir + ribavirin for 12 weeks in treatment-experienced patients with chronic HCV genotype 1
- **Setting**: 76 sites in Australia, North America, and Europe
- **Entry Criteria**
  - Chronic HCV infection with genotype 1
  - Prior treatment experience with peginterferon plus ribavirin
  - Age 18-70
  - Plasma HCV RNA greater than 10,000 IU/mL
  - Absence of cirrhosis
  - Absence of coinfection with HBV or HIV
- **Primary End-Point**: SVR12

**Source: Zeuzem S, et al. N Engl J Med. 2014;370:1604-14.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir + RBV in GT1 SAPPHIRE-II: Regimens




**RTV** = Ritonavir

**Drug Dosing**

Ombitasvir-Paritaprevir-Ritonavir (25/150/100 mg once daily) + Dasabuvir: 250 mg twice daily

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

**Source: Zeuzem S, et al. N Engl J Med. 2014;370:1604-14.**

# Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir + RBV in GT1 SAPPHIRE-II Study: Baseline Characteristics

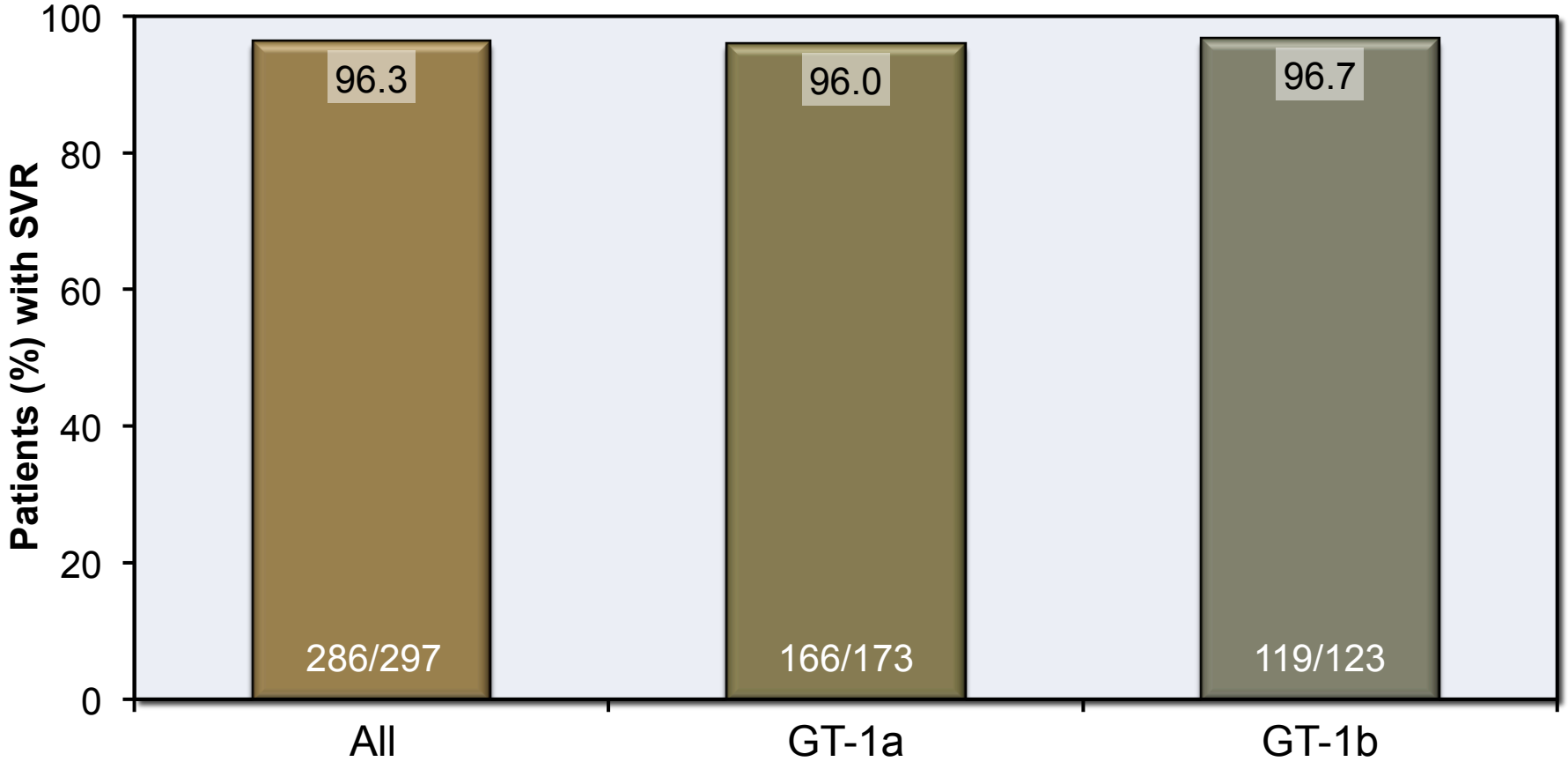
| Baseline Characteristic | 3D + RBV (n=297) | Placebo Arm (n=97) |
|---|---|---|
| Age (years), Mean | 51.7 | 54.9 |
| Male sex % | 56.2 | 61.9 |
| Race (%)<br>White<br>Black<br>Asian | <br>90.6<br>7.4<br>2.0 | <br>88.7<br>10.3<br>0 |
| Body Mass Index (Mean) | 26.3 | 26.4 |
| HCV genotype (%)<br>1a<br>1b | <br>58.2<br>41.4 | <br>58.8<br>41.2 |
| IL28B CC genotype, (%) | 11.4 | 7.2 |
| Type of Prior Response<br>Relapse<br>Partial Response<br>Null Response | <br>29.0<br>21.9<br>49.2 | <br>29.9<br>21.6<br>48.5 |
| HCV RNA, $\log_{10}$ IU/ml (mean) | 6.55 | 6.52 |
| Fibrosis score F2 or F3 (%) | 32.0 | 33.0 |

**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = Ribavirin

**Source: Zeuzem S, et al. N Engl J Med. 2014;370:1604-14.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir + RBV in GT1
# SAPPHIRE-II: Results

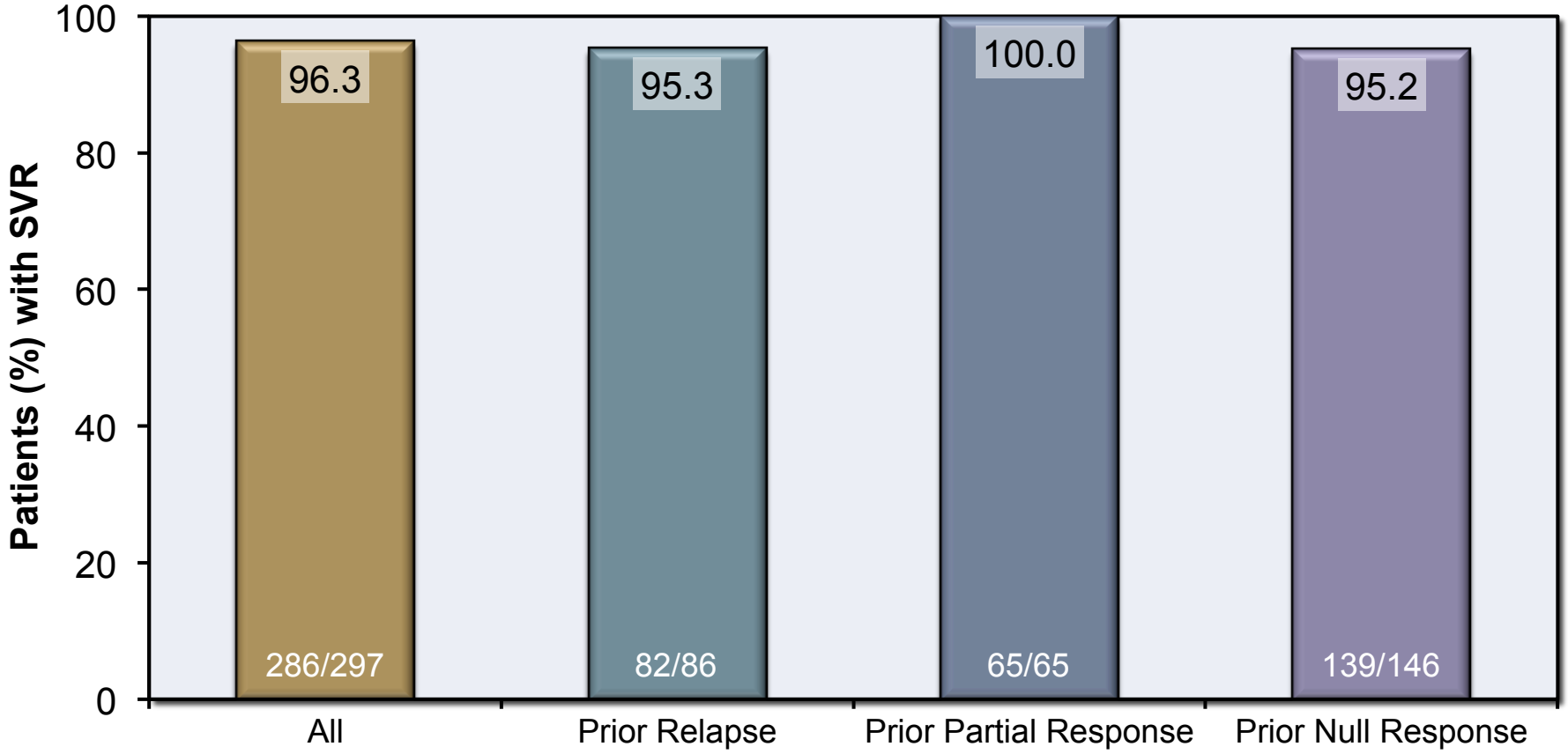
## SAPPHIRE-II: Results by Genotype 1 Subtype




Source: Zeuzem S, et al. N Engl J Med. 2014;370:1604-14.

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir + RBV in GT1
# SAPPHIRE-II: Results

## SAPPHIRE-II: Results by Prior Treatment Response




Source: Zeuzem S, et al. N Engl J Med. 2014;370:1604-14.

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir + RBV in GT1 SAPPHIRE-II Study: Key Adverse Events

| Event | 3D + RBV (n=297) | Placebo (n=97) |
|---|---|---|
| Any adverse events % | 91.2 | 82.5 |
| Any serious adverse event % | 2.0 | 1.0 |
| Common adverse events: | | |
| Headache % | 36.4 | 35.1 |
| Fatigue % | 33.3 | 22.7 |
| Nausea % | 20.2 | 17.5 |
| Asthenia % | 15.8 | 11.3 |
| Insomnia % | 14.1 | 7.2 |
| Pruritus % | 13.8 | 5.2 |
| Diarrhea % | 13.1 | 12.4 |
| Dyspnea % | 12.5 | 10.3 |
| Cough % | 10.8 | 5.2 |
| Myalgia % | 7.7 | 10.3 |
| Abnormalities in laboratory values of grade 3 or 4 % | | |
| Alanine aminotransferase | 1.7 | 3.1 |
| Total bilirubin | 2.4 | 0 |

**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = Ribavirin

**Source: Zeuzem S, et al. N Engl J Med. 2014;370:1604-14.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir + RBV in GT1
## SAPPHIRE-II: Conclusions

**Conclusions**: “Rates of response to a 12-week interferon-free combination regimen were more than 95% among previously treated patients with HCV genotype 1 infection, including patients with a prior null response.”

Source: Zeuzem S, et al. N Engl J Med. 2014;370:1604-14.

Treatment Experienced

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir +/- RBV in GT1b

# PEARL-II

Andreone P, et al. Gastroenterology. 2014;147:359-65.

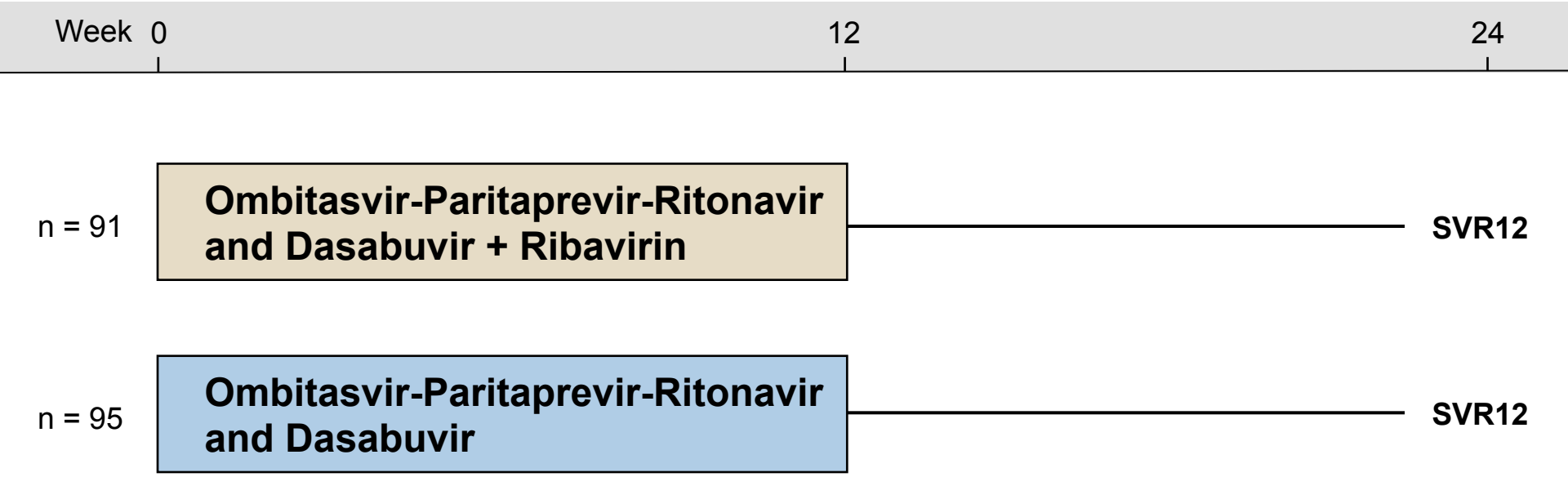
# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir +/- RBV in GT1b
# PEARL-II: Study Design

## PEARL-II: Features

- **Design**: Phase 3, randomized, open-label trial evaluating safety and efficacy of 3D (ombitasvir-paritaprevir-ritonavir + dasabuvir) with or without ribavirin for 12 weeks in treatment-experienced patients with chronic HCV GT 1b
- **Setting**: 43 international sites
- **Entry Criteria**
  - Chronic HCV infection with genotype 1b
  - Prior treatment experience with peginterferon plus ribavirin
  - Age 18-70
  - Plasma HCV RNA greater than 10,000 IU/mL
  - Absence of cirrhosis
  - Absence of coinfection with HBV or HIV
- **Primary End-Point**: SVR12

**Source: Andreone P, et al. Gastroenterology. 2014;147:359-65.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir +/- RBV in GT1b
# PEARL-II: Regimens




**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir

**Drug Dosing**

Ombitasvir-Paritaprevir-Ritonavir (25/150/100 mg once daily) + Dasabuvir: 250 mg twice daily

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

**Source: Andreone P, et al. Gastroenterology. 2014;147:359-65.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir +/- RBV in GT1b
## PEARL-II: Baseline Characteristics

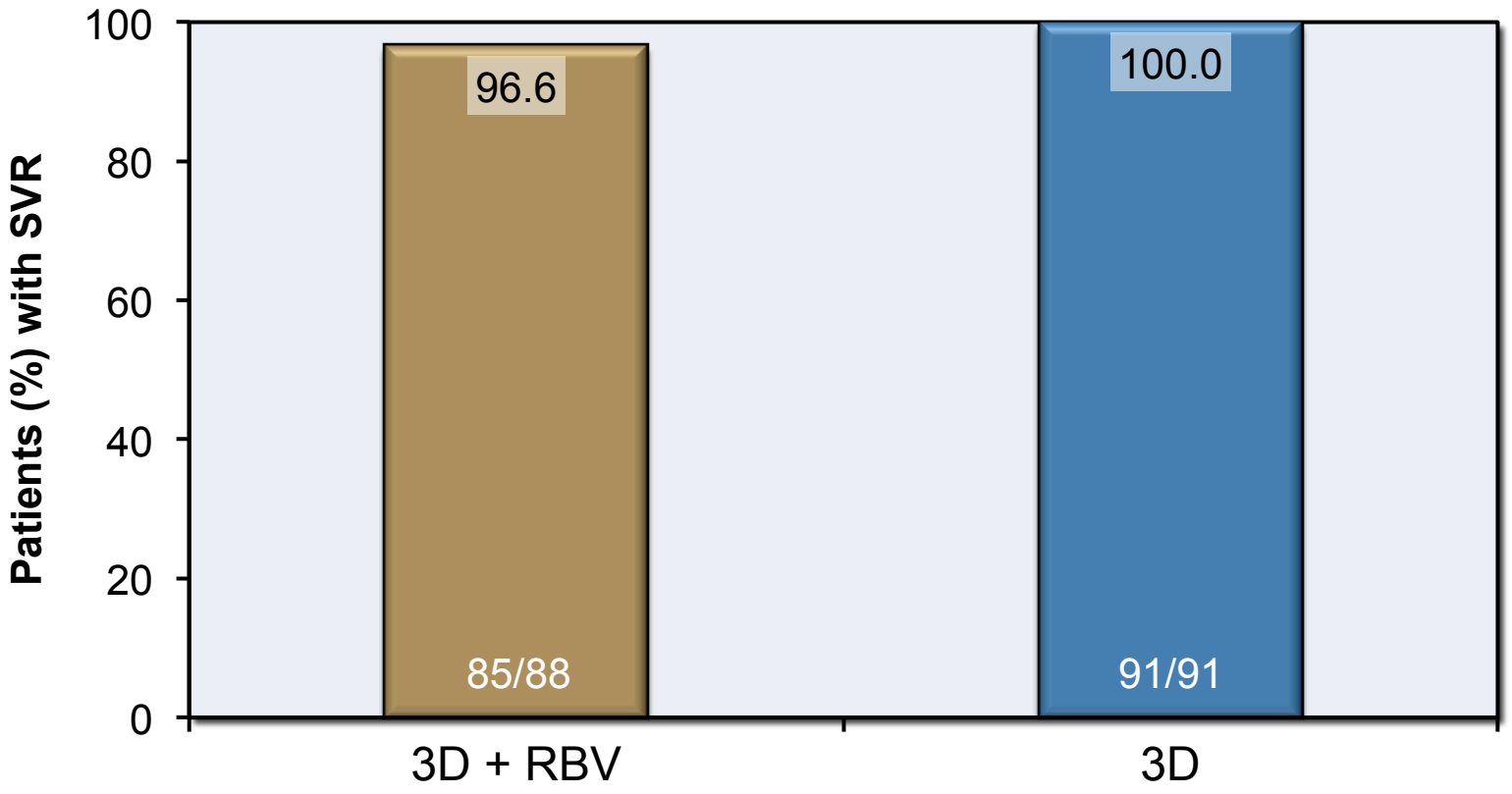
| Baseline Characteristic | 3D + RBV (n=91) | 3D (n=95) |
|---|---|---|
| Age (years), Mean | 54.2 | 54.2 |
| Male sex % | 49.5 | 60.0 |
| Race (%) | | |
| White | 92.3 | 90.5 |
| Black | 3.4 | 6.3 |
| Body Mass Index (Mean) | 26.2 | 27.5 |
| Previous Response to PEG + RBV | | |
| Null responder | 35.2 | 34.7 |
| Partial responder | 28.6 | 28.4 |
| Relapser | 36.3 | 36.8 |
| IL28B Non-CC genotype, (%) | 89.0 | 92.6 |
| HCV RNA, $\log_{10}$ IU/ml (mean) | 6.56 | 6.48 |
| Fibrosis score F3 (%) | 15.4 | 13.7 |

**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = Ribavirin

**Source: Andreone P, et al. Gastroenterology. 2014;147:359-65.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir +/- RBV in GT1b PEARL-II: Results

## PEARL-II: SVR 12 Rates*



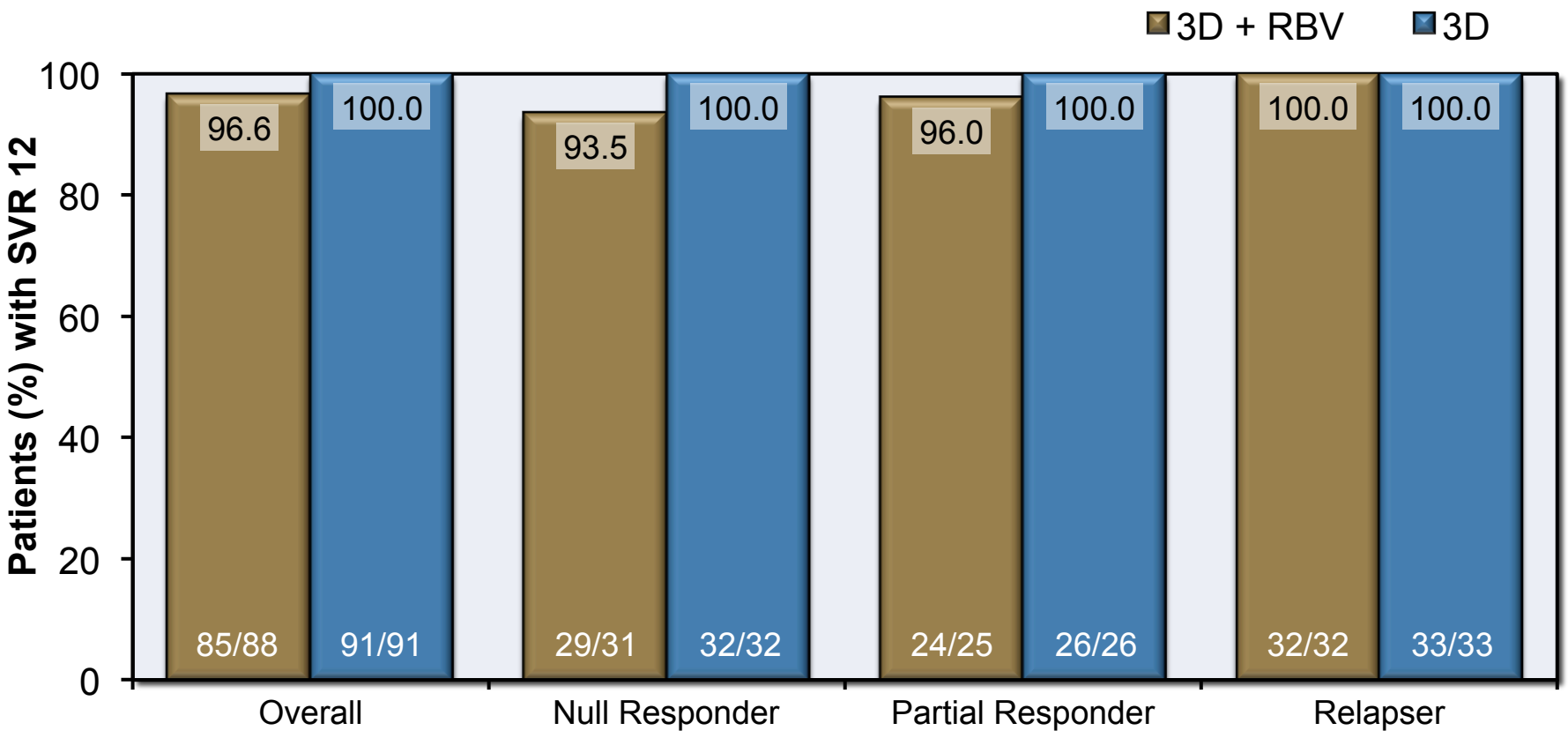

*Primary endpoint by intention-to-treat analysis

**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = ribavirin

**Source: Andreone P, et al. Gastroenterology. 2014;147:359-65.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir +/- RBV in GT1b PEARL-II: Results by Prior Treatment Response

## PEARL-II: Results by Prior Treatment Response




**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = ribavirin

**Source: Andreone P, et al. Gastroenterology. 2014;147:359-65.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir +/- RBV in GT1b PEARL-II: Treatment-Emergent Adverse Effects

| Event | 3D + RBV (n=91) | 3D (n=95) |
|---|---|---|
| Any Treatment Emergent Adverse Effect % | 79.1 | 77.9 |
| Any serious Treatment Emergent Adverse Effect % | 2.2 | 0 |
| Common Treatment Emergent Adverse Events: | | |
| Fatigue % | 31.9 | 15.8 |
| Headache % | 24.2 | 23.2 |
| Nausea % | 20.9 | 6.3 |
| Insomnia % | 14.3 | 3.2 |
| Pruritus % | 14.3 | 8.4 |
| Diarrhea % | 13.2 | 12.6 |
| Asthenia % | 12.1 | 7.4 |
| Anemia % | 11.0 | 0 |
| Blood bilirubin level increased % | 8.8 | 0 |
| Rash % | 8.8 | 1.1 |
| Laboratory abnormalities (%): | | |
| Hemoglobin (< lower limit of normal at end of treatment) | 42.0 | 5.5 |
| Total bilirubin > 3x ULN | 8.8 | 0 |

**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = Ribavirin

**Source: Andreone P, et al. Gastroenterology. 2014;147:359-65.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir +/- RBV in GT1b PEARL-II: Conclusions

**Conclusions**: “The interferon-free regimen of ABT-450, ritonavir, ombitasvir, and dasabuvir, with or without ribavirin, produces a high rate of SVR12 in treatment-experienced patients with HCV genotype 1b infection. Both regimens are well tolerated, as shown by the low rate of discontinuations and generally mild adverse events.”

**Note:** ABT-450 = Paritaprevir

**Source: Andreone P, et al. Gastroenterology. 2014;147:359-65.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir in Treatment-Naïve and Treatment-Experienced Patients

Treatment Naïve and Treatment Experienced

HIV Coinfection

# 3D (Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir) + RBV in GT1

# TURQUOISE-I

Sulkowski MS, et al. JAMA. 2015:313:1223-31.

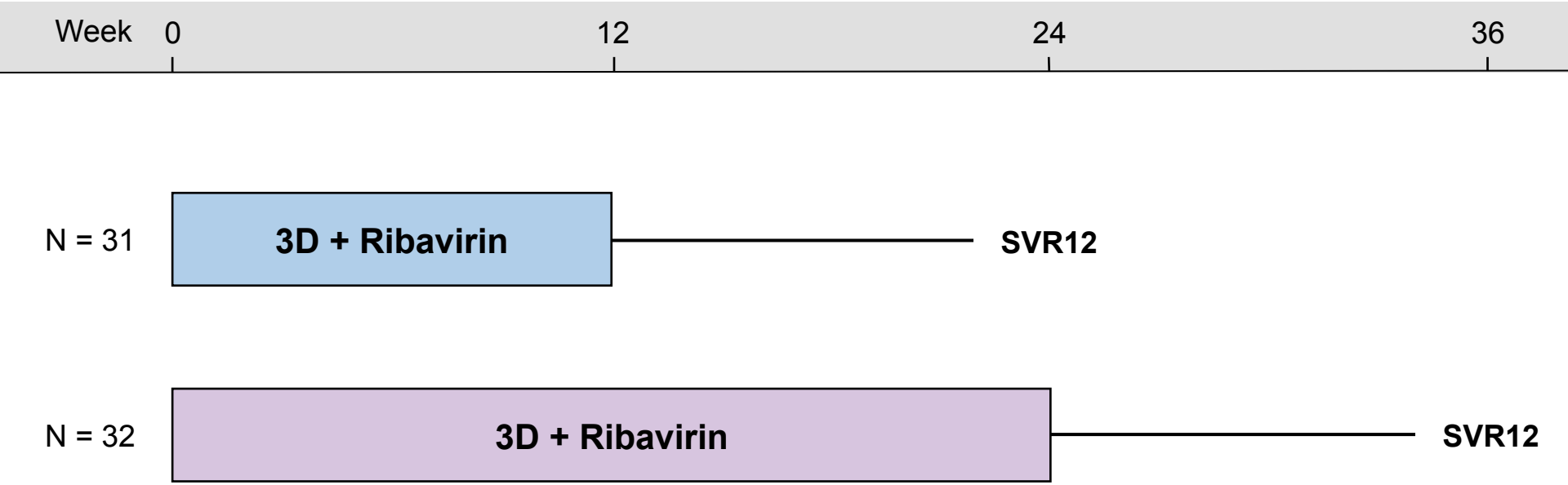
# 3D + Ribavirin for HCV-HIV Coinfection and GT1
# TURQUOISE-I: Part 1a Study Design

## TURQUOISE-I: Features

- **Design**: Multipart, phase 2/3, randomized, open-label trial evaluating safety and efficacy of 3D (ombitasvir-paritaprevir-ritonavir and dasabuvir) plus ribavirin for 12 or 24 weeks in treatment-naïve and experienced patients with chronic HCV GT 1 and HIV coinfection, including patients with cirrhosis
- **Setting:** Multicenter study in United States and Puerto Rico
- **Entry Criteria**
  - Chronic HCV infection with genotype 1 and HIV coinfection
  - Treatment-naïve or previously treated with peginterferon + ribavirin
  - Age 18-70
  - Plasma HCV RNA greater than 10,000 IU/mL
  - Child-Pugh A cirrhosis permitted
  - CD4 count ≥200 cells/$mm^3$ (or CD4% ≥14) and HIV RNA level <40 copies/ml
  - Receiving atazanavir- or raltegravir-based regimen
- **Primary End-Point**: SVR12

**Source: Sulkowski MS, et al. JAMA. 2015:313:1223-31.**

# 3D + Ribavirin for HCV-HIV Coinfection and GT1
# TURQUOISE-I: Part 1a Study Regimens




**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir

**Drug Dosing**

Ombitasvir-Paritaprevir-Ritonavir (25/150/100 mg once daily) and Dasabuvir: 250 mg twice daily

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

**Source: Sulkowski MS, et al. JAMA. 2015:313:1223-31.**

# 3D + Ribavirin for HCV-HIV Coinfection and GT 1
# TURQUOISE-I: Patient Population

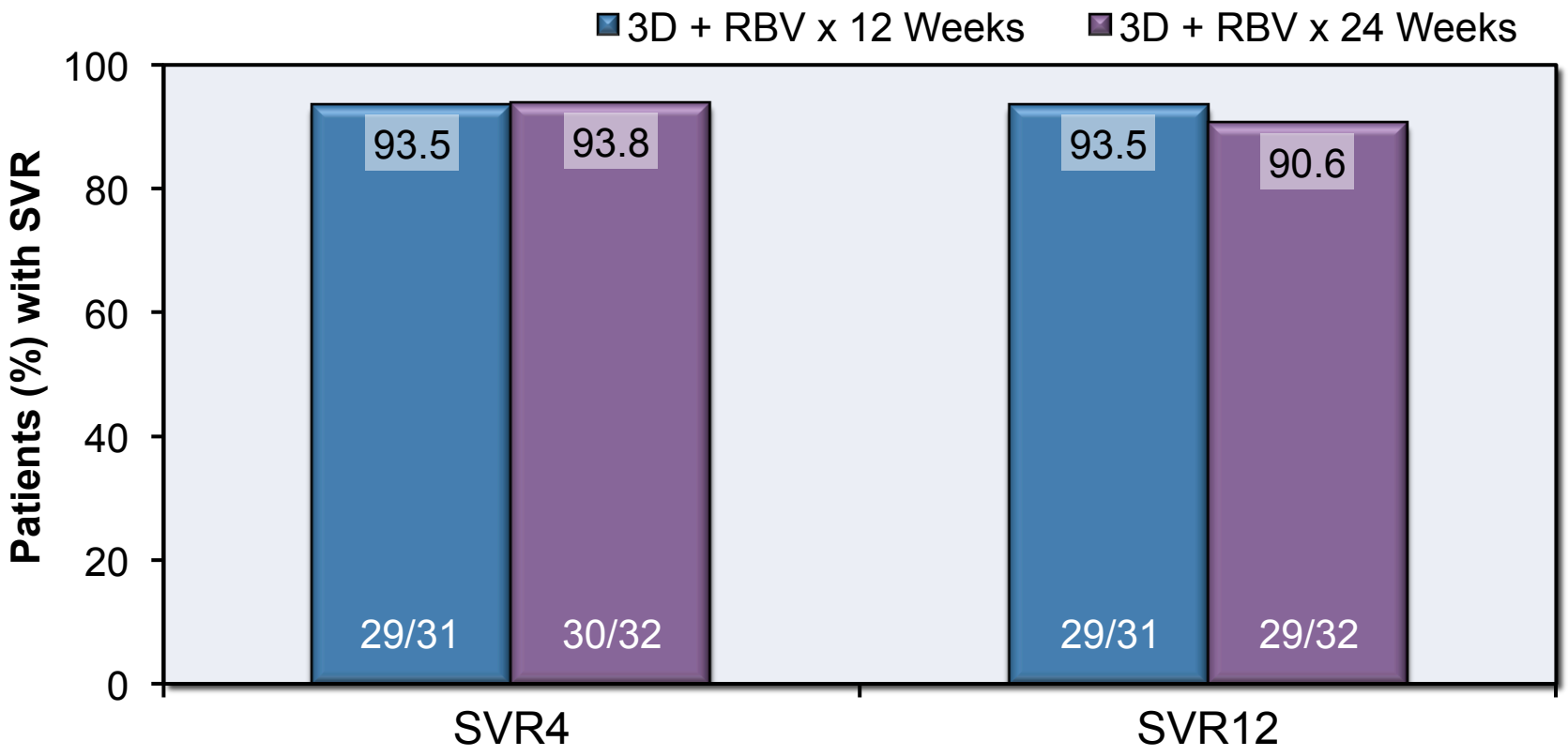
| Baseline Characteristic | 12-Week Arm (n=31) | 24-Week Arm (n=32) |
|---|---|---|
| Age (years), Mean | 50.9 | 50.9 |
| Male sex % | 94 | 91 |
| Black Race (%) | 23 | 25 |
| Cirrhosis (%) | 19 | 19 |
| HCV genotype (%)<br>1a<br>1b | <br>87<br>13 | <br>91<br>9 |
| HCV RNA, $\log_{10}$ IU/ml (mean) | 6.54 | 6.60 |
| IL28B non-CC genotype, (%) | 84 | 78 |
| Previous Response to PEG + RBV<br>Naïve<br>Relapse<br>Partial response<br>Null response | <br>65<br>3<br>16<br>16 | <br>69<br>9<br>6<br>16 |
| CD4 Count, cells/$mm^3$ (mean) | 633 | 625 |

**Source: Sulkowski MS, et al. JAMA. 2015:313:1223-31.**

Hepatitis web study

# 3D + Ribavirin for HCV-HIV Coinfection and GT 1
# TURQUOISE-I: Part 1a Results

## TURQUOISE-I: SVR Rates (to date)




**3D =** Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = Ribavirin

**Source: Sulkowski MS, et al. JAMA. 2015:313:1223-31.**

Hepatitis web study

# 3D + Ribavirin for HCV-HIV Coinfection and GT 1 TURQUOISE-I: Part 1a Results

## Details of Five Patients NOT Achieving SVR 12

- One patient in 12-week arm withdrew consent prior to finishing treatment; had undetectable HCV RNA at week 10
- One patient in 12-week arm had virologic relapse at week 4 post treatment; had new resistant HCV variants at 3 viral targets (D168V in NS3/4A, M28T in NS5A, and S556G in NS5B)
- One patient in 24-week arm had virologic breakthrough during treatment; had new resistant HCV variants at 3 viral targets (R155K in NS3/4A, Q30R in NS5A, and S556G in NS5B)
- Two patients in 24-week arm achieved early SVR but appeared to be reinfected with GT1a isolate distinct from baseline HCV isolate; both patients had engaged in high-risk sexual activity post treatment

**Source: Sulkowski MS, et al. JAMA. 2015:313:1223-31.**

# 3D + Ribavirin for HCV-HIV Coinfection and GT 1 TURQUOISE-I: Part 1a Conclusions and Relevance

**Conclusions and Relevance**: “In this open-label, randomized uncontrolled study, treatment with the all-oral, interferon-free 3D-plus-ribavirin regimen resulted in high SVR rates among patients co-infected with HCV genotype 1 and HIV-1 whether treated for 12 or 24 weeks. Further phase 3 studies of this regimen are warranted in patients with co-infection.”

**Source: Sulkowski MS, et al. JAMA. 2015:313:1223-31.**

Phase 3

Treatment Naïve and Treatment Experienced

Compensated Cirrhosis

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir + RBV in GT1

# TURQUOISE-II

Poordad F, et al. N Engl J Med. 2014;370:1973-82.

Hepatitis web study

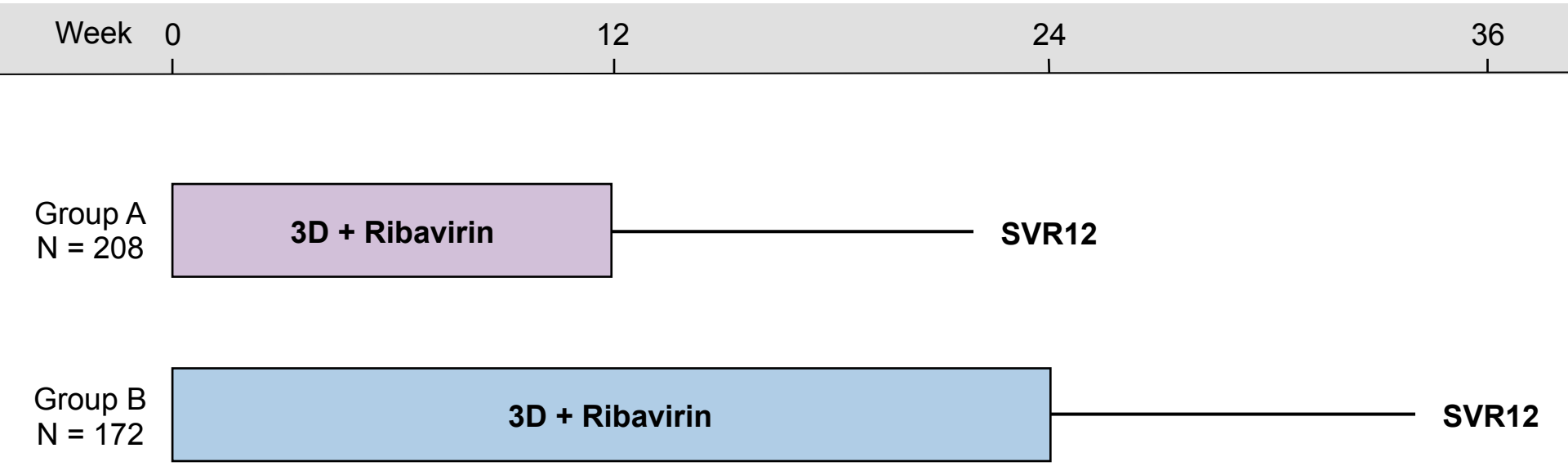
# 3D + Ribavirin in GT1 and Compensated Cirrhosis
# TURQUOISE-II: Study Design

## TURQUOISE-II: Features

- **Design**: Phase 3, randomized, open-label trial evaluating safety and efficacy of 3D (ombitasvir-paritaprevir-ritonavir & dasabuvir) + ribavirin for 12 or 24 weeks in treatment-naïve and experienced patients with chronic HCV GT 1 and compensated cirrhosis
- **Setting:** 78 sites in North America and Europe
- **Entry Criteria**
  - Chronic HCV infection with genotype 1
  - Treatment-naïve or previously treated with peginterferon + RBV
  - Age 18-70
  - Plasma HCV RNA greater than 10,000 IU/mL
  - Cirrhosis (Metavir >3, Ishak score >4 or Fibroscan ≥14.6 kPa)
  - Cirrhosis is compensated (Child-Pugh score <7 at screening)
  - Absence of coinfection with HBV or HIV
- **Primary End-Point**: SVR12

**Source: Poordad F, et al. N Engl J Med. 2014;370:1973-82.**

# 3D + Ribavirin in GT1 and Compensated Cirrhosis
# TURQUOISE-II: Regimens




**3D =** Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir

**Drug Dosing**

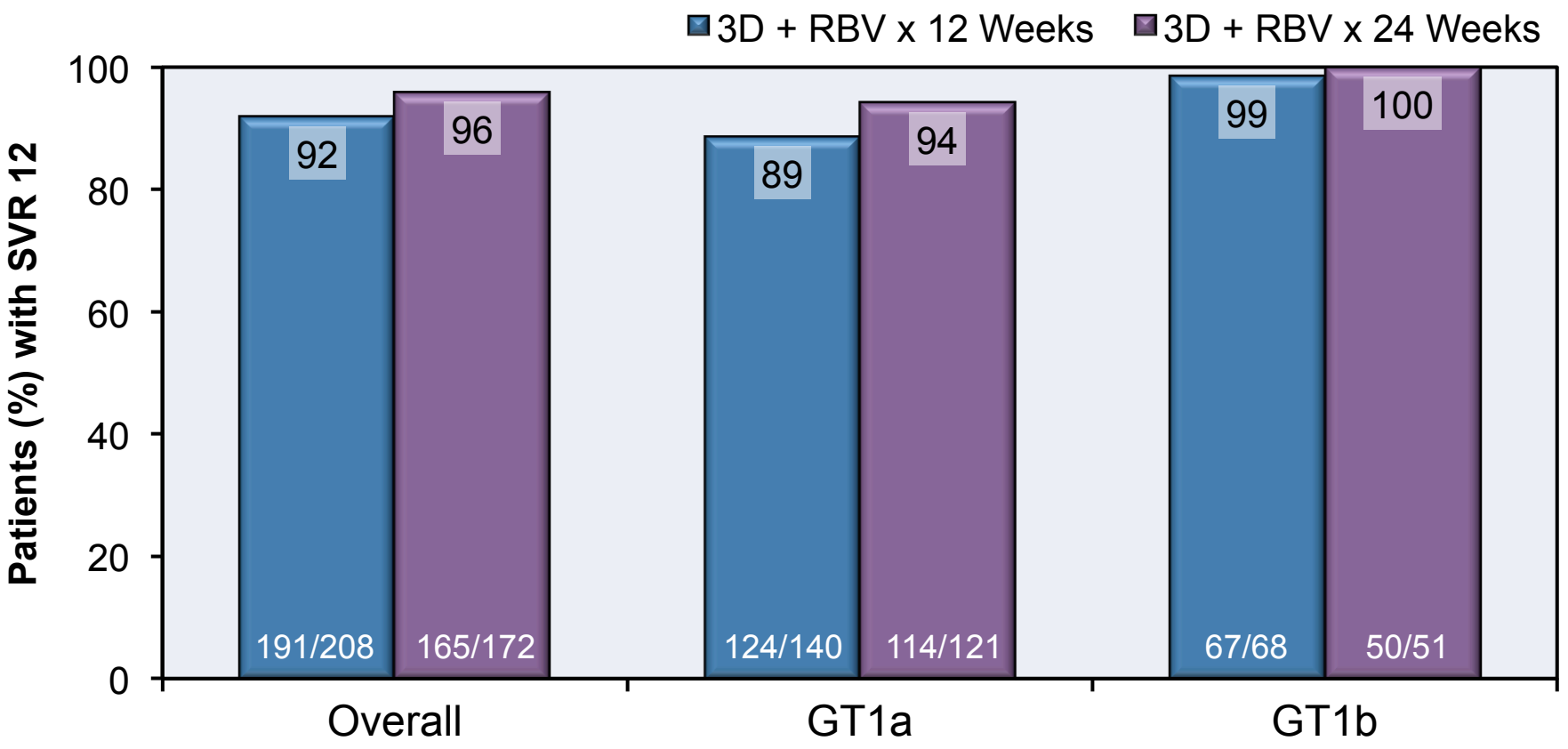
Ombitasvir-Paritaprevir-Ritonavir (25/150/100 mg once daily) + Dasabuvir: 250 mg twice daily

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

**Source: Poordad F, et al. N Engl J Med. 2014;370:1973-82.**

# 3D + Ribavirin in GT1 and Compensated Cirrhosis
# TURQUOISE-II: Results

## TURQUOISE II: SVR12 by Genotype 1 Subtype

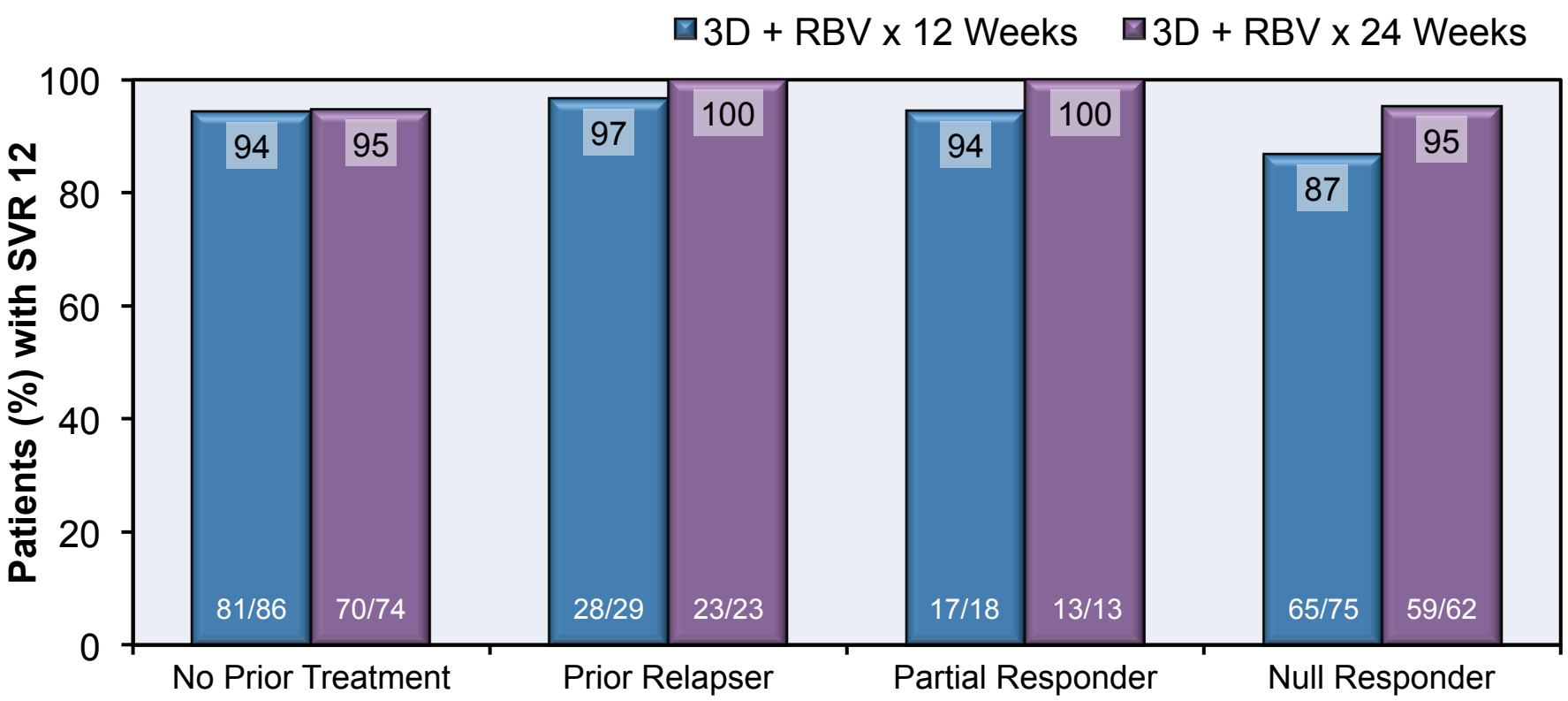



**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = ribavirin

**Source: Poordad F, et al. N Engl J Med. 2014;370:1973-82.**

# 3D + Ribavirin in GT1 and Compensated Cirrhosis
# TURQUOISE-II: Results

## TURQUOISE II: SVR12 Based on Prior Treatment

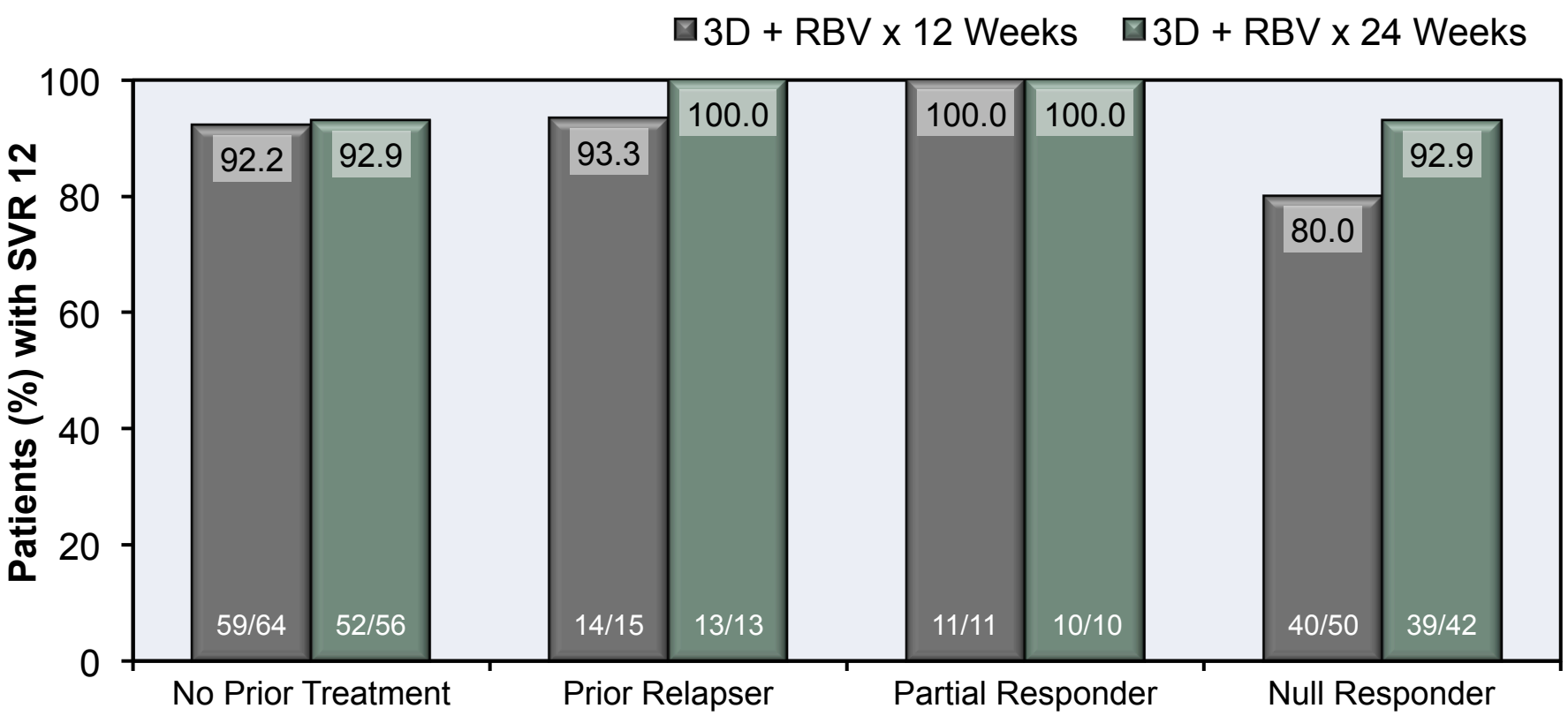



**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = ribavirin

**Source: Poordad F, et al. N Engl J Med. 2014;370:1973-82.**

# 3D + Ribavirin in GT1 and Compensated Cirrhosis
# TURQUOISE-II: Results for GT1a

## TURQUOISE II: **Genotype 1a** SVR12 Based on Prior Treatment

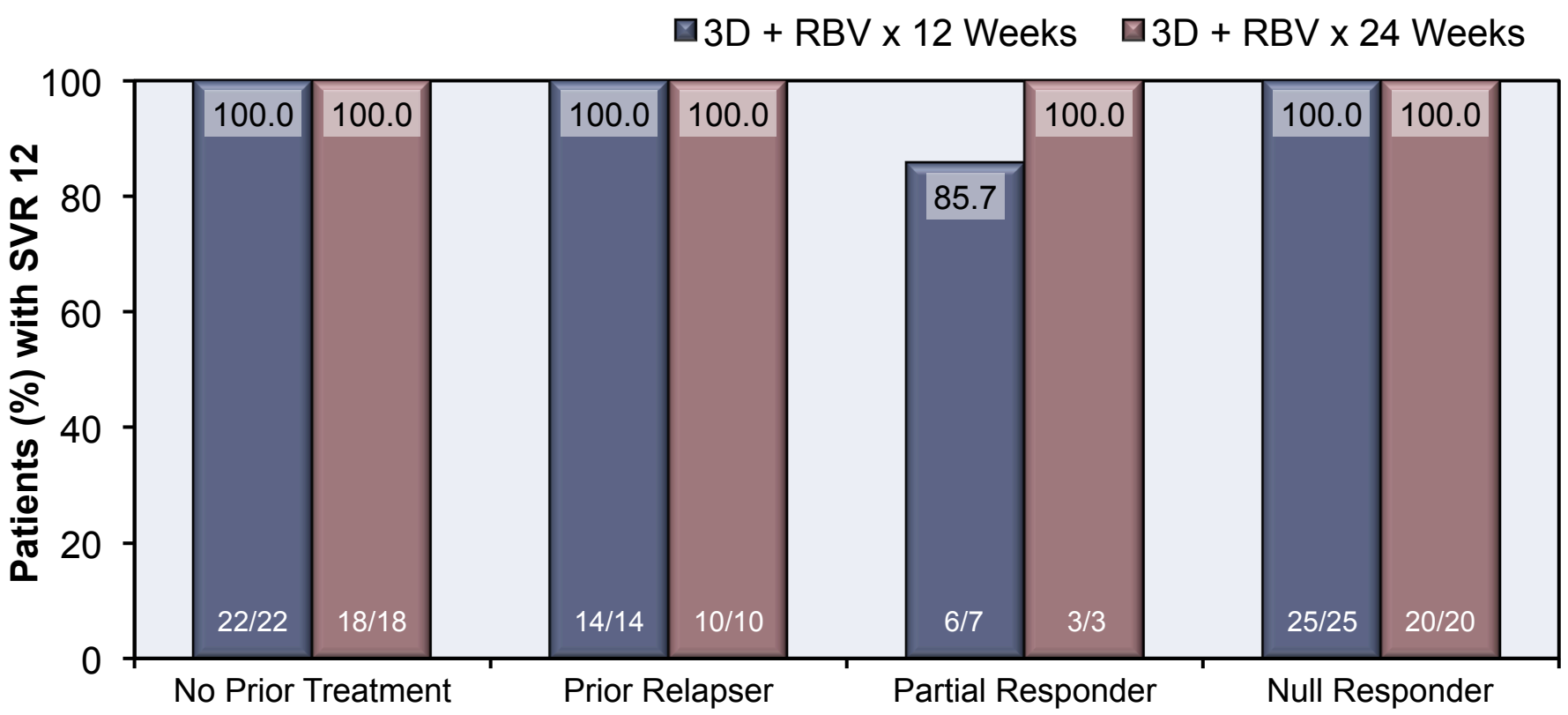



**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = ribavirin

**Source: Poordad F, et al. N Engl J Med. 2014;370:1973-82.**

# 3D + Ribavirin in GT1 and Compensated Cirrhosis
# TURQUOISE-II: Results for GT1b

## TURQUOISE II: **Genotype 1b** SVR12 Based on Prior Treatment




**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = ribavirin

**Source: Poordad F, et al. N Engl J Med. 2014;370:1973-82.**

Hepatitis web study

# 3D + Ribavirin in GT1 and Compensated Cirrhosis
# TURQUOISE-II: Adverse Effects

| Event | 3D + RBV x 12 weeks (n=208) | 3D + RBV x 24 weeks (n=172) |
|---|---|---|
| Any adverse event (%) | 91.8 | 90.7 |
| Adverse event leading to stopping study drug (%) | 1.9 | 2.3 |
| Any serious adverse event | 6.2 | 4.7 |
| Most common adverse event | | |
| Fatigue (%) | 32.7 | 46.5 |
| Headache (%) | 27.9 | 30.8 |
| Nausea (%) | 17.8 | 20.3 |
| Pruritis (%) | 18.3 | 19.2 |
| Insomnia (%) | 15.4 | 18.0 |
| Diarrhea (%) | 14.4 | 16.9 |
| Asthenia (%) | 13.9 | 12.8 |
| Rash (%) | 11.1 | 14.5 |
| Irritability (%) | 7.2 | 12.2 |
| Anemia (%) | 7.7 | 10.5 |
| Dyspnea (%) | 5.8 | 12.2 |

**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = ribavirin

**Source: Poordad F, et al. N Engl J Med. 2014;370:1973-82.**

# 3D + Ribavirin in GT1 and Compensated Cirrhosis
# TURQUOISE-II: Adverse Effects

| Lab Abnormalities | 3D + RBV x 12 weeks (n=208) | 3D + RBV x 24 weeks (n=172) |
|---|---|---|
| Alanine aminotransferase, grade 3 or 4 | 6 (2.9) | 0 |
| Aspartate aminotransferase, grade 3 or 4 | 1 (0.5) | 0 |
| Alkaline phosphatase, grade 3 or 4 | 0 | 0 |
| Total bilirubin, grade 3 or 4 | 28 (13.5) | 9 (5.2) |
| Hemoglobin | | |
| Grade 1 | 103 (49.5) | 97 (56.4) |
| Grade 2 | 12 (5.8) | 18 (10.5) |
| Grade 3 | 2 (1.0) | 1 (0.6) |
| Grade 4 | 1 (0.5) | 0 |

**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = ribavirin

**Source: Poordad F, et al. N Engl J Med. 2014;370:1973-82.**

# 3D + Ribavirin in GT1 and Compensated Cirrhosis
# TURQUOISE-II: Conclusions

**Conclusions**: “In this phase 3 trial of an oral, interferon-free regimen evaluated exclusively in patients with HCV genotype 1 infection and cirrhosis, multitargeted therapy with the use of three new antiviral agents and ribavirin resulted in high rates of sustained virologic response. Drug discontinuations due to adverse events were infrequent.”

**Source: Poordad F, et al. N Engl J Med. 2014;370:1973-82.**

Phase 3

Treatment Naïve and Treatment Experienced

Compensated Cirrhosis

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir in GT1b

# TURQUOISE-III

Feld JJ, et al. J Hepatol. 2016;64:301-7.

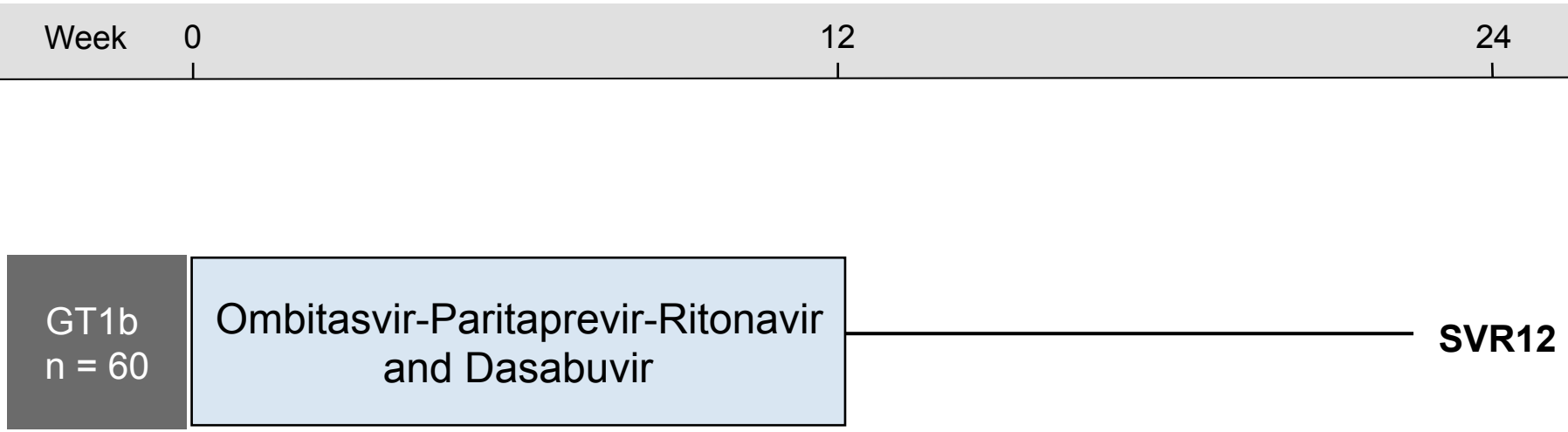
# OMB-PTV-RTV + DSV in GT1b and Compensated Cirrhosis
# TURQUOISE-III: Study Design

**TURQUOISE-III: Features**

- **Design**: Phase 3, open-label trial evaluating safety and efficacy of ombitasvir-paritaprevir-ritonavir and dasabuvir given for 12 weeks in treatment-naïve and treatment-experienced adults with chronic HCV GT 1b and compensated cirrhosis
- **Setting:** 19 sites in United States, Canada, and Belgium
- **Entry Criteria**
  - Chronic HCV infection with genotype 1b
  - Treatment-naïve or previously treated with peginterferon + ribavirin
  - Age ≥18 years
  - Plasma HCV RNA greater than 1,000 IU/mL
  - Documented cirrhosis Cirrhosis (Metavir >3, Ishak score >4 or Fibroscan ≥12.5 kPa)
  - Cirrhosis is compensated (Child-Pugh score <7 at screening)
  - Absence of coinfection with HBV or HIV
- **Primary End-Point**: SVR12

**Source: Feld JJ, et al. J Hepatol. 2016;64:301-7.**

# OMB-PTV-RTV + DSV in GT1b and Compensated Cirrhosis
# TURQUOISE-III: Study Design



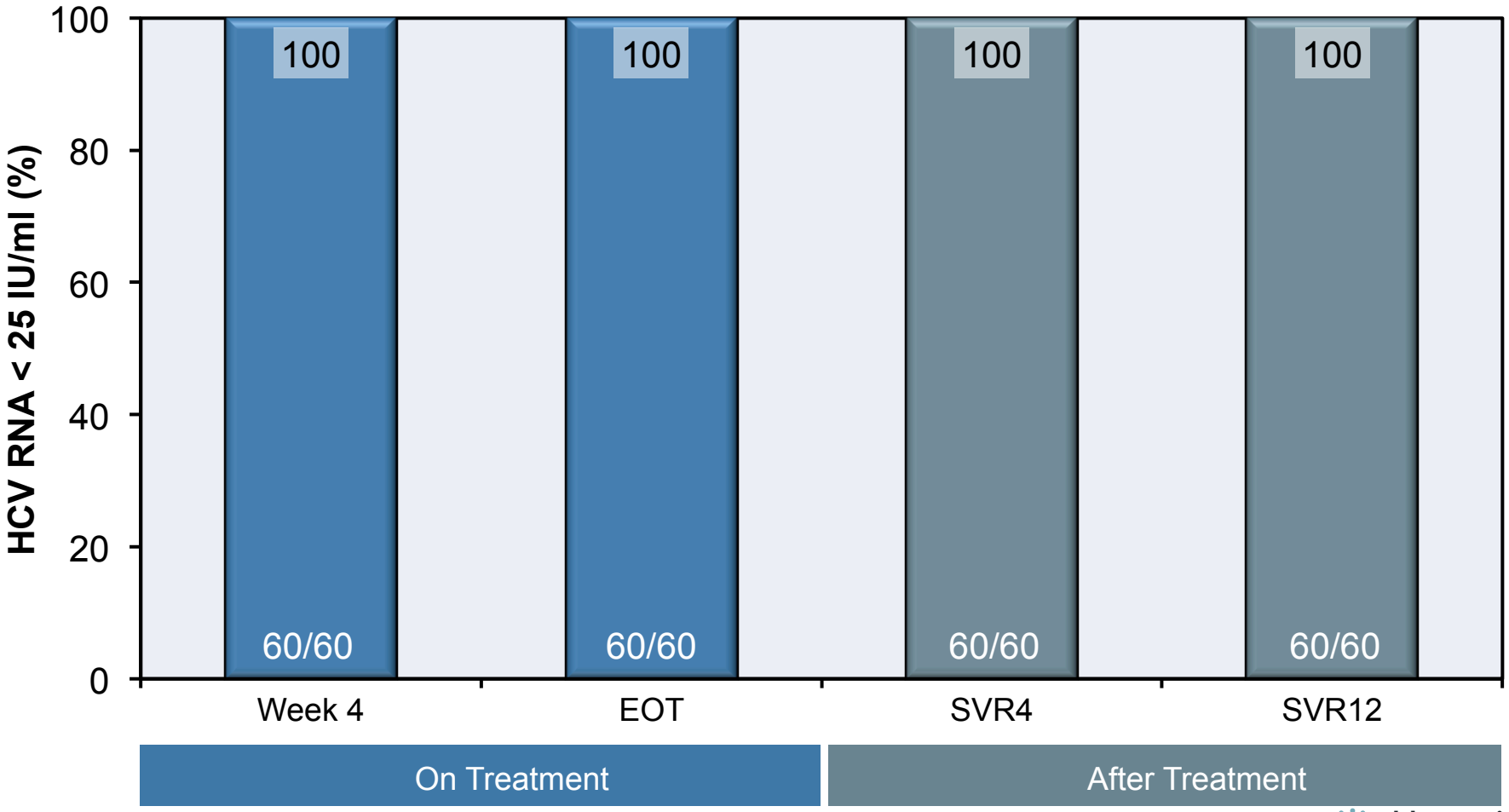

**Drug Dosing**

Ombitasvir-Paritaprevir-Ritonavir (25/150/100 mg once daily) + Dasabuvir: 250 mg twice daily

**Source: Feld JJ, et al. J Hepatol. 2016;64:301-7.**

# OMB-PTV-RTV + DSV in GT1b and Compensated Cirrhosis
# TURQUOISE-III: Results

## Virologic Response to Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir




Source: Feld JJ, et al. J Hepatol. 2016;64:301-7.

Hepatitis web study

# OMB-PTV-RTV + DSV in GT1b and Compensated Cirrhosis TURQUOISE-III: Adverse Effects

| **Common Adverse Events (≥10% of patients)** | **OMB-PTV-RTV + DSV x 12 weeks** (n = 60) |
|---|---|
| Fatigue (%) | 13 (21.7) |
| Diarrhea (%) | 12 (20.0) |
| Headache (%) | 11 (18.3) |
| Arthralgia (%) | 6 (10.0) |
| Dizziness (%) | 6 (10.0) |
| Insomnia (%) | 6 (10.0) |
| Pruritis (%) | 6 (10.0) |

**Abbreviations**: OMB= Ombitasvir; PTV = Paritaprevir; RTV = Ritonavir; DSV= Dasabuvir

**Source: Feld JJ, et al. J Hepatol. 2016;64:301-7.**

# OMB-PTV-RTV + DSV in GT1b and Compensated Cirrhosis TURQUOISE-III: Adverse Effects

| Laboratory Abnormalities | OMB-PTV-RTV + DSV x 12 weeks (n = 60) |
|---|---|
| Hemoglobin(%) | 13 (21.7) |
| Total bilirubin<br>Grade 2 (>1.5-3 x ULN)<br>Grade 3 (>3-10 x ULN) | <br>12 (20.0)<br>0 |
| Alanine aminotransferase (%)<br>Grade 3 (>5-20 x ULN) | <br>1 (1.7) |
| Aspartate aminotransferase (%)<br>Grade 3 (>5-20 x ULN) | <br>0 |

**Abbreviations**: OMB= Ombitasvir; PTV = Paritaprevir; RTV = Ritonavir; DSV= Dasabuvir

**Source: Feld JJ, et al. J Hepatol. 2016;64:301-7.**

# OMB-PTV-RTV + DSV in GT1b and Compensated Cirrhosis TURQUOISE-III: Conclusions

**Conclusions**: “The HCV regimen of ombitasvir/paritaprevir/ritonavir and dasabuvir without ribavirin for 12 weeks achieved 100% SVR12 and was well tolerated in HCV genotype 1b-infected patients with cirrhosis, suggesting that this 12-week ribavirin-free regimen is sufficient in this population.”

**Source: Feld JJ, et al. J Hepatol. 2016;64:301-7.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir in Patients with HCV-HIV Coinfection

Hepatitis web study

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir in Patients Pre and Post Liver Transplant

Hepatitis web study

Phase 2

Treatment Naïve and Treatment Experienced

Liver Transplantation

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir + RBV in Liver Transplant Recipients with Recurrent HCV GT1

# CORAL-I

Kwo PY, et al. N Engl J Med. 2014;371:2375-82.

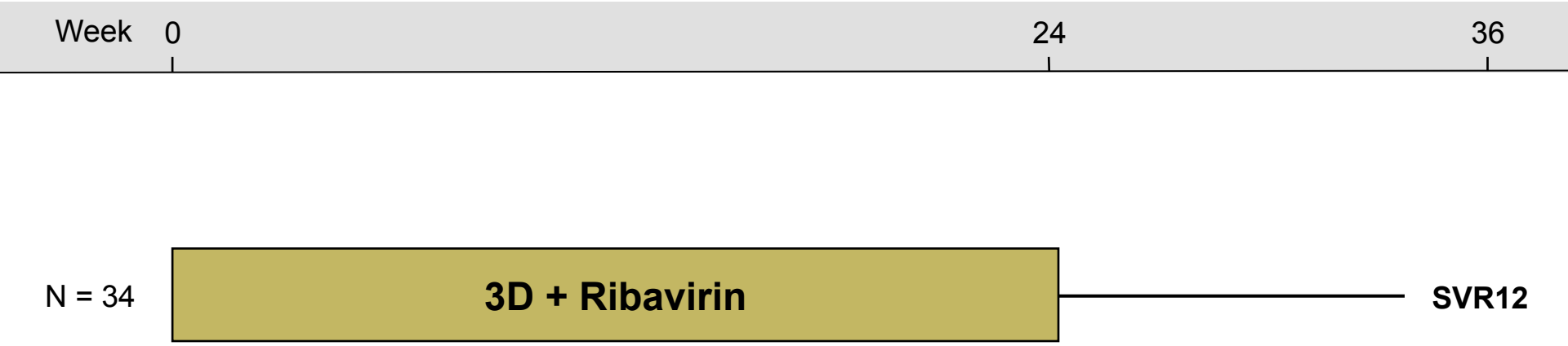
# 3D + RBV in Liver Transplant Recipients with Recurrent HCV GT1
# CORAL-I Trial: Study Design

**CORAL-I: Features**

- **Design**: Phase 2, open-label, single-arm trial evaluating safety and efficacy of 3D (ombitasvir-paritaprevir-ritonavir + dasabuvir) + ribavirin x 24 weeks in liver transplant recipients with recurrent HCV GT 1
- **Setting**: International
- **Entry Criteria**
  - Chronic HCV infection with genotype 1
  - Liver transplantation due to HCV at least 12 months prior
  - Treatment-naïve after transplantation
  - Pre-transplant treatment with peginterferon + ribavirin allowed
  - Age 18-70
  - Metavir score ≤F2 confirmed by liver biopsy
- **Use of Immunosuppressants**
  - Receiving stable immunosuppressant regimen (tacrolimus or cyclosporin)
  - Tacrolimus or cyclosporin dose based on phase I pharmacokinetic study
  - Prednisone at dose ≤ 5 mg/day permitted but not use of mTOR inhibitors
- **Primary End-Point**: SVR12

**Source: Kwo PY, et al. N Engl J Med. 2014;371:2375-82.**

# 3D + RBV in Liver Transplant Recipients with Recurrent HCV GT1
## CORAL-I Trial: Regimen




**3D** = Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir

**Drug Dosing**

Ombitasvir-Paritaprevir-Ritonavir- (25/150/100 mg once daily) + Dasabuvir: 250 mg twice daily

Ribavirin (RBV): dosing managed per investigator discretion; most patients received 600-800 mg/day

**Source: Kwo PY, et al. N Engl J Med. 2014;371:2375-82.**

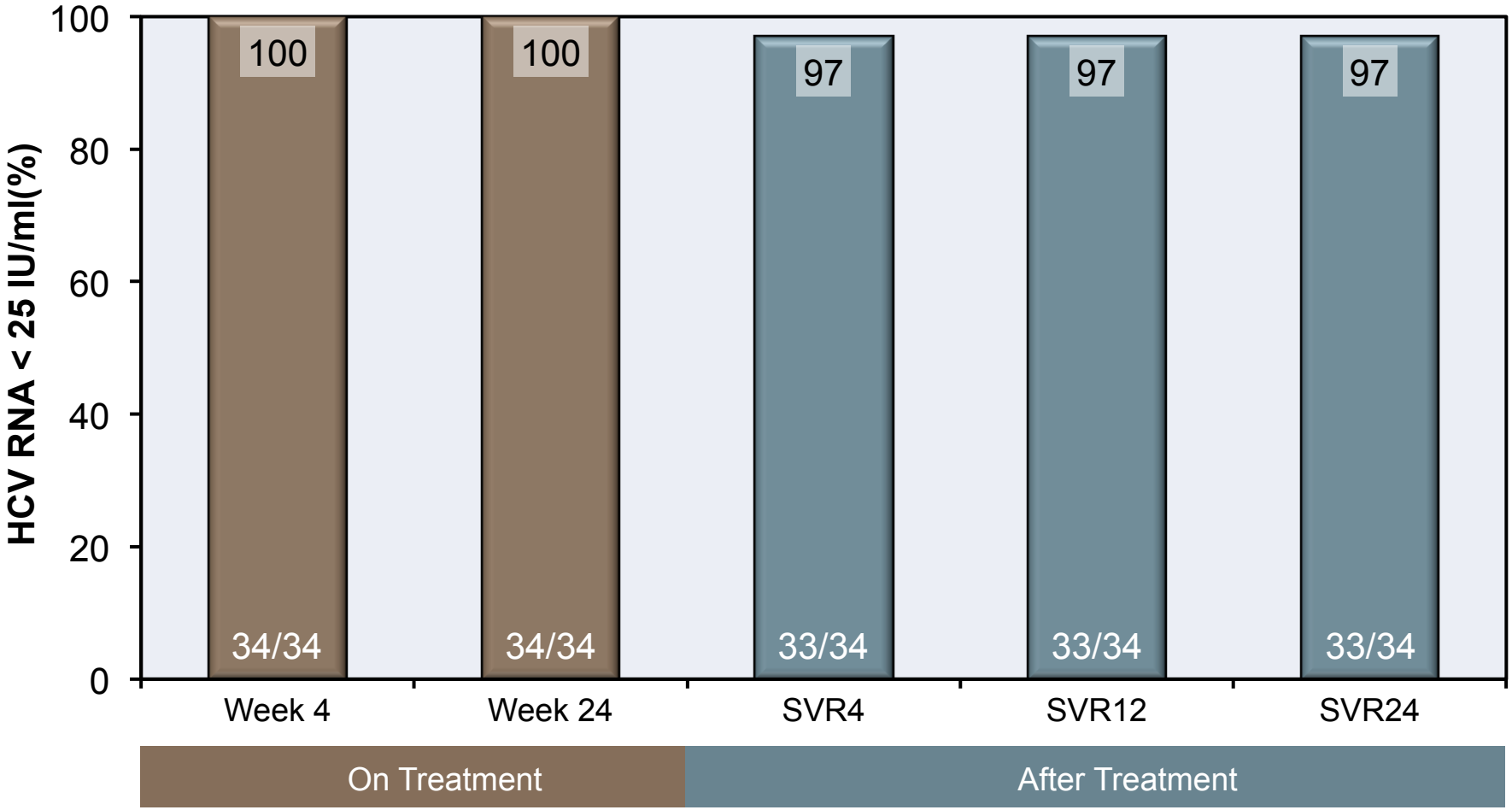
# 3D + RBV in Liver Transplant Recipients with Recurrent HCV GT1
## CORAL-I Trial: Baseline Characteristics

| **Baseline Characteristic** | **3D + Ribavirin** (n=34) |
|---|---|
| Age (years), Mean | 59.6 |
| Male sex–no. (%) | 27 (79) |
| Race–no. (%)<br>White<br>Black<br>Multiple | <br>29 (85)<br>4 (12)<br>1 (3) |
| Body Mass Index (kg/m$^2$) Mean | 29.7 |
| HCV genotype–no. (%)<br>1a<br>1b | <br>29 (85)<br>5 (15) |
| IL28B, non-CC genotype–no. (%) | 26 (76) |
| HCV RNA, $\log_{10}$ IU/ml | 6.6 |
| Fibrosis stage (%)<br>F0<br>F1<br>F2 | <br>6 (18)<br>13 (38)<br>15 (44) |

**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = ribavirin

**Source: Kwo PY, et al. N Engl J Med. 2014;371:2375-82.**

# 3D + RBV in Liver Transplant Recipients with Recurrent HCV GT1
## CORAL-I Trial: Results




Source: Kwo PY, et al. N Engl J Med. 2014;371:2375-82.

Hepatitis web study

# 3D + RBV in Liver Transplant Recipients with Recurrent HCV GT1
## CORAL-I Trial: Adverse Events

| Adverse Event Occurring in > 15% of the 34 Patients Receiving 3D + RBV | |
|---|---|
| **Event** | **N (%)** |
| Any adverse event | 33 (97) |
| Fatigue | 17 (50) |
| Headache | 15 (44) |
| Cough | 11 (32) |
| Anemia | 10 (29) |
| Diarrhea | 9 (26) |
| Insomnia | 9 (26) |
| Asthenia | 8 (24) |
| Nausea | 8 (24) |
| Muscle spasms | 7 (21) |
| Rash | 7 (21) |
| Back pain | 6 (18) |
| Dizziness | 6 (18) |
| Peripheral edema | 6 (18 |
| Rhinorrhea | 6 (18) |

**3D** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = ribavirin

**Source: Kwo PY, et al. N Engl J Med. 2014;371:2375-82.**

# 3D + RBV in Liver Transplant Recipients with Recurrent HCV GT1
# CORAL-I Trial: Conclusions

**Conclusions**: “Treatment with the multitargeted regimen of ombitasvir-ABT-450/r and dasabuvir with ribavirin was associated with a low rate of serious adverse events and a high rate of sustained virologic response among liver-transplant recipients with recurrent HCV genotype 1 infection, a historically difficult-to-treat population.”

**Note:** ABT-450/r = Paritaprevir-Ritonavir

**Source: Kwo PY, et al. N Engl J Med. 2014;371:2375-82.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir in Patients with Renal Disease

Phase 3b

Treatment-Naive

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir in GT1 and Renal Disease

# RUBY-I

Pockros PJ, Gastroenterology. 2016;150:1590-8.

Hepatitis web study

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir in GT1 & Renal Disease

## RUBY-I: Study Design

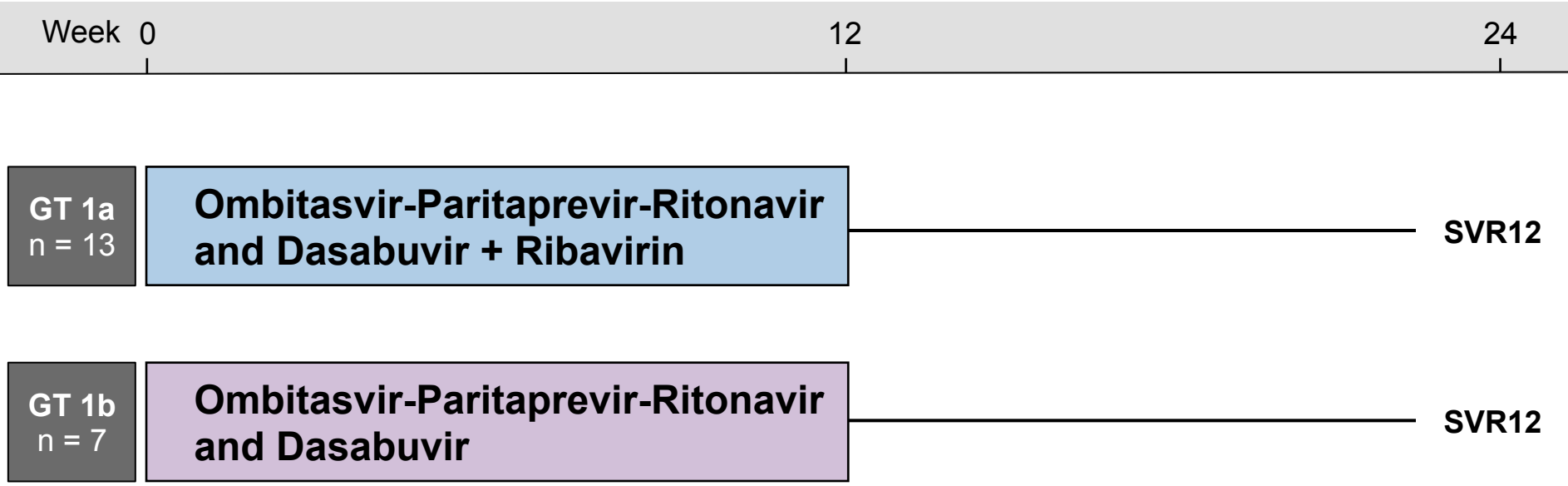
### RUBY-I: Features

- **Design**: Phase 3b, randomized, open-label trial evaluating safety and efficacy of 3D (ombitasvir-paritaprevir-ritonavir and dasabuvir) with or without ribavirin for 12 weeks in treatment-naïve patients with chronic HCV GT1 and advanced kidney disease
- **Setting**: 9 sites in United States
- **Entry Criteria**
  - Adults with chronic HCV genotype 1 infection
  - Chronic kidney disease stage 4 or 5 (eGFR <30 mL/min/1.73 $m^2$) +/- HD
  - Plasma HCV RNA greater than 1,000 IU/mL
  - Absence of cirrhosis
  - Absence of coinfection with HBV or HIV
  - Baseline Hb ≥10 g/dL
- **Primary End-Point**: SVR12

**Source: Pockros PJ, Gastroenterology. 2016;150:1590-8.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir in GT1 & Renal Disease

## RUBY-I: Regimens




**Drug Dosing**

Ombitasvir-Paritaprevir-Ritonavir (25/150/100 mg once daily) + Dasabuvir: 250 mg twice daily

Ribavirin for patients not on hemodialysis: 200 mg once daily

Ribavirin for patients on hemodialysis: 200 mg given 4 hours before each hemodialysis session

**Source: Pockros PJ, Gastroenterology. 2016;150:1590-8.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir in GT1 & Renal Disease

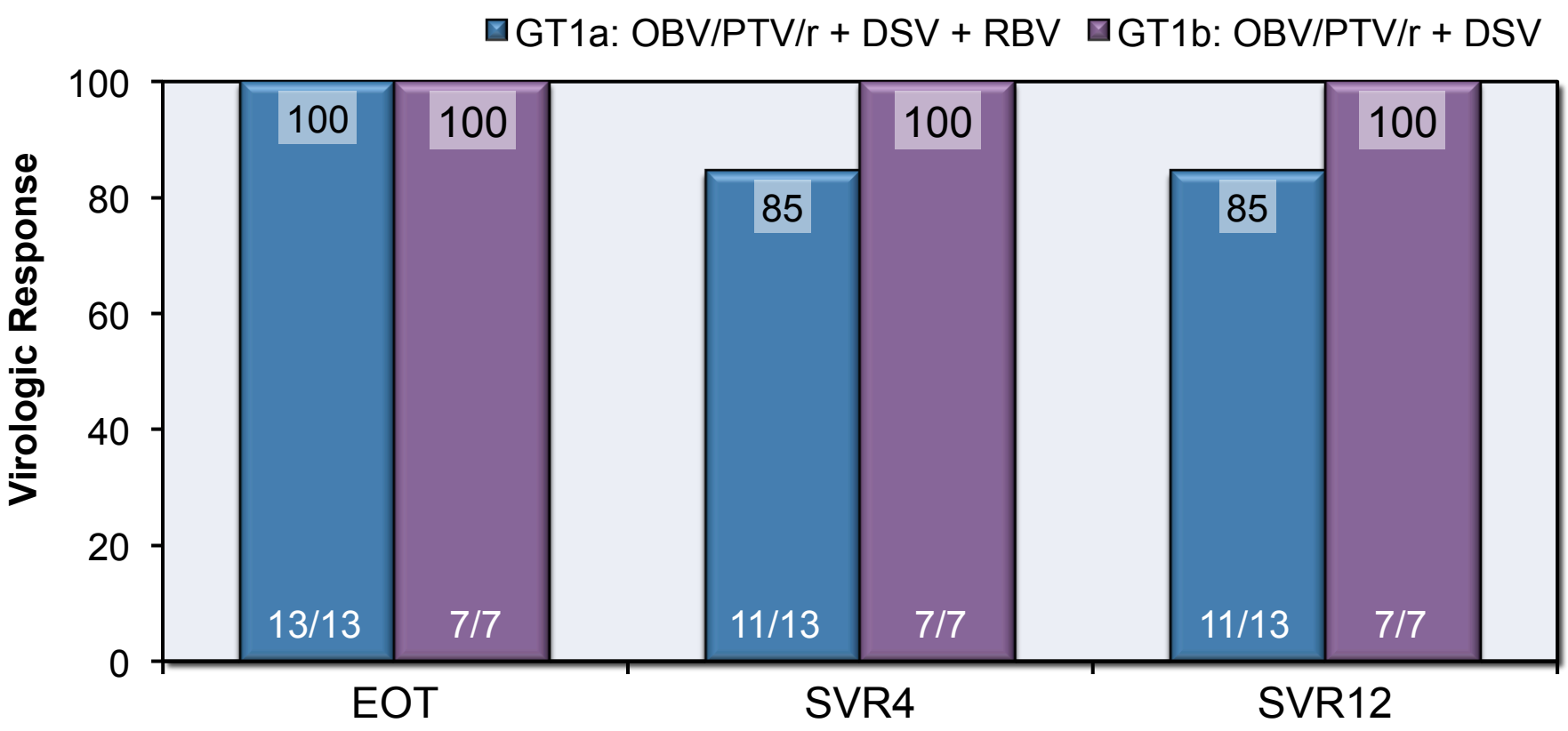
## RUBY-I: Baseline Characteristics

| Baseline Characteristic | All Patients (n = 20) |
|---|---|
| Male, % | 17 (85%) |
| Median age, years (range) | 60 (49-69) |
| Race<br>Black<br>Hispanic | <br>14 (70%)<br>3 (15%) |
| Median HCV RNA, $log_{10}$ IU/ml (range) | 6.6 (5.5-7.6) |
| Degree of Fibrosis, n (%)<br>F0-F1<br>F2<br>F3 | <br>10 (50%)<br>6 (30%)<br>4 (20%) |
| CKD Stage; n (%)<br>4 (eGFR 15-30 mL/min/1.73 $m^2$)<br>5 (eGFR <15 mL/min/1.73 $m^2$ or requiring HD) | <br>6 (30)<br>14 (70) |
| eGFR, mL/min/1.73 $m^2$ | 10.9 (5.4-29.9) |

**Source: Pockros PJ, Gastroenterology. 2016;150:1590-8.**

# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir in GT1 & Renal Disease
## RUBY-I: Baseline Results

### RUBY-I: SVR 12 Rates*




**OBV/PTV/r + DSV** = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = ribavirin

**Source: Pockros PJ, Gastroenterology. 2016;150:1590-8.**

# RUBY-I: Conclusions

**Conclusions**: “In a clinical trial, the combination of ombitasvir, paritaprevir, and ritonavir, administered with dasabuvir, led to an SVR12 in 90% of patients with HCV genotype 1 infection and stage 4 or 5 CKD. The regimen is well tolerated, though ribavirin use may require a reduction or interruption to manage anemia.”

**Source: Pockros PJ, Gastroenterology. 2016;150:1590-8.**

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