HEPATITIS C ONLINE

Glecaprevir-Pibrentasvir (*Mavyret*)

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Glecaprevir-Pibrentasvir (*Mavyret*)

- **Indications and Usage**
  - Treatment-naïve adults and pediatric patients ≥12 years of age (or weight ≥45 kg) with chronic HCV genotypes 1, 2, 3, 4, 5, or 6 without cirrhosis and with compensated cirrhosis (Child-Pugh class A)
  - HCV genotype 1 previously treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both
- **Class & Mechanism**
  - Glecaprevir (GLE): HCV NS3/4A protease inhibitor
  - Pibrentasvir (PIB): HCV NS5A inhibitor
- **Medication Form (Tablet)**
  - 100 mg Glecaprevir and 40 mg Pibrentasvir
- **Dosing**
  - Three tablets orally once daily, with food (total daily dose of Glecaprevir 300 mg and Pibrentasvir 120 mg)
- **Adverse Effects (AE)**
  - Most common headache and fatigue

Source: *Mavyret* Prescribing Information. AbbVie., Inc.

Glecaprevir-Pibrentasvir (*Mavyret*) Recommended Duration for Treatment-Naïve Patients

Glecaprevir-Pibrentasvir in HCV Treatment-Naïve Patients		
HCV Genotype	**Recommended Treatment Duration**	
	No Cirrhosis	**Compensated Cirrhosis (Child-Pugh Class A)**
Genotype 1	8 weeks	8 weeks
Genotype 2	8 weeks	8 weeks
Genotype 3	8 weeks	8 weeks
Genotype 4	8 weeks	8 weeks
Genotype 5	8 weeks	8 weeks
Genotype 6	8 weeks	8 weeks

Source: *Mavyret* Prescribing Information. AbbVie.

Glecaprevir-Pibrentasvir (*Mavyret*) Indications: Treatment Experienced-Patients

Glecaprevir-Pibrentasvir in HCV Treatment-Experienced Patients			
HCV Genotype	**Patients Previously Treated With a Regimen Containing:**	**Treatment Duration**	
		No Cirrhosis	**Compensated Cirrhosis (Child-Pugh Class A)**
1	An NS5A inhibitor[1] without prior treatment with an NS3/4A protease inhibitor	16 weeks	16 weeks
	An NS3/4A PI[2] without prior treatment with an NS5A inhibitor	12 weeks	12 weeks
1, 2, 4, 5, or 6	PEG + RIB +/- sofosbuvir (NS5B inhibitor)[3]	8 weeks	12 weeks
3	PEG + RIB +/- sofosbuvir (NS5B inhibitor)[3]	16 weeks	16 weeks

[1]In clinical trials, subjects were treated with prior regimens containing ledipasvir and sofosbuvir or daclatasvir with pegylated interferon and ribavirin.
[2]In clinical trials, subjects were treated with prior regimens containing simeprevir and sofosbuvir, or simeprevir, boceprevir, or telaprevir with pegylated interferon and ribavirin
[3]Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor.

Source: *Mavyret* Prescribing Information. AbbVie.

Glecaprevir-Pibrentasvir (GLE-PIB): Participants without Cirrhosis

Summary of Key Phase 3 Trials

- **ENDURANCE 1**: GLE-PIB x 8 or 12 weeks in GT1 without cirrhosis
- **ENDURANCE 2**: GLE-PIB x 12 weeks in GT2 without cirrhosis
- **ENDURANCE 3**: GLE-PIB x 8 or 12 weeks vs SOF + DCV in GT3 without cirrhosis
- **ENDURANCE 4**: GLE-PIB x 12 weeks in GT 4, 5, 6 without cirrhosis
- **ENDURANCE 5, 6**: GLE-PIB x 8 or 12 weeks in GT 5 or 6 without cirrhosis

Summary of Key Phase 2 Trials

- **MEGALLAN-1 (Part 1)**: GLE-PIB +/- RBV x 12 weeks, GT1, prior DAA without cirrhosis

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Glecaprevir-Pibrentasvir (GLE-PIB): Summary of Key Phase 3 Trials Participants with Compensated Cirrhosis Allowed

- **EXPEDITION-1**: GLE-PIB x 12 weeks in GT 1, 2, 4, 5, or 6 with compensated cirrhosis
- **EXPEDITION-2**: GLE-PIB x 8 or 12 weeks in GT 1-6 with HIV coinfection +/- cirrhosis
- **EXPEDITION-4**: GLE-PIB x 12 weeks in GT 1-6 with renal disease +/- cirrhosis
- **EXPEDITION-5**: GLE-PIB x 8, 12, or 16 weeks in GT 1-6 with renal disease +/- cirrhosis
- **EXPEDITION-8**: GLE-PIB x 8 weeks in GT 1-6 with compensated cirrhosis
- **POOLED ANALYSIS**: GLE-PIB x 8-16 weeks in GT 1-6 with compensated cirrhosis
- **MEGALLAN-1 (Part 2)**: GLE-PIB x 12 or 16 weeks, GT 1 or 4, prior DAA, +/- cirrhosis
- **MEGALLAN-3**: GLE-PIB + SOF + RBV x 12 or 16 weeks, GT 1-3, prior GLE-PIB, +/- cirrhosis
- **SURVEYOR-II (Part 3)**: GLE-PIB x 12 or 16 weeks, GT 3, +/- prior treatment, +/- cirrhosis
- **HCV TARGET**: GLE-PIB +/- RBV x 12 or 16 weeks, GT 1, prior NS5A/NS5B Rx +/- cirrhosis

Glecaprevir-Pibrentasvir x 8 or 12 Weeks in GT1 without Cirrhosis

ENDURANCE-1

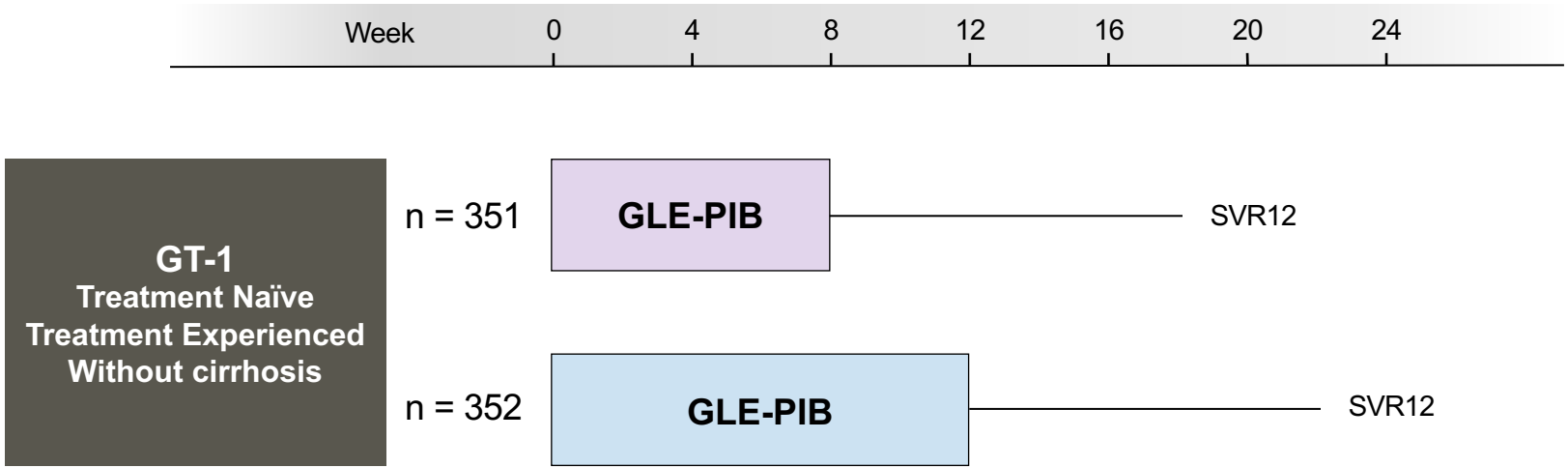
Source: Zeuzem S, et al. N Engl J Med. 2018;378:354-69.

Glecaprevir-Pibrentasvir for 8 or 12 weeks in Non-Cirrhotic GT 1 ENDURANCE-1: Study Features

- **Design:** Randomized, open-labeled, phase 3 trial to evaluate the safety and efficacy of the fixed-dose combination of glecaprevir-pibrentasvir for 8 versus 12 weeks in treatment-naïve or treatment-experienced adults with GT 1 chronic HCV infection without cirrhosis
- **Key Eligibility Criteria**
  - Chronic HCV GT 1
  - Age ≥18
  - HCV RNA ≥1,000 IU/mL at screening
  - Naïve or treated with peginterferon +/- ribavirin (PR) or PR +/- sofosbuvir
  - Absence of cirrhosis
  - HIV coinfection allowed; chronic HBV coinfection excluded
- **Primary End Point:** SVR12

Source: Zeuzem S, et al. N Engl J Med. 2018;378:354-69.

Glecaprevir-Pibrentasvir for 8 or 12 weeks in Non-Cirrhotic GT 1 ENDURANCE-1: Study Design



Abbreviations: GLE-PIB= Glecaprevir-pibrentasvir

Drug Dosing: Glecaprevir-pibrentasvir (100/40 mg) fixed-dose combination, three pills (300/120 mg) once daily

Source: Zeuzem S, et al. N Engl J Med. 2018;378:354-69.

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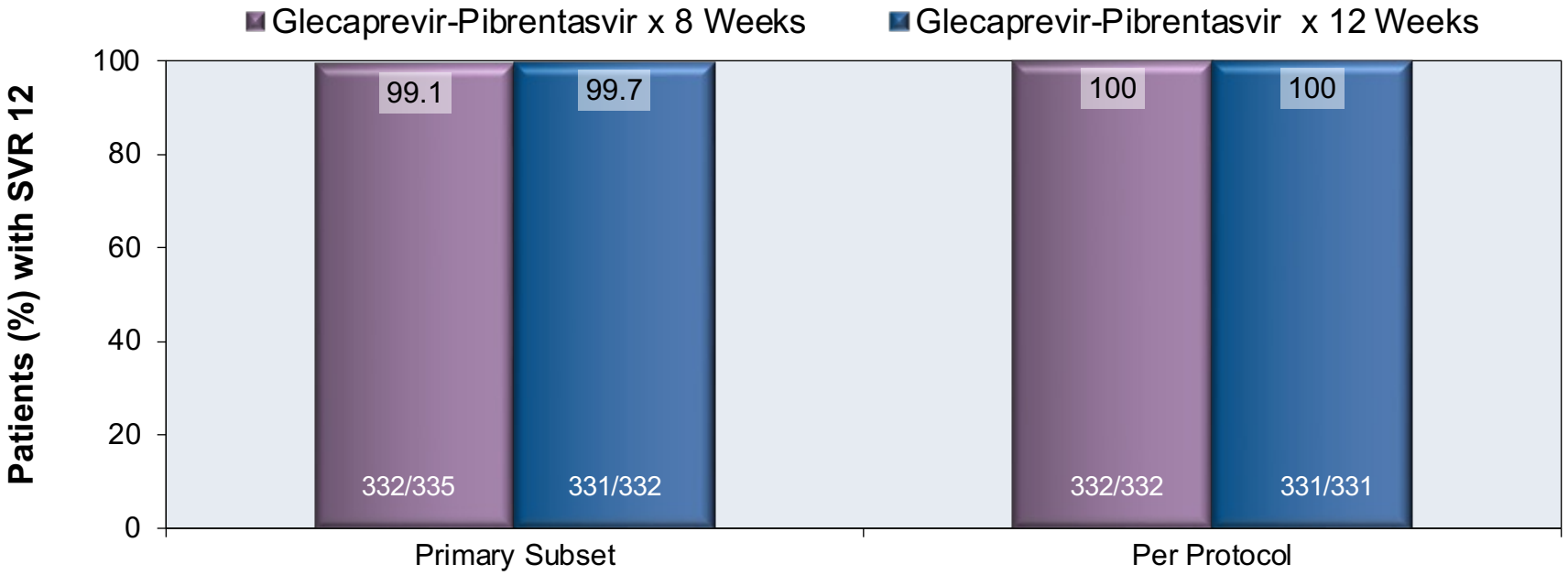
Glecaprevir-Pibrentasvir for 8 or 12 weeks in Non-Cirrhotic GT 1 ENDURANCE-1: Baseline Characteristics

Baseline Characteristics	GLE-PIB 8 weeks (n = 351)	GLE-PIB 12 weeks (n = 352)
Median age, (range), years	53 (19-84)	52 (21-77)
Male, n (%)	167 (48)	176 (50)
Black race, n (%)	14 (4)	13 (4)
HCV subtype 1a, n (%)	151 (43)	144 (41)
Body mass index, median kg/m^2 (range)	25 (18-41)	25 (18-54)
Median HCV RNA, log$_{10}$ IU/mL (range)	6.1 (1.2-7.6)	6.1 (3.3-7.4)
Non-CC IL28B genotype, n (%)	249 (71)	266 (76)
Fibrosis Stage, n (%)		
F0 or F1	296/348 (85)	298/351 (85)
F2	22/348 (6)	24/351 (7)
F3	30/348 (9)	29/351 (8)
Injection drug use, n (%)	98 (28)	98 (28)
HIV coinfection n (%)	15 (4)	18 (5)

Source: Zeuzem S, et al. N Engl J Med. 2018;378:354-69.

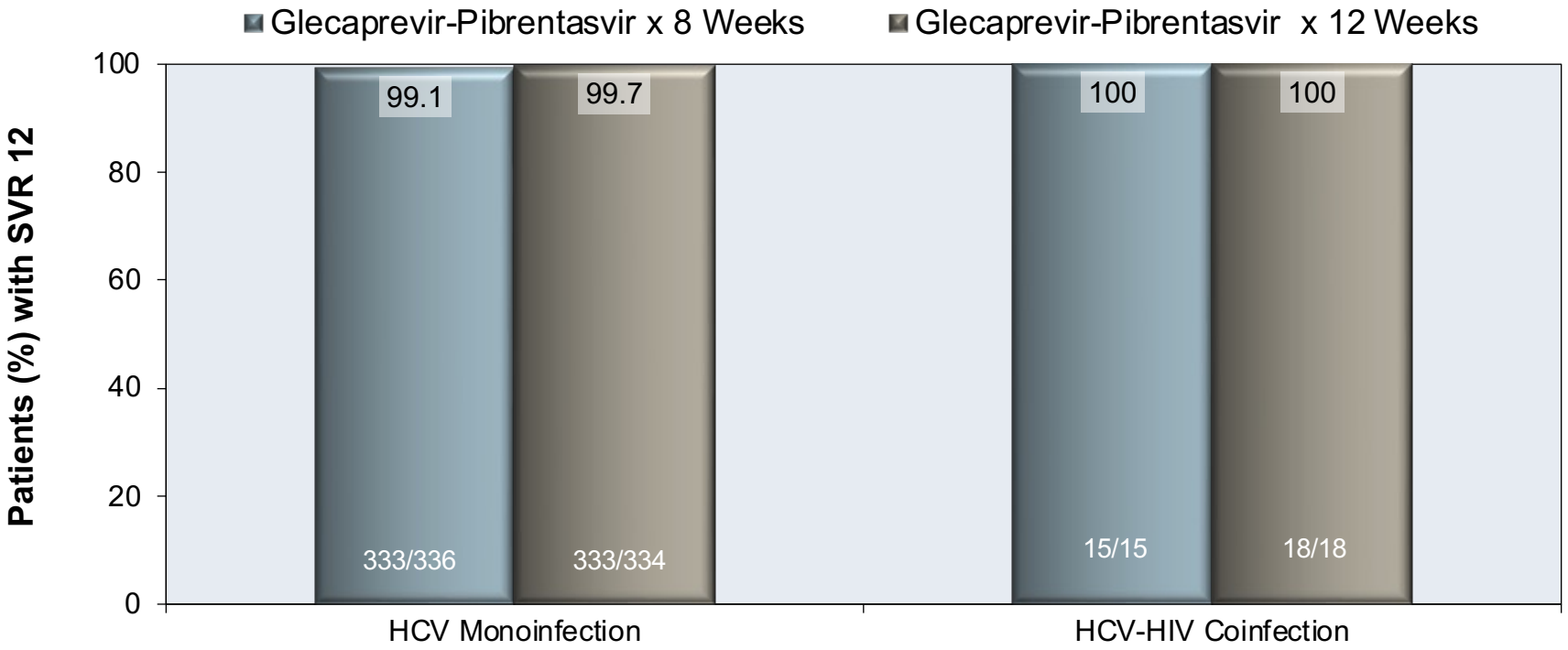
Glecaprevir-Pibrentasvir for 8 or 12 weeks in Non-Cirrhotic GT 1 ENDURANCE-1: Baseline Characteristics



Primary Subset: excludes patients with HIV or previous treatment with sofosbuvir
Per-Protocol: excludes patients in primary subset who (1) prematurely discontinued treatment or had virologic failure during treatment before week 8, or (2) patients without virologic failure who had no HCV RNA value in the SVR12 assessment window

Source: Zeuzem S, et al. N Engl J Med. 2018;378:354-69.

Glecaprevir-Pibrentasvir for 8 or 12 weeks in Non-Cirrhotic GT 1 ENDURANCE-1: Baseline Characteristics



Source: Zeuzem S, et al. N Engl J Med. 2018;378:354-69.

Glecaprevir-Pibrentasvir for 8 or 12 weeks in Non-Cirrhotic GT 1 *ENDURANCE-1: Conclusions

Conclusion: “Once-daily treatment with glecaprevir–pibrentasvir for either 8 weeks or 12 weeks achieved high rates of sustained virologic response among patients with HCV genotype 1 or 3 infection who did not have cirrhosis.”

***Note**: ENDURANCE-1 was published in conjunction with ENDURANCE-3

Source: Zeuzem S, et al. N Engl J Med. 2018;378:354-69.

Glecaprevir-Pibrentasvir in Genotype 2 without Cirrhosis

ENDURANCE-2

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2018;16:417-26.

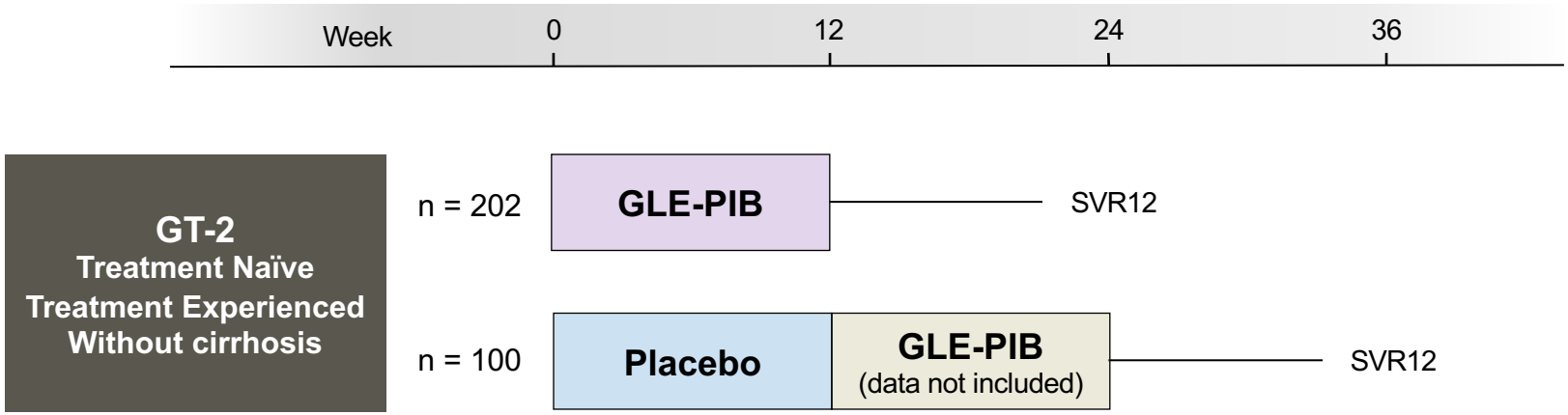
Glecaprevir-Pibrentasvir in Non-Cirrhotic GT 2 *ENDURANCE-2: Study Features

- **Design:** Randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the safety and efficacy of the fixed-dose combination of glecaprevir-pibrentasvir for 12 weeks in treatment-naïve or treatment-experienced adults with GT 2 chronic HCV (without cirrhosis).
- **Setting:** Multiple centers in United States, Europe, and Asia
- **Key Eligibility Criteria**
  - Chronic HCV genotype 2
  - Age ≥18 years
  - HCV RNA ≥1,000 IU/mL at screening
  - Naïve or treated with (1) PEG (or IFN) +/- RBV or (2) SOF + RBV +/- PEG
  - Absence of cirrhosis
  - HIV or HBV coinfection excluded
- **Primary End Point:** SVR12 time

***Note**: ENDURANCE-2 was published in conjunction with ENDURANCE-4 and SURVEYOR-II (Part 4)

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2018;16:417-26.

Glecaprevir-Pibrentasvir in Non-Cirrhotic GT 2 ENDURANCE-2: Study Design



Note: Four patients enrolled in GT2 arm later determined to be infected with GT1 by phylogenetic analysis

Abbreviations: GLE-PIB = Glecaprevir-pibrentasvir

Drug Dosing: Glecaprevir-pibrentasvir (100/40 mg) fixed-dose combination, three pills (300/120 mg) once daily

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2018;16:417-26.

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Glecaprevir-Pibrentasvir in Non-Cirrhotic GT 2
ENDURANCE-2: Baseline Characteristics

Baseline Characteristic	GLE-PIB (n = 202)	Placebo (n = 100)
Age, mean ± SD, years	57 ± 12.8	58 ± 12.0
Male, n (%)	98 (49)	45 (45)
Race, n (%) White Black Asian	 121 (60) 7 (3) 69 (34)	 60 (60) 7 (7) 32 (32)
BMI, mean, ± SD kg/m^2	25.8 ± 4.7	26.4 ± 4.1
HCV RNA, median (range), log_{10} IU/mL	6.25 (2.5-7.3)	6.39 (3.4-7.2)
IL28B non-CC, n (%)	111 (55)	50 (50)
Former IDU, n (%)	32 (16)	18 (18)

*One patient in active arm with subtype 2i.

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2018;16:417-26.

Glecaprevir-Pibrentasvir in Non-Cirrhotic GT 2
ENDURANCE-2: Baseline Characteristics

Baseline Characteristic	GLE-PIB (n = 202)	Placebo (n = 100)
Fibrosis Stage, n (%) F0-1 F2 F3	 154 (76) 18 (9) 30 (15)	 85 (85) 9 (9) 6 (6)
Treatment-naïve, n (%)	141 (70)	71 (71)
Treatment-experienced, n (%) IFN or PEG ± RBV, n (%) SOF + RBV ± PEG, n (%)	61 (30) 55 (27) 6 (3)	29 (29) 27 (27) 2 (2)
Concomitant PPI use, n (%)	22 (11)	11 (11)

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2018;16:417-26.

Glecaprevir-Pibrentasvir in Non-Cirrhotic GT 2
ENDURANCE-2: Baseline Polymorphisms

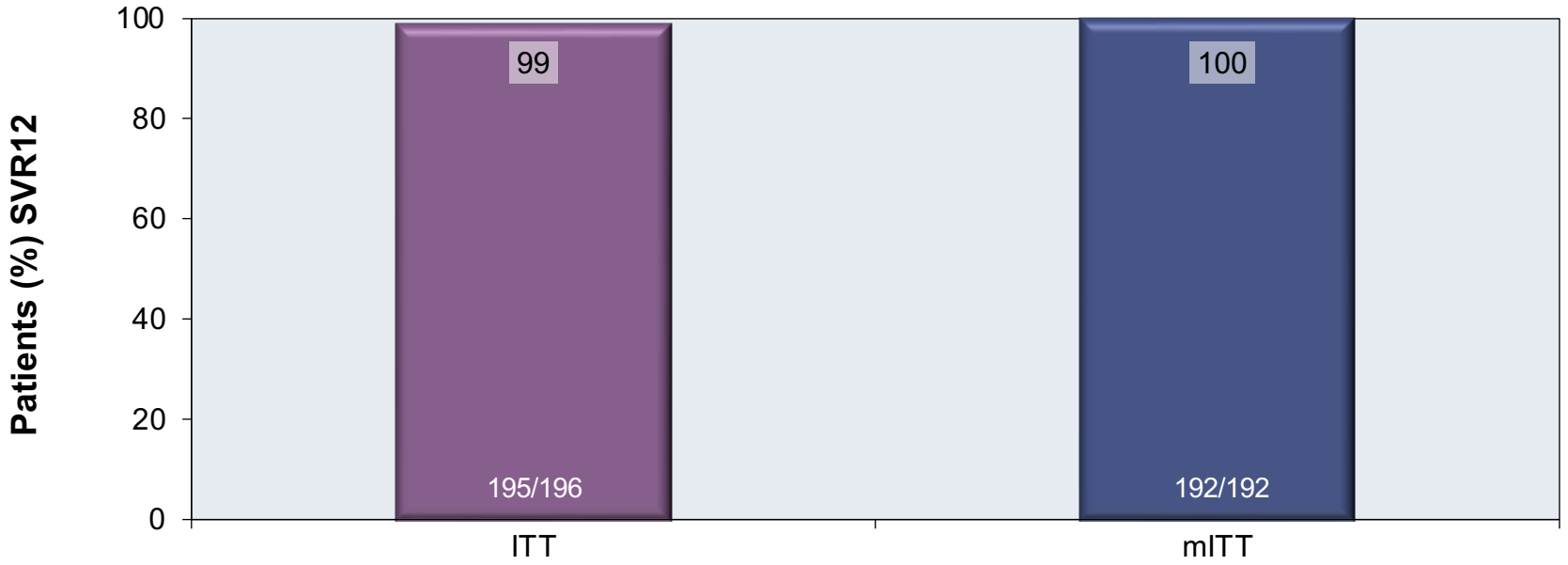
Prevalence of Baseline Polymorphism*, n (%)*	Genotype 2 (n = 160)
None	28 (18)
NS3 only	0
NS5A only	132 (83)
Both NS3 + NS5A	0

*Baseline polymorphisms detected by next generation sequencing at a 15% threshold in samples that had sequences available for both targets (N) at the following amino acid positions: NS3 at positions 155, 156, and 168; NS5A at positions 24, 28, 30, 31, 58, 92, and 93

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2018;16:417-26.

Glecaprevir-Pibrentasvir in Non-Cirrhotic GT 2 ENDURANCE-2: Results

ENDURANCE-2: Overall SVR, by Analysis



ITT (intent-to-treat): excludes 6 sofosbuvir-experienced patients, all of whom achieved SVR12
mITT (modified intent-to-treat): excludes patients with non-virologic failure and those with ineligible genotype

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2018;16:417-26.

Glecaprevir-Pibrentasvir in Non-Cirrhotic GT 2 ENDURANCE-2: Adverse Events

Adverse Event (AE), n (%)	**GLE-PIB** 12 weeks (n = 202)	**Placebo** (n = 100)
Discontinuation due to AE	0	0
Serious Adverse Events (SAEs)§	3 (1)	1 (1)
Deaths	0	0
Any AE in >10% of patients		
Headache	24 (12)	12 (12)
Fatigue	23 (11)	10 (10)
Laboratory AEs		
AST elevation, grade 3-4 (>5x ULN)	2 (1)	1 (1)
ALT elevation, grade 3-4 (>5x ULN)*	1 (0.5)	2 (2)
Total bilirubin, grade 3 (3-10x ULN)#	1 (0.5)	0

§ No serious AEs were deemed to be DAA-related; no SAEs led to drug discontinuation.
Event occurred with grade 3 AST and grade 3 alkaline phosphatase elevation in context of cholelithiasis.
#Indirect hyperbilirubinemia; no associated ALT elevation. Declined with treatment.

Abbreviations: AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit normal

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2018;16:417-26.

Glecaprevir-Pibrentasvir in Non-Cirrhotic GT 2 *ENDURANCE-2: Conclusions

Conclusion: “The SVR12 rate in all genotype 2-infected patients treated for 12 weeks (including those with sofosbuvir experience) was 99.5%, with no virologic failures.”

***Note**: ENDURANCE-2 was published in conjunction with ENDURANCE-4 and SURVEYOR-II (Part 4)

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2018;16:417-26.

Glecaprevir-Pibrentasvir in Treatment-Naïve, GT 3 without Cirrhosis

ENDURANCE-3

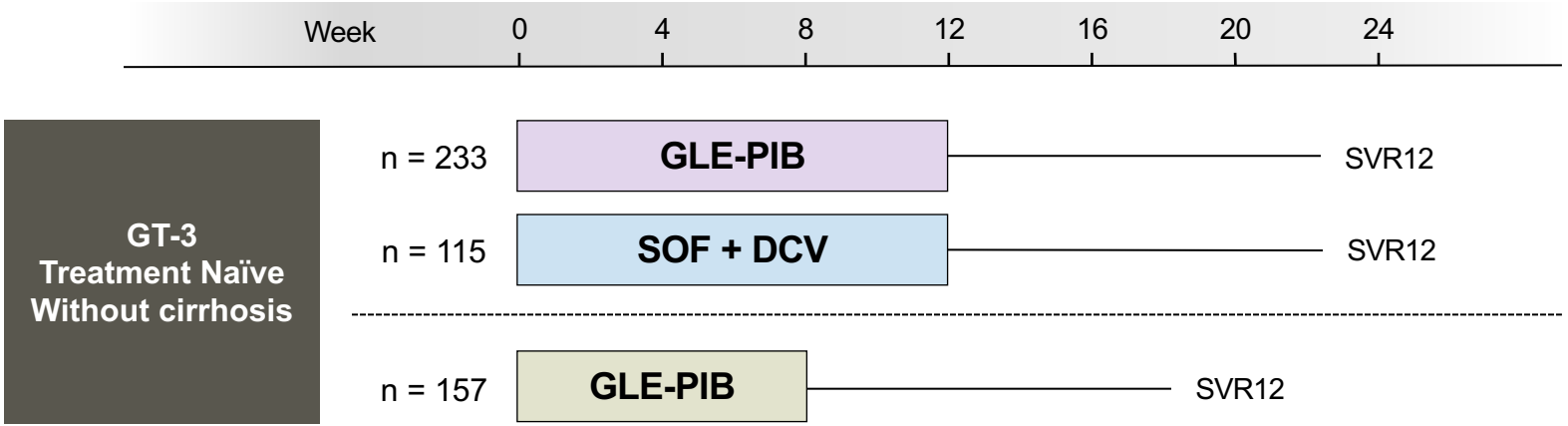
Source: Zeuzem S, et al. N Engl J Med. 2018;378:354-69.

Glecaprevir-Pibrentasvir in Treatment-Naïve, Non-Cirrhotic GT 3 ENDURANCE-3: Study Features

- **Design**: Randomized, phase 3 trial to evaluate the safety and efficacy of the fixed-dose combination of glecaprevir-pibrentasvir for 8 or 12 weeks compared with 12 weeks of sofosbuvir and daclatasvir in treatment-naïve adults with GT 3 chronic HCV infection without cirrhosis
- **Key Eligibility Criteria**
  - Chronic HCV GT 3
  - Age ≥18 years
  - HCV RNA ≥1,000 IU/mL at screening
  - Treatment-naïve
  - No cirrhosis (METAVIR score ≤3 or equivalent)
  - HIV or chronic HBV coinfection excluded
- **Primary End Point**: SVR12

Source: Zeuzem S, et al. N Engl J Med. 2018;378:354-69.

Glecaprevir-Pibrentasvir in Treatment-Naïve Non-Cirrhotic GT 3 ENDURANCE-3: Study Design



348 patients were randomized in 2:1 ratio to 12 weeks of GLE-PIB vs SOF + DCV.
157 were not randomized but assigned to 8 weeks of GLE-PIB.

Abbreviations: GLE-PIB = glecaprevir-pibrentasvir; SOF = sofosbuvir; DCV = daclatasvir

Drug Dosing: Glecaprevir-pibrentasvir 300/120 mg once daily *or* Sofosbuvir 400 mg once daily plus Daclatasvir 60 mg once daily

Source: Zeuzem S, et al. N Engl J Med. 2018;378:354-69.

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Glecaprevir-Pibrentasvir in Treatment-Naïve Non-Cirrhotic GT 3 ENDURANCE-3: Baseline Characteristics

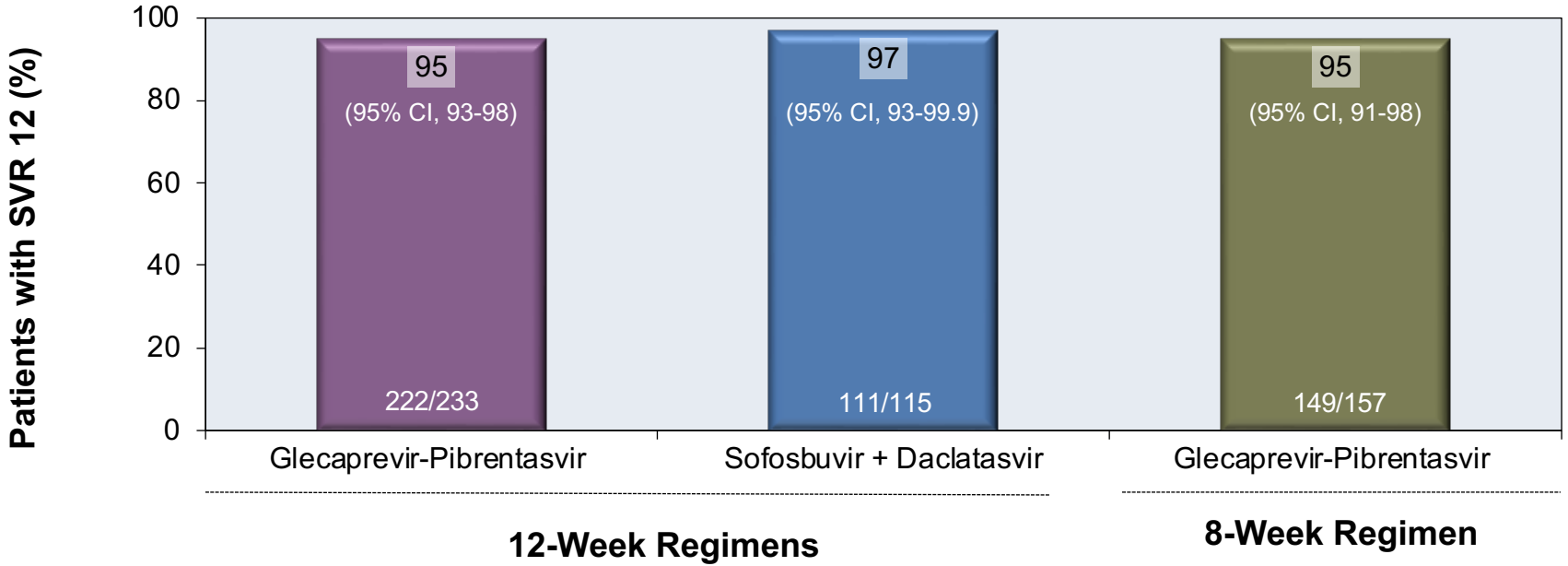
Characteristics	2:1 randomization		Non-randomized
	eGLE-PIB 12 wk (n = 233)	SOF + DCV 12 wk (n = 115)	GLE-PIB 8 wk (n = 157)
Median age, (range) years	48 (22-71)	49 (20-70)	47 (20-76)
Male sex, n (%)	121 (52)	52 (45)	92 (59)
Black race, n (%)	4 (2)	4 (3)	3 (2)
History of injection drug use, n (%)	149 (64)	73 (63)	104 (66)
BMI, median kg/m^2 (range)	25 (17-49)	25 (18-42)	26 (18-44)
Median HCV RNA (range), $\log_{10}$ IU/ml	6.1 (3.5-7.5)	6.0 (3.8-7.4)	6.1 (1.2-7.6)
Fibrosis stage, n (%) F0 or F1 F2 F3	 201/233 (86) 12/233 (5) 20/233 (9)	 97/115 (84) 8/115 (7) 10/115 (9)	 122/157 (78) 8/157 (5) 27/157 (17)
HCV subtype 3a, n (%)	217 (93)	110 (96)	151 (96)

Abbreviations: GLE-PIB = glecaprevir-pibrentasvir; SOF = sofosbuvir; DCV = daclatasvir; BMI = body mass index

Source: Zeuzem S, et al. N Engl J Med. 2018;378:354-69.

Glecaprevir-Pibrentasvir in Treatment-Naïve Non-Cirrhotic GT 3 ENDURANCE-3 Study: Results

ENDURANCE-3: SVR 12 by Treatment Duration and Regimen (ITT Analysis)



GLE-PIB = glecaprevir-pibrentasvir; SOF = sofosbuvir; DCV = daclatasvir; ITT = Intent-to-treat

Source: Zeuzem S, et al. N Engl J Med. 2018;378:354-69.

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Glecaprevir-Pibrentasvir in Treatment-Naïve Non-Cirrhotic GT 3 ENDURANCE-3: Treatment Outcomes

Outcomes, n (%)	2:1 randomization		Non-randomized
	GLE-PIB x 12 weeks (n = 233)	SOF + DCV x 12 weeks (n = 115)	GLE-PIB x 8 weeks (n = 157)
SVR12	222 (95)	111 (97)	149 (95)
Virologic Failure			
Breakthrough	1 (<1)	0	1 (1)
Relapse	3 (1)	1 (1)	5 (3)
Failure due to other reasons			
Discontinuation due to AE	1 (<1)	1 (1)	0
Withdrawal of consent	1 (<1)	0	0
Non-compliance	1 (<1)	0	0
Lost to follow-up / missing SVR12	4 (2)	2 (2)	2 (1)

Abbreviations: SVR = Sustained virologic response; GLE-PIB = glecaprevir-pibrentasvir; SOF = sofosbuvir; DCV = daclatasvir

Source: Zeuzem S, et al. N Engl J Med. 2018;378:354-69.

Glecaprevir-Pibrentasvir in Treatment-Naïve Non-Cirrhotic GT 3
ENDURANCE-3: Resistance Analysis

SVR12 by Baseline Polymorphism, n (%)	2:1 randomization		Non-randomized
	GLE-PIB x 12 weeks	SOF + DCV x 12 weeks	GLE-PIB x 8 weeks
NS3 only	26/26 (100)	--	14/15 (93)
NS5A only	35/36 (97)	20/21 (95)	34/36 (94)
NS3 + NS5A	6/7 (86)	--	5/7 (71)
None	151/153 (99)	89/89 (100)	94/95 (99)

*Detected at 15% threshold by next-generation sequencing in samples that had sequences available at a key subset of amino acid positions: NS3 at positions 36, 55, 56, 80, 155, 156, 166, 168; NS5A at positions 24, 28, 29, 30, 31, 32, 58, 92, 93

Abbreviations: GLE-PIB = glecaprevir-pibrentasvir; SOF = sofosbuvir; DCV = daclatasvir

Source: Zeuzem S, et al. N Engl J Med. 2018;378:354-69.

Glecaprevir-Pibrentasvir in Treatment-Naïve Non-Cirrhotic GT 3 ENDURANCE-3: Adverse Events

Adverse Event (AE), n (%)	Randomized		Non-randomized
	GLE-PIB x 12 weeks (n = 233)	SOF + DCV x 12 weeks (n = 115)	GLE-PIB x 8 weeks (n = 157)
Any adverse event	177 (76)	80 (70)	98 (62)
AE possibly drug-related	112 (48)	50 (43)	63 (40)
Serious adverse event	5 (2)	2 (2)	3 (2)
AE leading to drug discontinuation	3 (1)	1 (1)	0
AE occurring in ≥10% patients			
Headache	60 (26)	23 (20)	31 (20)
Fatigue	44 (19)	16 (14)	20 (13)
Nausea	32 (14)	15 (13)	19 (12)
Laboratory abnormalities			
Grade ≥3 ALT (>5x ULN)	0	1 (1)	0
Grade ≥3 total bilirubin (>3x ULN)	0	0	1 (1)
Grade ≥3 neutrophil count (< 1 x 10^9/L)	1 (<1)	0	0

Source: Zeuzem S, et al. N Engl J Med. 2018;378:354-69.

Glecaprevir-Pibrentasvir for 8 or 12 weeks in Non-Cirrhotic GT 1 *ENDURANCE-3: Conclusions

Conclusion: “Once-daily treatment with glecaprevir–pibrentasvir for either 8 weeks or 12 weeks achieved high rates of sustained virologic response among patients with HCV genotype 1 or 3 infection who did not have cirrhosis.”

***Note**: ENDURANCE-3 was published in conjunction with ENDURANCE-1

Source: Zeuzem S, et al. N Engl J Med. 2018;378:354-69.

Glecaprevir-Pibrentasvir in Non-Cirrhotic Genotype 4, 5, or 6

ENDURANCE-4

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2018;16:417-26.

Glecaprevir-Pibrentasvir in Non-Cirrhotic Genotype 4, 5, or 6 *ENDURANCE-4: Study Features

- **Design**: Open-label single-arm phase 3 trial to evaluate the safety and efficacy of the fixed-dose combination of glecaprevir-pibrentasvir for 12 weeks in treatment-naïve and treatment-experienced adults with GT 4, 5, or 6 chronic HCV infection without cirrhosis
- **Setting:** Canada, Europe, and South Africa
- **Key Eligibility Criteria**
  - Chronic HCV GT 4, 5, or 6
  - HCV RNA ≥1,000 IU/mL at screening
  - Naïve or treated with (1) PEG (or IFN) +/- RBV or (2) SOF + RBV +/- PEG
  - No cirrhosis
  - HIV or chronic HBV coinfection excluded
- **Primary End Point**: SVR12

***Note**: ENDURANCE-4 was published in conjunction with ENDURANCE-2 and SURVEYOR-II (Part 4)

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2018;16:417-26.

Glecaprevir-Pibrentasvir in Non-Cirrhotic Genotype 4, 5, or 6
ENDURANCE-4: Baseline Characteristics

Baseline Characteristic	Glecaprevir-Pibrentasvir (n = 121)
Fibrosis Stage, n (%) F0-1 F2 F3	 104 (86) 8 (7) 9 (7)
HCV Treatment-Naïve, n (%)	82 (68)
Treatment-Experienced, n (%) IFN or PEG ± RBV, n (%) SOF + RBV ± PEG, n (%)	39 (32) 39 (32) 0 (0)
Concomitant PPI use, n (%)	11 (9)

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2018;16:417-26.

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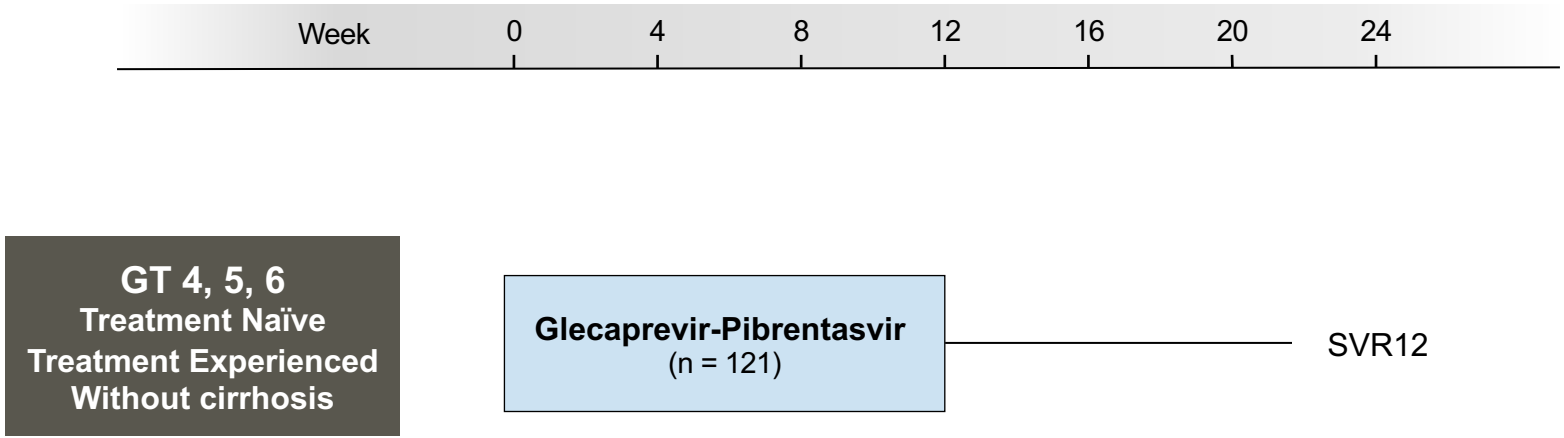
Glecaprevir-Pibrentasvir in Non-Cirrhotic Genotype 4, 5, or 6 ENDURANCE-4: Study Design



Drug Dosing: Glecaprevir-pibrentasvir (100/40 mg) fixed-dose combination; three pills once daily

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2018;16:417-26.

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Glecaprevir-Pibrentasvir in Non-Cirrhotic Genotype 4, 5, or 6 ENDURANCE-4: Baseline Characteristics

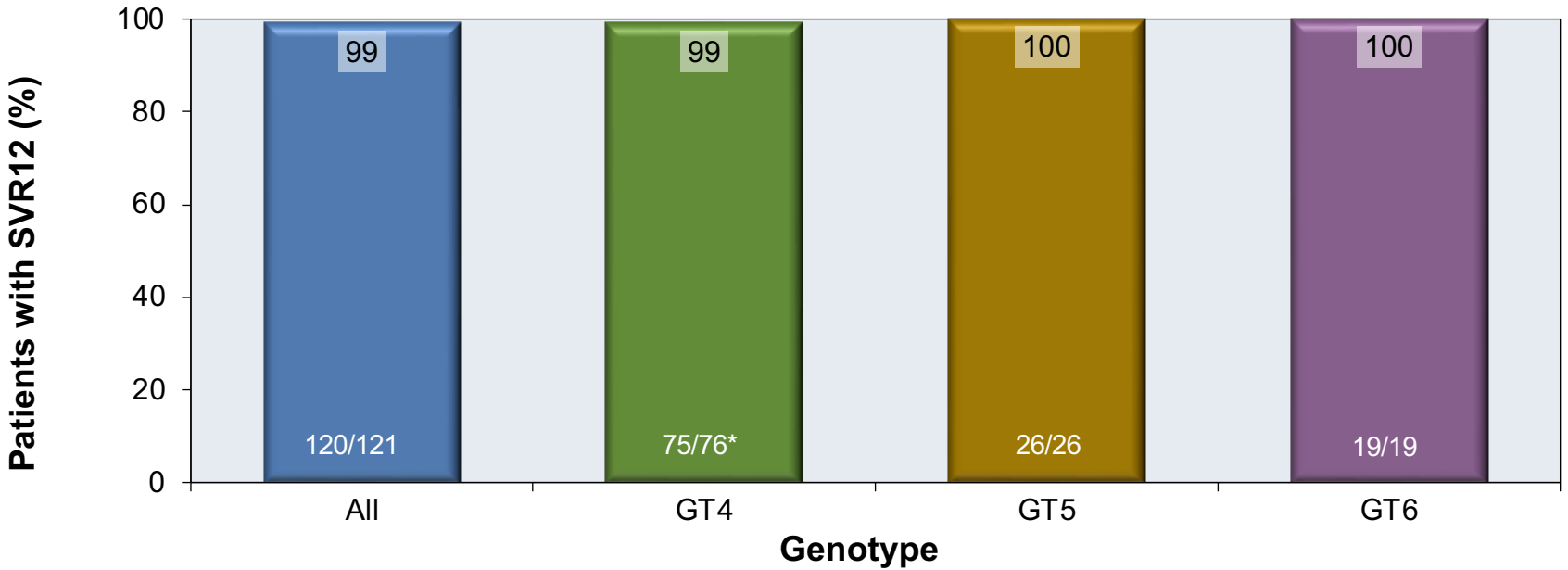
Baseline Characteristic	Glecaprevir-Pibrentasvir (n = 121)
Age, mean ± SD, years	53 ± 11.0
Male, n (%)	77 (64)
Race, n (%)	
White	84 (71)
Black	10 (8)
Asian	24 (20)
BMI, mean, ± SD kg/m^2	25.7 ± 4.8
IL28B genotype non-CC, n (%)	91 (75)
HCV Genotype, n (%)	
4	76 (63)
5	26 (21)
6	19 (16)
HCV RNA, median (range), log_{10} IU/mL	6.3 (3.6-7.3)
Former IDU, n (%)	32 (26)

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2018;16:417-26.

Hepatitis C Online

Glecaprevir-Pibrentasvir in Non-Cirrhotic Genotype 4, 5, or 6 ENDURANCE-4: Results

SVR12 (ITT analysis), Overall and by Genotype



*1 patient stopped drug on day 12

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2018;16:417-26.

Hepatitis C Online

Glecaprevir-Pibrentasvir in Non-Cirrhotic Genotype 4, 5, or 6 ENDURANCE-4: Adverse Events

Adverse Events (AEs), n (%)	Glecaprevir-Pibrentasvir (n = 121)
AEs leading to drug discontinuation	3 (2.5)*
Serious AEs	1 (0.8)§
AEs occurring in ≥10% of patients	
Fatigue	21 (17)
Headache	25 (21)
Laboratory AEs	
AST grade ≥2 (>3x ULN)	0
ALT grade ≥2 (>3x ULN)	0
Total bilirubin grade ≥3 (>3x ULN)	0

*One patient with anxiety, another with heartburn, third with transient ischemic attack (TIA).
§Patient with baseline risk factors discontinued drug on day 12 due to TIA.

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2018;16:417-26.

Glecaprevir-Pibrentasvir in Non-Cirrhotic Genotype 4, 5, or 6 *ENDURANCE-4: Conclusions

Conclusion: “In 3 Phase 3 studies, 8 weeks' treatment with glecaprevir/pibrentasvir produced an SVR12 in at least 93% of patients with chronic HCV genotype 2, 4, 5, or 6 infection without cirrhosis, with virologic failure in less than 1%. The drug combination had a safety profile comparable to 12 week's treatment with glecaprevir/pibrentasvir.”

***Note**: ENDURANCE-4 was published in conjunction with ENDURANCE-2 and SURVEYOR-II (Part 4)

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2018;16:417-26.

Glecaprevir-Pibrentasvir in Genotype 5 or 6

ENDURANCE-5,6

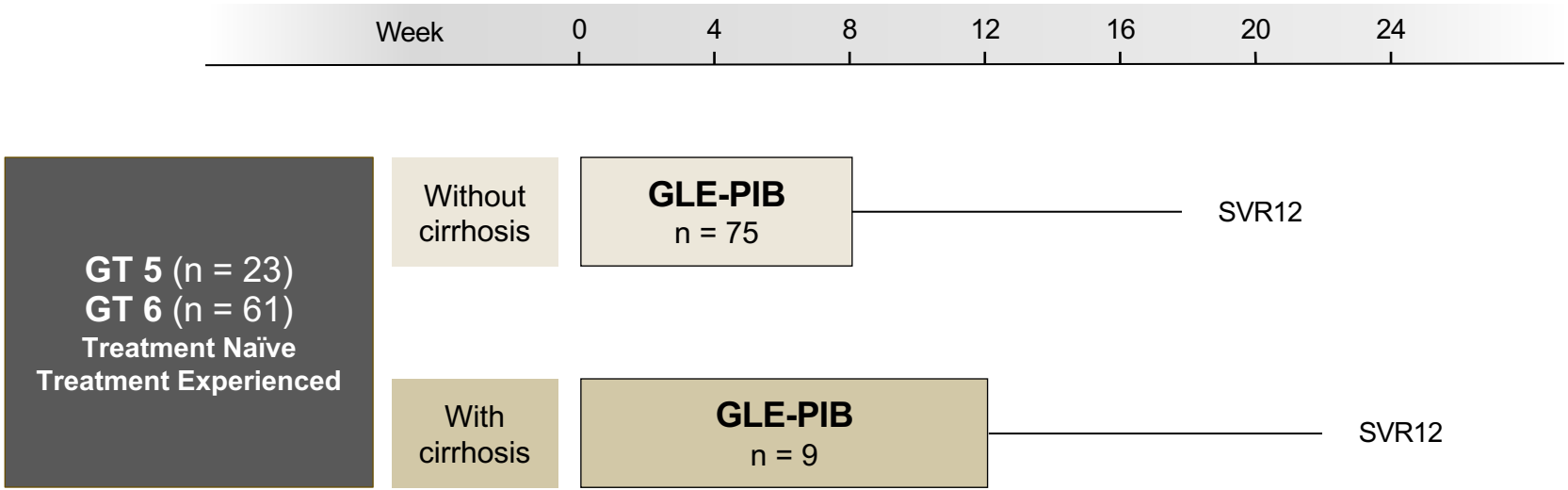
Source: Asselah T, et al. Lancet Gastroenterol Hepatol. 2019;4:45-51.

Glecaprevir-Pibrentasvir in Genotype 5 or 6
ENDURANCE-5,6: Study Features

- **Design**: Open-label, single-arm, phase 3b trial to evaluate the safety and efficacy of the fixed-dose combination of glecaprevir-pibrentasvir for 8 or 12 weeks in treatment-naïve and treatment-experienced adults with GT 5 or 6 chronic HCV infection with and without cirrhosis
- **Setting:** 24 clinics in Europe, N. America, Oceania, South Africa, SE Asia
- **Key Eligibility Criteria**
  - Chronic HCV GT 5 or 6
  - HCV RNA ≥1,000 IU/mL at screening
  - Naïve or treated with (1) PEG (or IFN) +/- RBV or (2) SOF + RBV +/- PEG
  - Compensated cirrhosis permitted (Child-Pugh score >6 excluded)
  - HIV or chronic HBV coinfection excluded
- **Primary End Point**: SVR12

Source: Asselah T, et al. Lancet Gastroenterol Hepatol. 2019;4:45-51.

Glecaprevir-Pibrentasvir in Genotype 5 or 6 ENDURANCE-5,6: Study Design



Abbreviations: GLE-PIB= Glecaprevir-pibrentasvir

Drug Dosing: Glecaprevir-pibrentasvir (100/40 mg) fixed-dose combination; three pills (300/120 mg) once daily

Source: Asselah T, et al. Lancet Gastroenterol Hepatol. 2019;4:45-51.

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Glecaprevir-Pibrentasvir in Genotype 5 or 6 ENDURANCE-5,6: Baseline Characteristics

Baseline Characteristic	GT 5 (n = 23)	GT 6 (n = 61)
Age, median (range)	68 (24-76)	54 (30-79)
Male, n (%)	10 (43)	29 (48)
Race, n (%)		
White	21 (91)	4 (7)
Black	1 (4)	0
Asian	1 (4)	56 (92)
from Vietnam	0	9 (15)
from China	0	7 (11)
from Cambodia	0	0
Multirace	0	1 (2)
BMI, median (range), kg/m^2	27 (20-33)	24 (17-40)
Past Injection Drug Use, n (%)	0	5 (8)

*Last use >12 months ago

Source: Asselah T, et al. Lancet Gastroenterol Hepatol. 2019;4:45-51.

Hepatitis C Online

Glecaprevir-Pibrentasvir in Genotype 5 or 6 ENDURANCE-5,6: Baseline Characteristics

Baseline Characteristic	GT 5 (n = 23)	GT 6 (n = 61)
HCV RNA ≥1,000 IU/mL, n (%)	20 (87)	53 (87)
HCV treatment experienced*, n (%)	10 (43)	29 (48)
Race, n (%)		
F0-F1	17 (74)	45 (74)
F2	3 (13)	1 (2)
F3	0	9 (15)
F4/with cirrhosis	3 (13)	6 (10)
Baseline polymorphisms		
NS3 only	11/23 (48)	0
NS5A only	1/23 (4)	32/55 (58)
NS3 and NS5A	2/23 (9)	2/55 (4)
None	9/23 (39)	21/55 (38)

*No patient previously treated with sofosbuvir.

Source: Asselah T, et al. Lancet Gastroenterol Hepatol. 2019;4:45-51.

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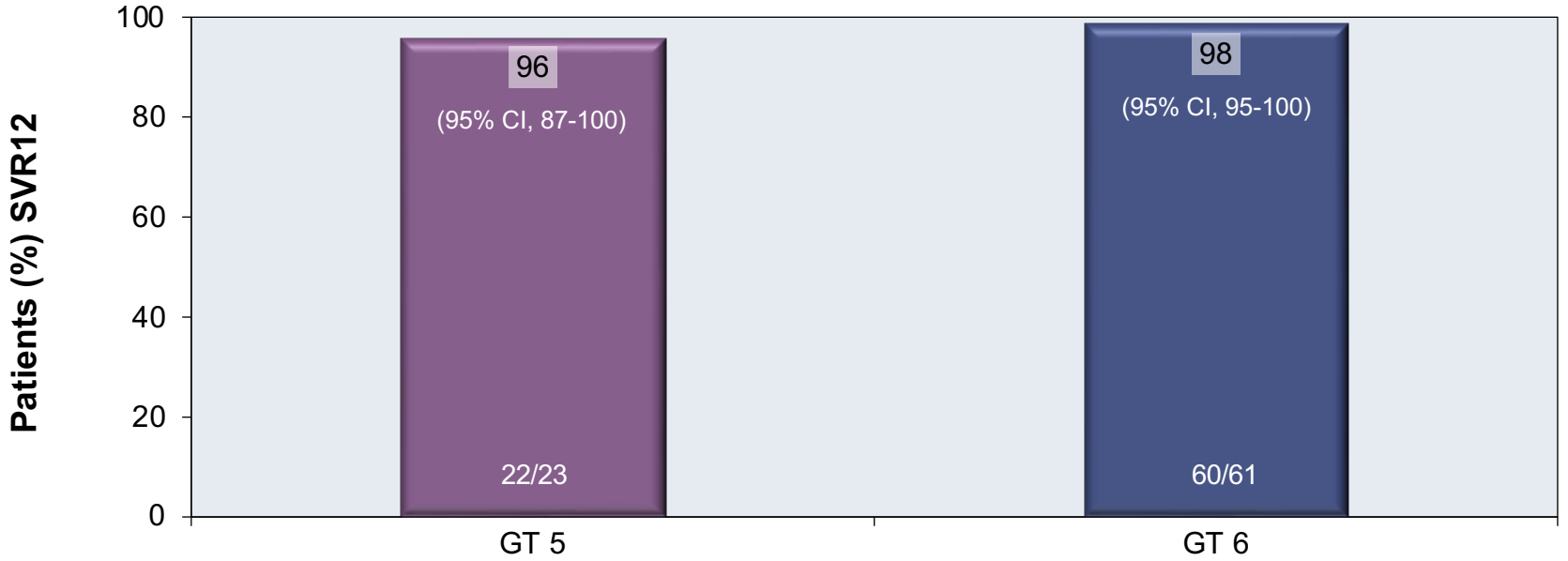
Glecaprevir-Pibrentasvir in Genotype 5 or 6 ENDURANCE-5,6: Results

ENDURANCE-5, 6: Overall SVR, by Genotype



Both patients with treatment failure had compensated cirrhosis and were adherent. GT 5 patient had subtype 5a and viral relapse. GT 6 patient had subtype 6f had on-treatment virologic failure by week 12.

Source: Asselah T, et al. Lancet Gastroenterol Hepatol. 2019;4:45-51.

Glecaprevir-Pibrentasvir in Genotype 5 or 6 ENDURANCE-5,6: Adverse Events

Adverse Events (AEs), n (%)	Glecaprevir-Pibrentasvir (n = 84)
Any adverse event	46 (55)
Grade 1 adverse event	24 (52)
AEs leading to drug discontinuation	0
Serious AEs	5 (6)[§]
AEs occurring in ≥10% of patients	
Fatigue	11 (13)
Headache	11 (13)
Laboratory AEs	
AST grade ≥3 (>5 x ULN)	0
ALT grade ≥3 (>5 x ULN)	0
Total bilirubin grade ≥3 (>3 x ULN)	0

[§]No serious AE considered related to study drug.

Source: Asselah T, et al. Lancet Gastroenterol Hepatol. 2019;4:45-51.

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Glecaprevir-Pibrentasvir in Genotype 5 or 6
ENDURANCE-5,6: Conclusions

Interpretation: “Glecaprevir/pibrentasvir achieved high SVR12 rates, comparable with data reported in registrational studies, and was well tolerated in patients with HCV genotype 5 or 6 infection with compensated liver disease.”

Source: Asselah T, et al. Lancet Gastroenterol Hepatol. 2019;4:45-51.

Glecaprevir-Pibrentasvir in Cirrhotic Genotype 1, 2, 4, 5, and 6

EXPEDITION-1

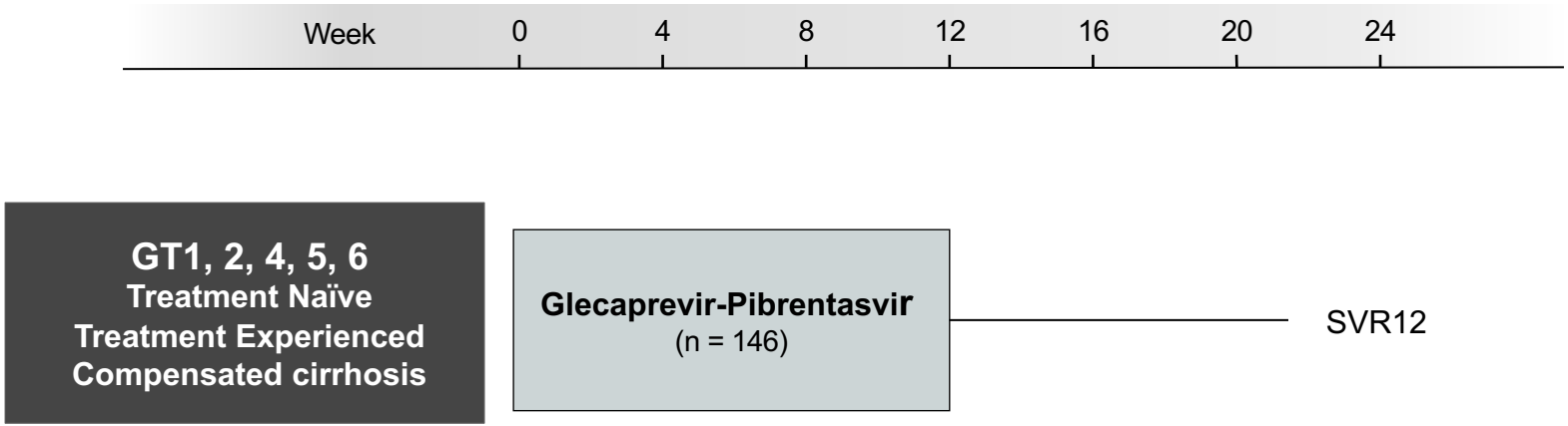
Source: Forns X, et al. Lancet Infect Dis. 2017;17:1062-8.

Glecaprevir-Pibrentasvir in Cirrhotic Genotype 1, 2, 4, 5, and 6 EXPEDITION-1: Study Features

- **Design**: Open-label, single-arm, phase 3 trial to evaluate the safety and efficacy of the fixed-dose combination of glecaprevir-pibrentasvir for 12 weeks in treatment-naïve and treatment-experienced adults with GT 1, 2, 4, 5, or 6 chronic HCV infection and compensated cirrhosis
- **Setting:** US, Belgium, Canada, Germany, South Africa, and Spain
- **Key Eligibility Criteria**
  - Chronic HCV GT 1, 2, 4, 5, or 6
  - Age ≥18 years
  - HCV RNA ≥1,000 IU/mL at screening
  - Naïve or treated with peginterferon +/- ribavirin (PR) or PR +/- sofosbuvir
  - Compensated cirrhosis
  - HIV or chronic HBV coinfection excluded
- **Primary End Point**: SVR12

Source: Forns X, et al. Lancet Infect Dis. 2017;17:1062-8.

Glecaprevir-Pibrentasvir in Cirrhotic Genotype 1, 2, 4, 5, and 6 EXPEDITION-1: Study Design



Drug Dosing: Glecaprevir-pibrentasvir (100/40 mg) fixed dose combination, three pills once daily

Source: Forns X, et al. Lancet Infect Dis. 2017;17:1062-8.

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Glecaprevir-Pibrentasvir in Cirrhotic Genotype 1, 2, 4, 5, and 6 EXPEDITION-1: Baseline Characteristics

Baseline Characteristic	Glecaprevir-Pibrentasvir (n = 146)
Age, median (range)	60 (26-88)
Male, n (%)	90 (62)
White race, n (%)	120 (82)
Body Mass Index (BMI) ≥30 kg/m^2, n (%)	29 (18-55)
HCV Genotypes	
1a, n (%)	48 (33)
1b, n (%)	39 (27)
2, n (%)	34 (23)
4 / 5 / 6, n (%)	16 (11) / 2 (1) / 7 (5)
Treatment experienced, n (%)	36 (25)
Interferon-based, n/N (%)	25/36 (69)
Sofosbuvir-based, n/N (%)	11/36 (31)
Baseline HCV RNA	
Median log_{10} IU/ml (range)	6.1 (3.1-7.4)

Source: Forns X, et al. Lancet Infect Dis. 2017;17:1062-8.

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Glecaprevir-Pibrentasvir in Cirrhotic Genotype 1, 2, 4, 5, and 6 EXPEDITION-1: Baseline Characteristics

Baseline Characteristic	Glecaprevir-Pibrentasvir (n = 146)
Child-Pugh score at screening, n (%)	
5	133 (91)
6	13 (9)
Laboratory values, n (%)	
Platelet count <100,000 x 10^9/L	29 (20)
INR <1.7	144 (99)
Total bilirubin ≥2 mg/dL	5 (3)
Albumin ≥ lower limit of normal	145 (99)
Baseline Polymorphisms*, n (%)	(n = 133)
None	76 (57)
NS3 only	2 (2)
NS5A only	53 (40)
NS3 + NS5A	2 (2)

*Detected at baseline by next-generation sequencing with 15% detection cutoff in samples with sequences available at the following amino acid positions for both targets: NS3 at positions 155, 156, 168; NS5 at positions 24, 28, 30, 31, 58, 92, 93

Source: Forns X, et al. Lancet Infect Dis. 2017;17:1062-8.

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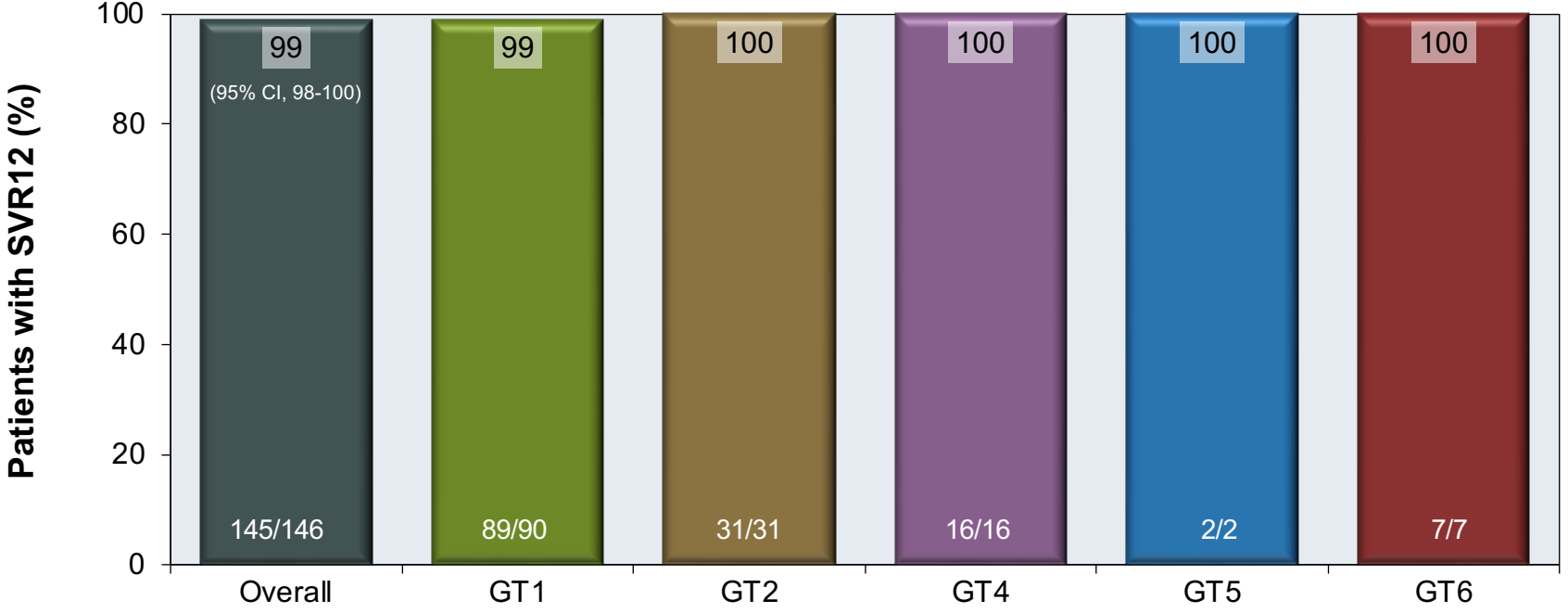
Glecaprevir-Pibrentasvir in Cirrhotic Genotype 1, 2, 4, 5, and 6 EXPEDITION-1: Results



SVR12 by intent-to-treat analysis. One patient with GT1a experienced viral relapse at week 8 post-treatment and the patient had Y93N detected at baseline and at time of viral relapse.

Source: Forns X, et al. Lancet Infect Dis. 2017;17:1062-8.

Hepatitis C Online

Glecaprevir-Pibrentasvir in Cirrhotic Genotype 1, 2, 4, 5, and 6 EXPEDITION-1: Adverse Events

Adverse Event (AE), n (%)	Glecaprevir-Pibrentasvir (n = 146)
Any serious AE	11 (8)
AE leading to treatment discontinuation	0
Death	1 (0.7)*
Common AEs	
Fatigue	28 (19)
Headache	20 (14)
Pruritus	14 (10)
Nausea	13 (9)
Diarrhea	12 (8)
Urinary tract infection	9 (6)
Laboratory AEs	
Grade 3 hemoglobin (< 8 mg/dL)	1 (0.7)
Grade ≥ 3 ALT or AST (> 5 x ULN)	0
Grade 3 platelet count (<50-25 x 10^9/L)	2 (1)
Grade ≥ 3 total bilirubin (>3 x ULN)	0
Grade 3 neutrophil count (< 1.0-0.5 x 10^9/L)	0

Source: Forns X, et al. Lancet Infect Dis. 2017;17:1062-8.

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Glecaprevir-Pibrentasvir in Cirrhotic Genotype 1, 2, 4, 5, and 6 EXPEDITION-1: Conclusions

Conclusion: “Our results show that 99% of patients treated with once-daily glecaprevir plus pibrentasvir achieved a sustained virological response at 12 weeks. Furthermore, this drug regimen had a favourable safety profile in previously treated or untreated patients with chronic HCV genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis. These findings could help simplify treatment algorithms and reduce treatment burden.”

Source: Forns X, et al. Lancet Infect Dis. 2017;17:1062-8.

Glecaprevir-Pibrentasvir in Patients with HCV-HIV Coinfection

EXPEDITION-2

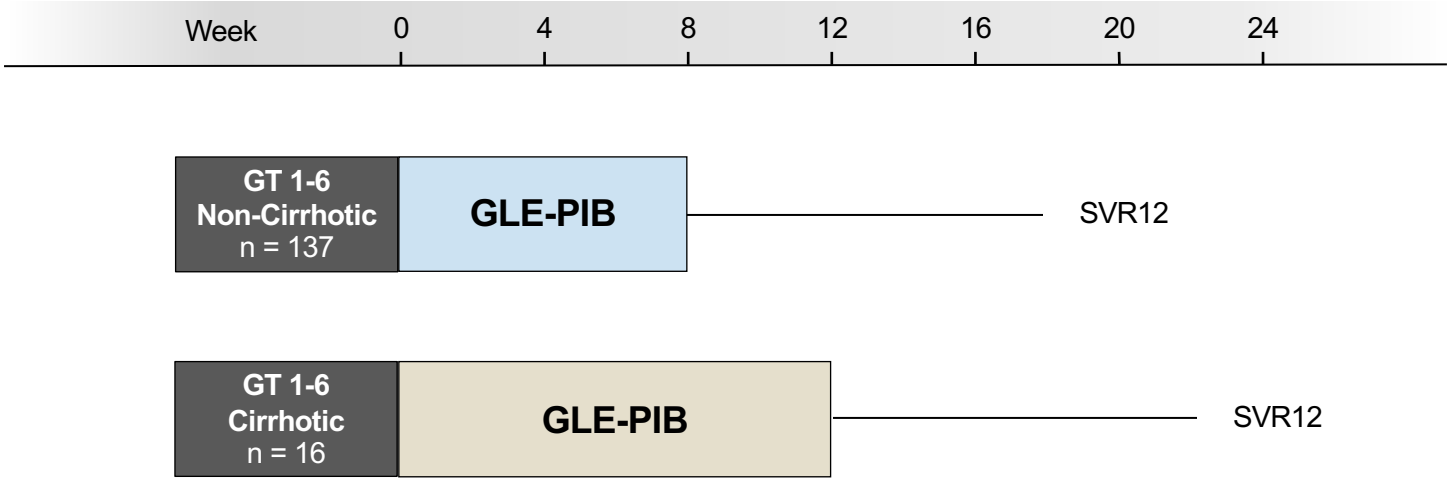
Source: Rockstroh JK, et al. Clin Infect Dis. 2018;67:1010-7

Glecaprevir-Pibrentasvir in HIV-HCV Coinfected Patients
EXPEDITION-2: Study Features

- **Design**: Open-label, phase 3 trial to evaluate the safety and efficacy of the fixed-dose combination of glecaprevir-pibrentasvir for 8 or 12 weeks in persons with HIV-HCV coinfection, without or with compensated cirrhosis
- **Setting:** Australia, Europe, Russian Federation, UK, US
- **Key Eligibility Criteria**
  - Adults with chronic HCV GT 1, 2, 3, 4, 5, or 6
  - HCV RNA ≥1,000 IU/mL at screening
  - Naïve or treated with peginterferon +/- ribavirin (PR) or PR +/- sofosbuvir
  - Compensated cirrhosis allowed
  - On ART or ART-naïve with CD4 ≥500 cells/mm^3 or CD4 percentage ≥29%
- **Primary End Point**: SVR12

Source: Rockstroh JK, et al. Clin Infect Dis. 2018;67:1010-7.

Glecaprevir-Pibrentasvir in HIV-HCV Coinfected Patients
EXPEDITION-2: Study Design



Abbreviations: GLE-PIB = Glecaprevir-pibrentasvir

Drug Dosing: Glecaprevir-pibrentasvir (100/40 mg) fixed-dose combination; three pills (300/120 mg) once daily

Source: Rockstroh JK, et al. Clin Infect Dis. 2018;67:1010-7.

Hepatitis C Online

Glecaprevir-Pibrentasvir in HIV-HCV Coinfected Patients
EXPEDITION-2: Baseline Characteristics

Baseline Characteristic	**GLE-PIB** x 8 weeks (n = 137)	**GLE-PIB** x 12 weeks (n = 16)
Age, mean (range), years	45 (23-74)	50 (35-62)
Male, n (%)	113 (82)	15 (94)
White, n (%) Black, n (%)	106 (77) 24 (18)	15 (94) 1 (6)
Genotype, n (%) 1a 1b 2 3 4 6	 66 (48) 21 (15) 9 (7) 22 (16) 16 (12) 3 (2)	 5 (31) 5 (31) 1 (6) 4 (25) 1 (6) 0
Body mass index, median kg/m^2 (range)	25 (18-41)	28 (22-38)
Median HCV RNA, $\log_{10}$ IU/mL (range)	6.2 (4.0-7.4)	6.1 (4.4-7.0)
Fibrosis Stage, n (%) F0-F1 F2 F3 F4	 122 (88) 2 (1) 15 (11) 0	 0 0 0 16 (100)

Source: Rockstroh JK, et al. Clin Infect Dis. 2018;67:1010-7.

Hepatitis C Online

Glecaprevir-Pibrentasvir in HIV-HCV Coinfected Patients
EXPEDITION-2: Baseline Characteristics

Baseline Characteristic	**GLE-PIB** x 8 weeks (n = 137)	**GLE-PIB** x 12 weeks (n = 16)
Treatment-experienced, n (%)	26 (19)	2 (13)
IFN-based, n/N (%)	23 (17)	2 (13)
SOF-based, n/N (%)	3 (2)	0
IDU within 12 months, n (%)	12 (9)	1 (6)
On opiate substitution therapy, n (%)	11 (8)	2 (13)
N(t)RTI backbone, n (%)		
Tenofovir disoproxil fumarate	74 (54)	13 (81)
Tenofovir alafenamide	6 (4)	0
Abacavir	49 (36)	3 (19)
Antiretroviral Anchor Agent, n (%)		
Raltegravir	39 (28)	6 (38)
Dolutegravir	62 (45)	5 (31)
Rilpivirine	27 (20)	5 (31)
Elvitegravir-cobicistat	1 (1)	0
Antiretroviral Therapy Naïve, n (%)	9 (7)	0
CD4 cell count ≥500 cells/mm^3	92 (67)	9 (56)

Source: Rockstroh JK, et al. Clin Infect Dis. 2018;67:1010-7.

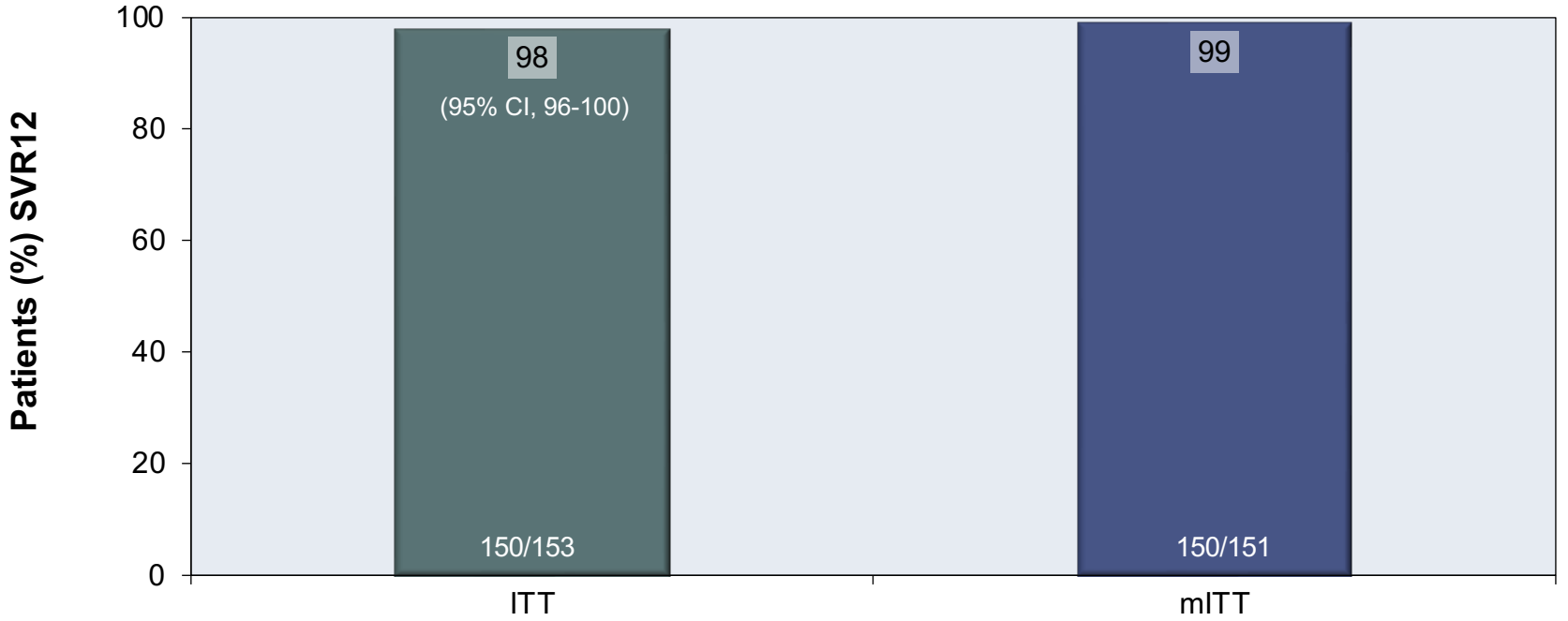
Glecaprevir-Pibrentasvir in HIV-HCV Coinfected Patients
EXPEDITION-2: Baseline Polymorphisms

Baseline Polymorphisms*	**GLE-PIB** x 8 weeks (n = 130)	**GLE-PIB** x 12 weeks (n = 16)
None, n (%)	92 (71)	9 (56)
NS3 only, n (%)	1 (1)	1 (6)
NS5A only, n (%)	36 (28)	6 (38)
NS3 and NS5A, n (%)	1 (1)	0

*Detected at 15% threshold by next-generation sequencing in samples that had sequences available at a key subset of amino acid positions: NS3 at positions 55, 156, 168; NS5A at positions 24, 28, 30, 31, 58, 92, 93

Source: Rockstroh JK, et al. Clin Infect Dis. 2018;67:1010-7.

Glecaprevir-Pibrentasvir in HIV-HCV Coinfected Patients
EXPEDITION-2: Results



One GT3 patient with cirrhosis and 85% compliance had on-treatment virologic failure

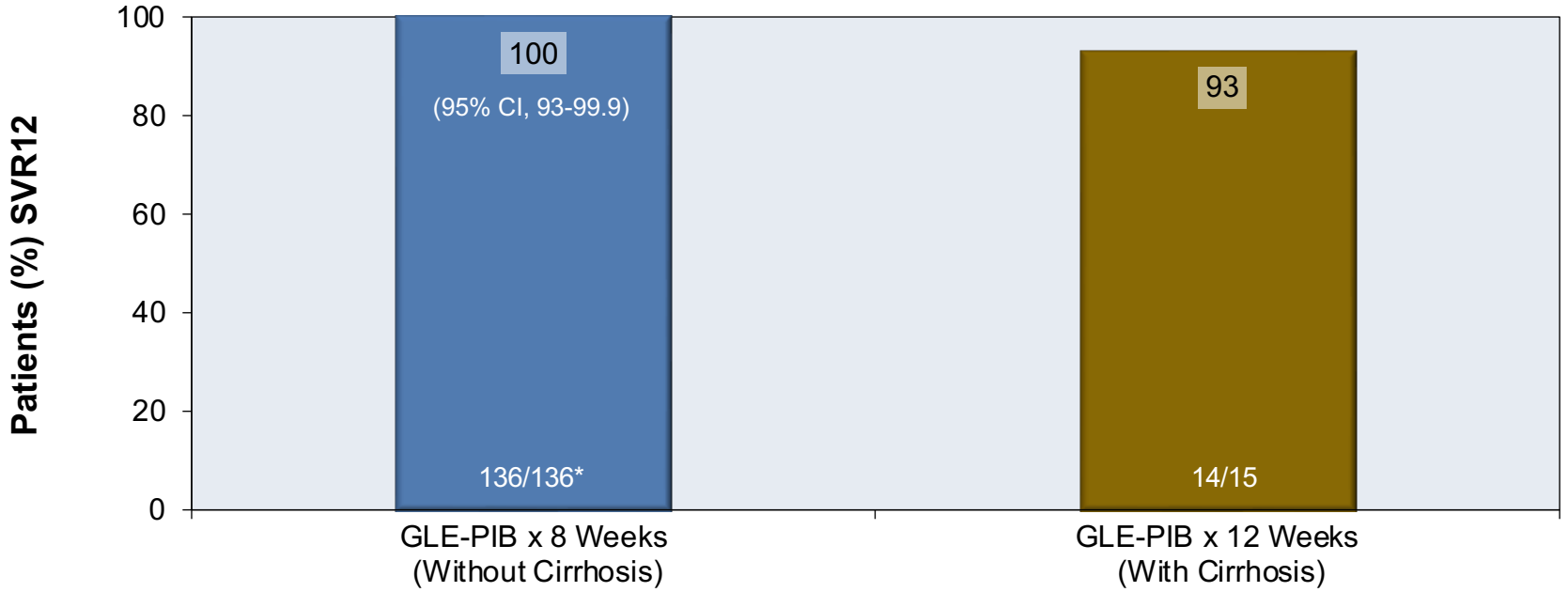
Abbreviations: ITT = Intent-to-treat; mITT = modified intent-to-treat

Source: Rockstroh JK, et al. Clin Infect Dis. 2018;67:1010-7.

Hepatitis C Online

Glecaprevir-Pibrentasvir in HIV-HCV Coinfected Patients
EXPEDITION-2: Results

EXPEDITION-2: Overall SVR by Treatment Regimen



*Excludes one patient with missing data who achieved SVR24

Source: Rockstroh JK, et al. Clin Infect Dis. 2018;67:1010-7.

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Glecaprevir-Pibrentasvir in HIV-HCV Coinfected Patients
EXPEDITION-2: Adverse Events

Adverse Event (AE), n (%)	**GLE-PIB** x 8 weeks (n = 137)	**GLE-PIB** x 12 weeks (n = 16)
Discontinuation due to AE	0	1 (6)§
Serious AEs	3 (2)*	1 (6)§
Any AE in ≥5% of patients		
Fatigue	18 (13)	0
Nausea	12 (9)	1 (6)
Headache	12 (9)	0
Nasopharyngitis	12 (9)	0
Laboratory AEs		
ALT elevation, grade ≥3 (>5x ULN)	0	0
AST elevation, grade ≥3 (>5x ULN)	0	0
Total bilirubin, grade ≥3 (3x ULN)	1 (0.7)	0

§ One GT2 patient with cirrhosis experienced cerebrovascular accident and cerebral hemorrhage.
* Upper GI bleed, obliterating arteriopathy and urolithiasis in one patient each, thought unrelated to G/P.

Abbreviations: AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit normal

Source: Rockstroh JK, et al. Clin Infect Dis. 2018;67:1010-7.

Glecaprevir-Pibrentasvir in HIV-HCV Coinfected Patients
EXPEDITION-2: Conclusions

Conclusion: “Glecaprevir/pibrentasvir for 8 weeks in non-cirrhotic and 12 weeks in cirrhotic patients is a highly efficacious and well-tolerated treatment for HCV/HIV-1 co-infection, regardless of baseline HCV viral load or prior treatment with interferon or sofosbuvir.”

Source: Rockstroh JK, et al. Clin Infect Dis. 2018;67:1010-7.

Glecaprevir-Pibrentasvir in GT 1-6 with Renal Disease

EXPEDITION-4

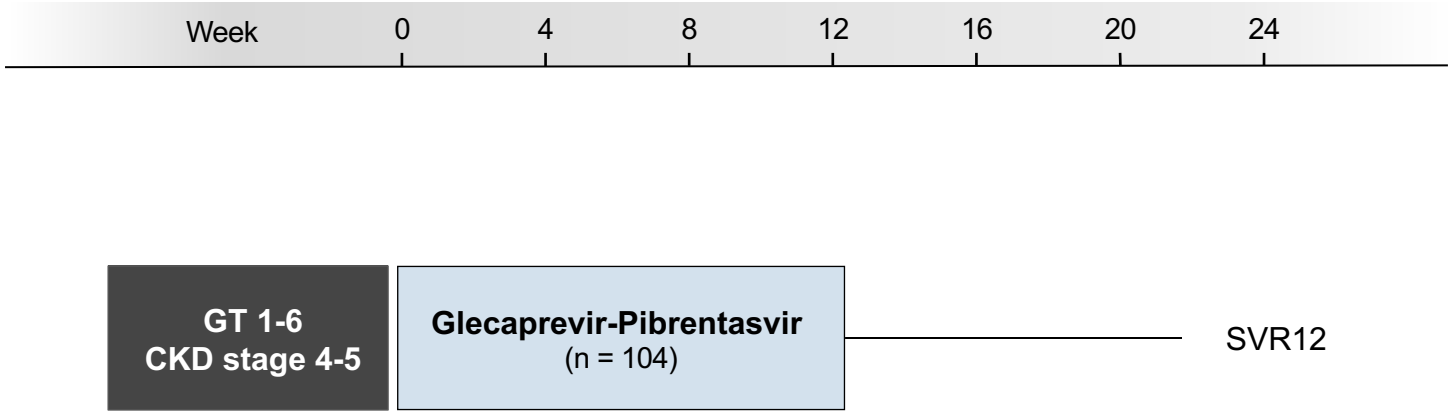
Source: Gane E, et al. N Engl J Med. 2017;377:1448-55.

Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease
EXPEDITION-4: Study Features

- **Design**: Open-label, single-arm, phase 3 trial to evaluate the safety and efficacy of the fixed-dose combination of glecaprevir-pibrentasvir for 12 weeks in treatment-naïve and treatment-experienced patients with GT 1, 2, 3, 4, 5, or 6 chronic HCV infection with advanced renal insufficiency
- **Setting:** US, Canada, Europe, Australia and New Zealand
- **Key Eligibility Criteria**
  - Age ≥18 years
  - Chronic HCV GT 1, 2, 3, 4, 5, or 6
  - Estimated eGFR <30 mL/min/1.73 m^2 (Stage 4 or 5 CKD)
  - HCV RNA ≥1,000 IU/mL at screening
  - Naïve or treated with peginterferon +/- ribavirin (PR) or PR +/- sofosbuvir
  - Without cirrhosis or with compensated cirrhosis
  - HIV or chronic HBV coinfection excluded
- **Primary End Point**: SVR12

Source: Gane E, et al. N Engl J Med. 2017;377:1448-55.

Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease
EXPEDITION-4: Treatment Regimen



Abbreviations: CKD = chronic kidney disease
Drug Dosing: Glecaprevir-pibrentasvir (100/40 mg) fixed-dose combination, three pills daily

Source: Gane E, et al. N Engl J Med. 2017;377:1448-55.

Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease
EXPEDITION-4: Baseline Characteristics

Baseline Characteristic	Glecaprevir-Pibrentasvir (n = 104)
Mean age (range), years	57 (28-83)
Male sex, n (%)	79 (76)
Race, n (%)	
White	64 (62)
Black	25 (24)
Asian	9 (9)
Other	6 (6)
Median body-mass index (range)	26 (18-45)
Compensated cirrhosis, n (%)	20 (19)

Source: Gane E, et al. N Engl J Med. 2017;377:1448-55.

Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease
EXPEDITION-4: Baseline Characteristics

Baseline Characteristic	Glecaprevir-Pibrentasvir (n = 104)
Median HCV RNA level, log_{10} IU/mL (range)	5.9 (3.4-7.5)
HCV Genotypes, n (%)	
1a	23 (22)
1b	29 (28)
1 (other)	2 (2)
2	17 (16)
3	11 (11)
4	20 (19)
5	1 (1)
6	1 (1)
HCV Treatment History, n (%)	
Treatment-Naïve	60 (58)
Interferon (or Peginterferon) ± Ribavirin	42 (40)
Sofosbuvir and Ribavirin ± Peginterferon	2 (2)

Source: Gane E, et al. N Engl J Med. 2017;377:1448-55.

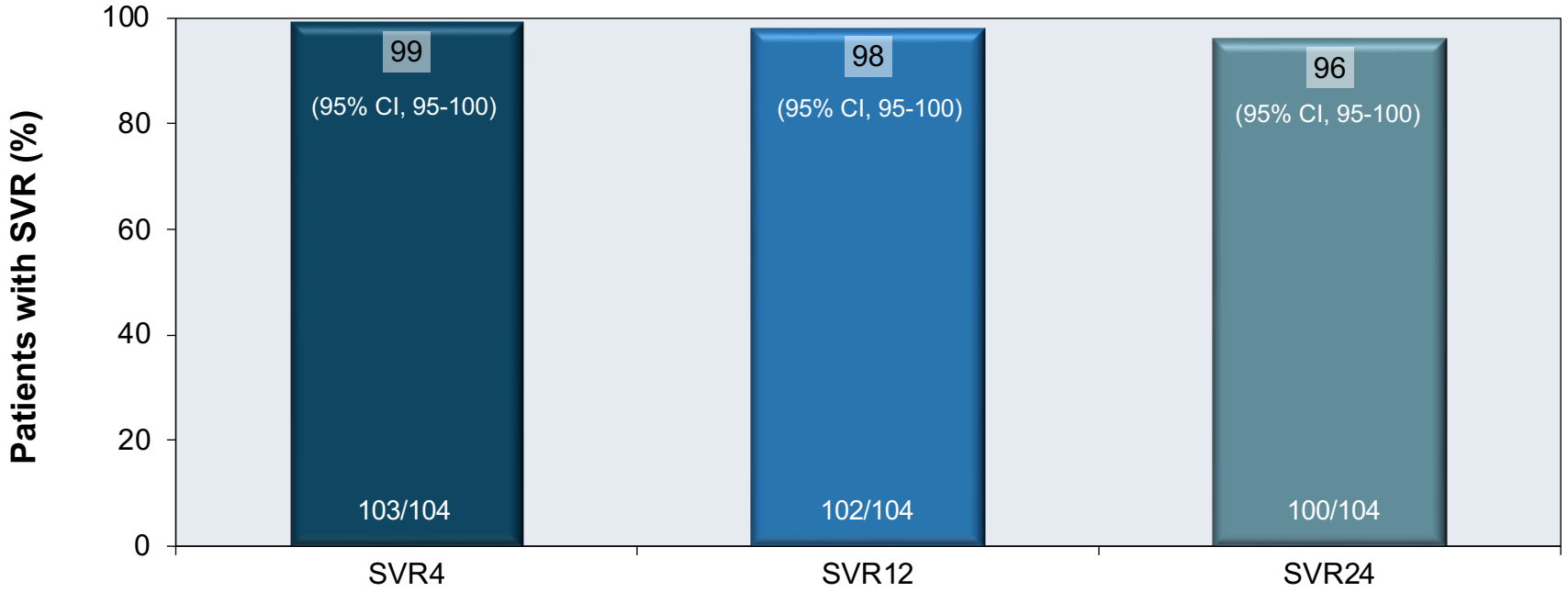
Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease
EXPEDITION-4: Baseline Characteristics (Renal)

Baseline Characteristics (Renal)	Glecaprevir-Pibrentasvir (n = 104)
eGFR in patients not undergoing hemodialysis, mL/min/1.73 m^2	20.6 ± 8.0
CKD stage, n (%)	
Stage 4	14 (13)
Stage 5	90 (87)
Hemodialysis, n (%)	85 (82)

Source: Gane E, et al. N Engl J Med. 2017;377:1448-55.

Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease EXPEDITION-4: Results

Sustained Virologic Response Rates (SVR)



Source: Gane E, et al. N Engl J Med. 2017;377:1448-55.

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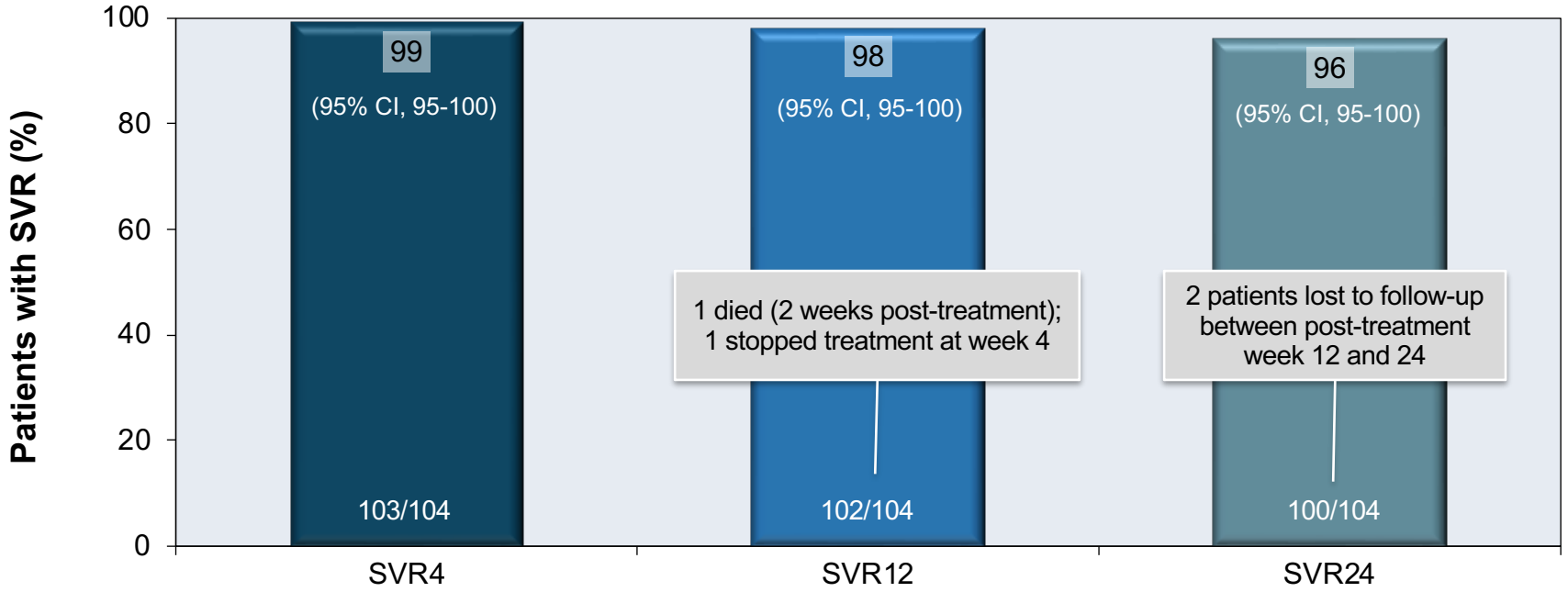
Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease EXPEDITION-4: Results

Sustained Virologic Response Rates (SVR)



Source: Gane E, et al. N Engl J Med. 2017;377:1448-55.

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Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease
EXPEDITION-4: Adverse Events

Adverse Event (AE), n (%)	Glecaprevir-Pibrentasvir (n = 104)
Serious AE	25 (24)
AE leading to treatment discontinuation	4 (4)*
Death	1 (1)[#]
AEs occurring in ≥10% of patients	
Pruritus	21 (20)
Fatigue	15 (14)
Nausea	12 (12)
Alanine aminotransferase >3x ULN, grade ≥2	0
Total bilirubin >3x ULN, grade ≥3	1 (1)
Hemoglobin <8 g/dL, grade ≥3	5 (5)

*AEs not considered related to study drug
[#]One death related to cerebral hemorrhage, post-treatment week 2, deemed not related to study drug.

Source: Gane E, et al. N Engl J Med. 2017;377:1448-55.

Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease
EXPEDITION-4: Conclusions

Conclusion: “Treatment with glecaprevir and pibrentasvir for 12 weeks resulted in a high rate of sustained virologic response in patients with stage 4 or 5 chronic kidney disease and HCV infection.”

Source: Gane E, et al. N Engl J Med. 2017;377:1448-55.

Glecaprevir-Pibrentasvir in GT 1-6 with Renal Disease

EXPEDITION-5

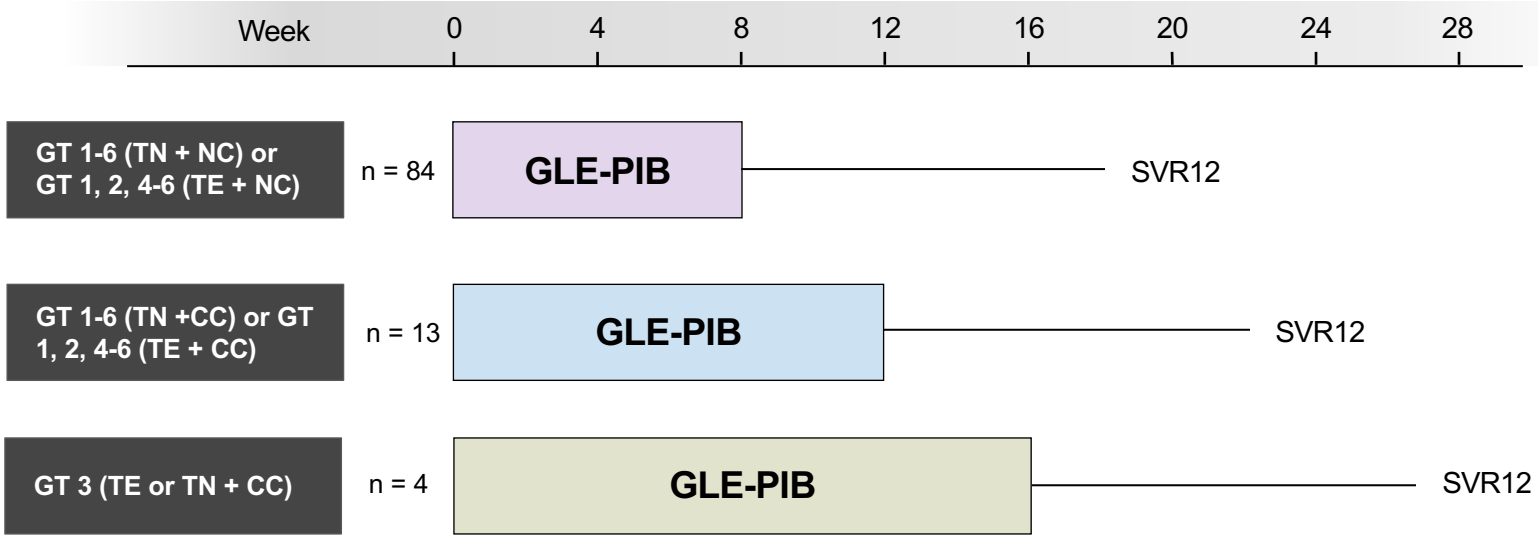
Source: Lawitz E, et al. Liver Int. 2020;40:1032-41.

Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease
EXPEDITION-5: Study Features

- **Design**: Open-label, single-arm, phase 3 trial to evaluate the safety and efficacy of the fixed-dose combination of glecaprevir-pibrentasvir for 8, 12, or 16 weeks in treatment-naïve and treatment-experienced participants with chronic HCV infection with advanced renal insufficiency
- **Setting:** United States, Canada, Europe, and Asia
- **Key Eligibility Criteria**
  - Age ≥18 years
  - Chronic HCV GT 1, 2, 3, 4, 5, or 6
  - Estimated eGFR <45 mL/min/1.73 m^2 (Stage 3b, 4 or 5 CKD)
  - HCV RNA ≥1,000 IU/mL at screening
  - Naïve or treated with peginterferon +/- ribavirin (PR) or PR +/- sofosbuvir
  - Without cirrhosis or with compensated cirrhosis
  - HIV or chronic HBV coinfection excluded
- **Primary End Point**: SVR12

Source: Lawitz E, et al. Liver Int. 2020;40:1032-41.

Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease
EXPEDITION-5: Study Design



Abbreviations: GLE-PIB = glecaprevir-pibrentasvir; GT, genotype; TN = treatment-naïve; TE = treatment-experienced; NC = non-cirrhotic; CC = compensated cirrhosis

Drug Dosing: Glecaprevir-pibrentasvir (300/120 mg), once daily

Source: Lawitz E, et al. Liver Int. 2020;40:1032-41.

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Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease
EXPEDITION-5: Baseline Characteristics

	GLE-PIB 8 weeks (n = 84)	**GLE-PIB** 12 weeks (n = 13)	**GLE-PIB** 16 weeks (n = 4)
Median age, (range) years	59 (32-84)	58 (49-87)	62 (54-70)
Male sex, n (%)	51 (61)	7 (54)	2 (50)
Race, n (%)			
White	62 (74)	8 (62)	4 (100)
Black	11 (13)	3 (23)	0
Asian	11 (13)	2 (15)	0
Latinx	16 (19)	1 (8)	1 (25)
BMI, median (range), kg/m^2	24.9 (16.8-53.5)	28.7 (17.1-41.1)	24.3 (17.7-26.8)
HCV RNA ≥1 million IU/ml, n (%)	34 (40)	5 (38)	3 (75)
HCV genotype, n (%)			
GT 1	46 (55)	9 (69)	0
GT 2	26 (31)	1 (8)	0
GT 3	9 (11)	2 (15)	4 (100)
GT 4	3 (4)	1 (8)	0

Abbreviations: GLE-PIB = glecaprevir-pibrentasvir; BMI = body mass index; GT, genotype

Source: Lawitz E, et al. Liver Int. 2020;40:1032-41.

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Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease
EXPEDITION-5: Baseline Characteristics

	GLE-PIB 8 weeks (n = 84)	**GLE-PIB** 12 weeks (n = 13)	**GLE-PIB** 16 weeks (n = 4)
Prior treatment experience, n (%)	15 (18)	12 (92)	0
Fibrosis stage, n (%)			
F0-1	61 (73)	0	4 (100)
F2	5 (6)	0	0
F3	16 (19)	0	0
F4	1 (1)	13 (100)	0
Missing	1	0	0
CKD stage, n (%)			
Stage 3b	4 (5)	3 (23)	0
Stage 4	14 (17)	2 (15)	1 (25)
Stage 5	66 (79)	8 (62)	3 (75)
On dialysis, n (%)	66 (79)	8 (62)	3 (75)
Hemodialysis	63 (96)	7 (88)	3 (100)
Peritoneal dialysis	3 (4)	1 (12)	0

Abbreviations: GLE-PIB = glecaprevir-pibrentasvir; CKD = chronic kidney disease

Source: Lawitz E, et al. Liver Int. 2020;40:1032-41.

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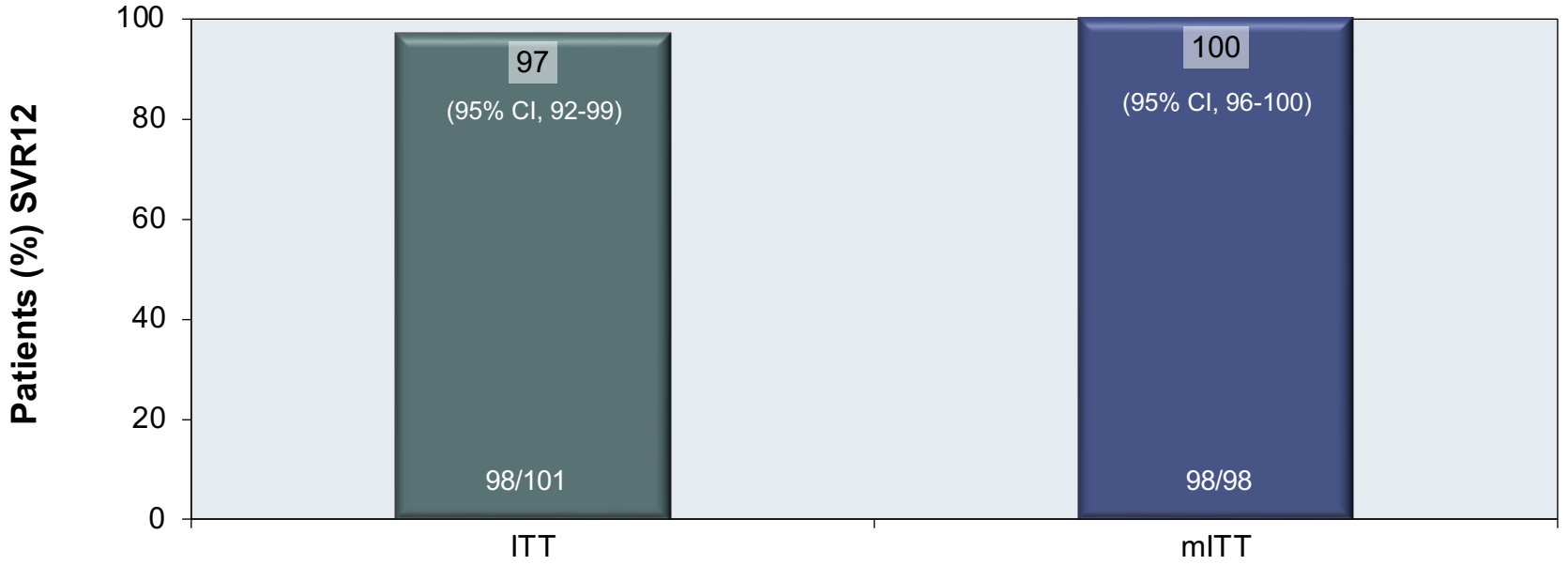
Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease
EXPEDITION-5: Results

EXPEDITION-5: Overall SVR by Analysis



ITT = Intent-to-treat; mITT = modified intent-to-treat

Source: Lawitz E, et al. Liver Int. 2020;40:1032-41.

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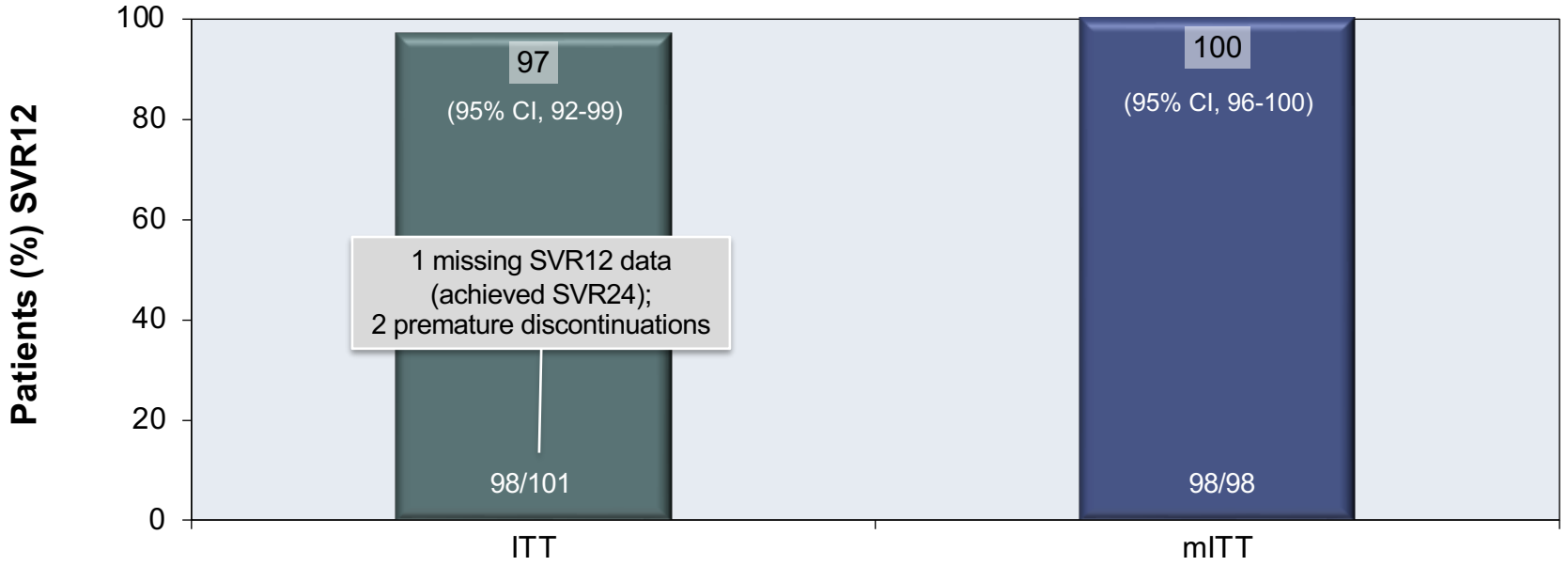
Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease
EXPEDITION-5: Results

EXPEDITION-5: Overall SVR by Analysis



ITT = Intent-to-treat; mITT = modified intent-to-treat

Source: Lawitz E, et al. Liver Int. 2020;40:1032-41.

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Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease
EXPEDITION-5: Adverse Events

Adverse Event (AE), n (%)	Glecaprevir-Pibrentasvir (n = 101)
Serious AE	12 (12)
AE leading to treatment discontinuation	2 (2)
Death	0
AEs occurring in ≥10% of patients	
Pruritus	16 (16)
Hypertension	6 (6)
Generalized pruritus	6 (6)
Bronchitis	6 (6)
Laboratory abnormalities (grade ≥3)	
ALT >5x ULN	0
AST >5x ULN	0
Total bilirubin >3x ULN	0

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

Source: Lawitz E, et al. Liver Int. 2020;40:1032-41.

Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease EXPEDITION-5: Conclusions

Conclusion: “Glecaprevir-pibrentasvir treatment yielded high SVR12 rates irrespective of the presence of stage 3b, 4 or 5 CKD. No safety signals were detected.”

Source: Lawitz E, et al. Liver Int. 2020;40:1032-41.

Glecaprevir-Pibrentasvir in GT 1-6 and Compensated Cirrhosis

EXPEDITION-8

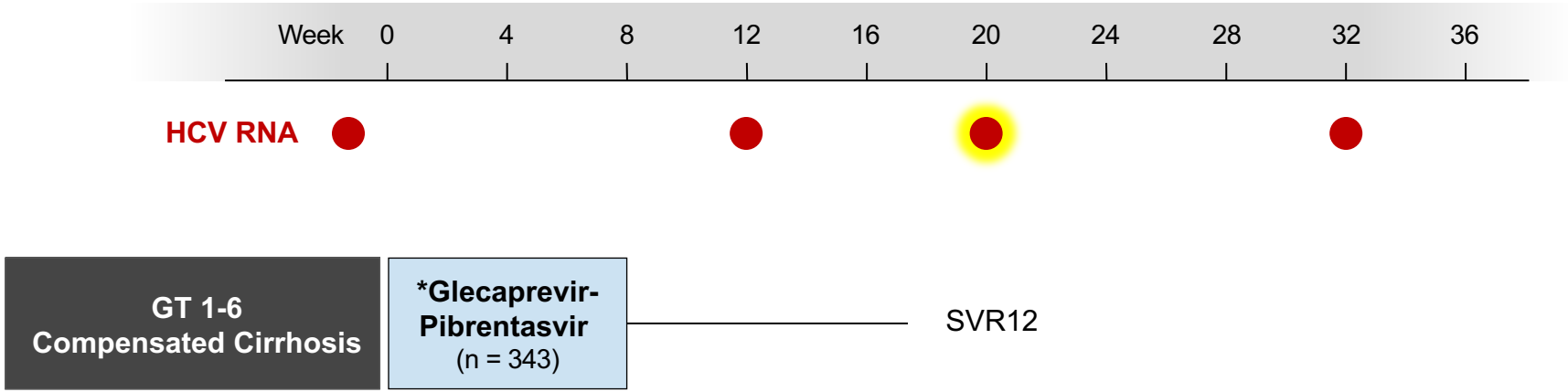
Source: Brown RS, et al. J Hepatol. 2020;72:441-8.

Glecaprevir-Pibrentasvir in GT 1-6 & Compensated Cirrhosis
EXPEDITION-8: Design

- **Design**: Single-arm, multicenter phase 3b trial to evaluate the efficacy of the fixed-dose combination of glecaprevir-pibrentasvir for 8 weeks in treatment-naïve participants with GT 1, 2, 3, 4, 5, or 6 chronic HCV and compensated cirrhosis
- **Setting:** 94 international sites
- **Key Eligibility Criteria**
  - Age ≥18 years
  - Chronic HCV GT 1, 2, 3, 4, 5, or 6
  - Compensated cirrhosis by (a) biopsy, (b) FibroScan, or (c) FibroTest + APRI
  - HCV RNA ≥1,000 IU/mL at screening
  - Treatment-naïve
  - Child-Pugh Score 5 or 6
  - Excluded: HIV or HBV or current/past decompensated cirrhosis
- **Primary End Point**: SVR12

Source: Brown RS, et al. J Hepatol. 2020;72:441-8.

Glecaprevir-Pibrentasvir in GT 1-6 & Compensated Cirrhosis
EXPEDITION-8: Treatment Protocol



*__Drug Dosing__: Glecaprevir-pibrentasvir (100/40 mg) fixed-dose combination, 3 pills once daily

Source: Brown RS, et al. J Hepatol. 2020;72:441-8.

Glecaprevir-Pibrentasvir in GT 1-6 & Compensated Cirrhosis
EXPEDITION-8: Baseline Characteristics

Baseline Characteristic	Glecaprevir-Pibrentasvir (n = 343)
Mean age (range), years	58 (51-65)
Male sex, n (%)	217 (63)
Race, n (%) White Black	 285 (83) 258 (8)
Hispanic or Latino ethnic origin, n (%)	43 (13)
Baseline Child-Pugh Score, n (%) 5 6 ≥6	 307 (90%) 33 (10) 3 (<1)

Source: Brown RS, et al. J Hepatol. 2020;72:441-8.

Glecaprevir-Pibrentasvir in GT 1-6 & Compensated Cirrhosis
EXPEDITION-8: Baseline Characteristics

Baseline Characteristic	Glecaprevir-Pibrentasvir (n = 343)
Median HCV RNA level, log_{10} IU/mL (range)	6.3 (5.7-6.6)
HCV Genotypes, n (%)	
1 (all)	231 (67)
1a	95 (28)
1b	136 (40)
2	26 (8)
3	63 (18)
4	13 (4)
5	1 (<1)
6	9 (13)
Baseline polymorphisms	
None	218/335 (65)
NS3 only	4/335 (1)
NS5A only	111/335 (33)
NS3 and NS5A	2/335 (<1)

Source: Brown RS, et al. J Hepatol. 2020;72:441-8.

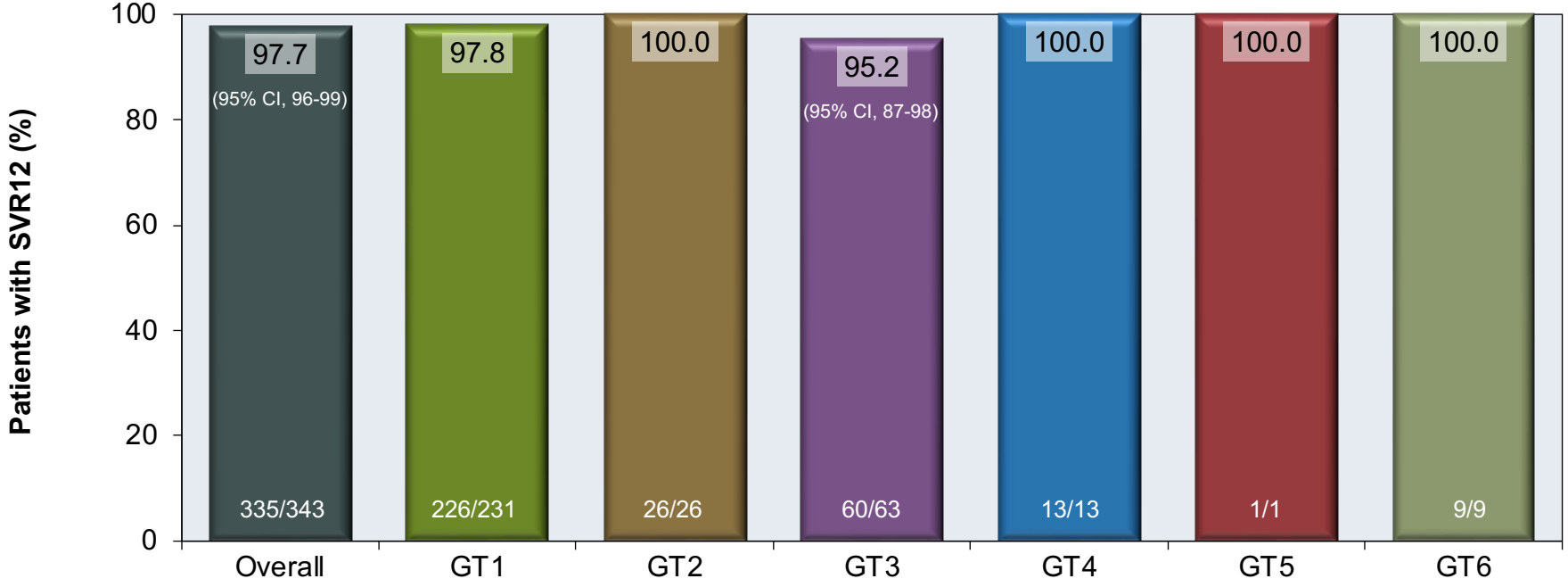
Glecaprevir-Pibrentasvir in GT 1-6 & Compensated Cirrhosis
EXPEDITION-8: Method to Determine Cirrhosis Eligibility

Method Used to Determine Cirrhosis Eligibility	Patients (%) (n = 343)
Histology (METAVIR F4 or equivalent)	32 (9.3)
FibroScan ≥14.6 kPa (no histology data available)	285 (83.1)
FibroTest ≥0.75 and APRI >2 (no histology or FibroScan data available)	26 (7.6)

Source: Brown RS, et al. J Hepatol. 2020;72:441-8.

Glecaprevir-Pibrentasvir in GT 1-6 & Compensated Cirrhosis
EXPEDITION-8: Results (Intent-to-Treat)

Sustained Virologic Response Rates (SVR): ITT Analysis



Source: Brown RS, et al. J Hepatol. 2020;72:441-8.

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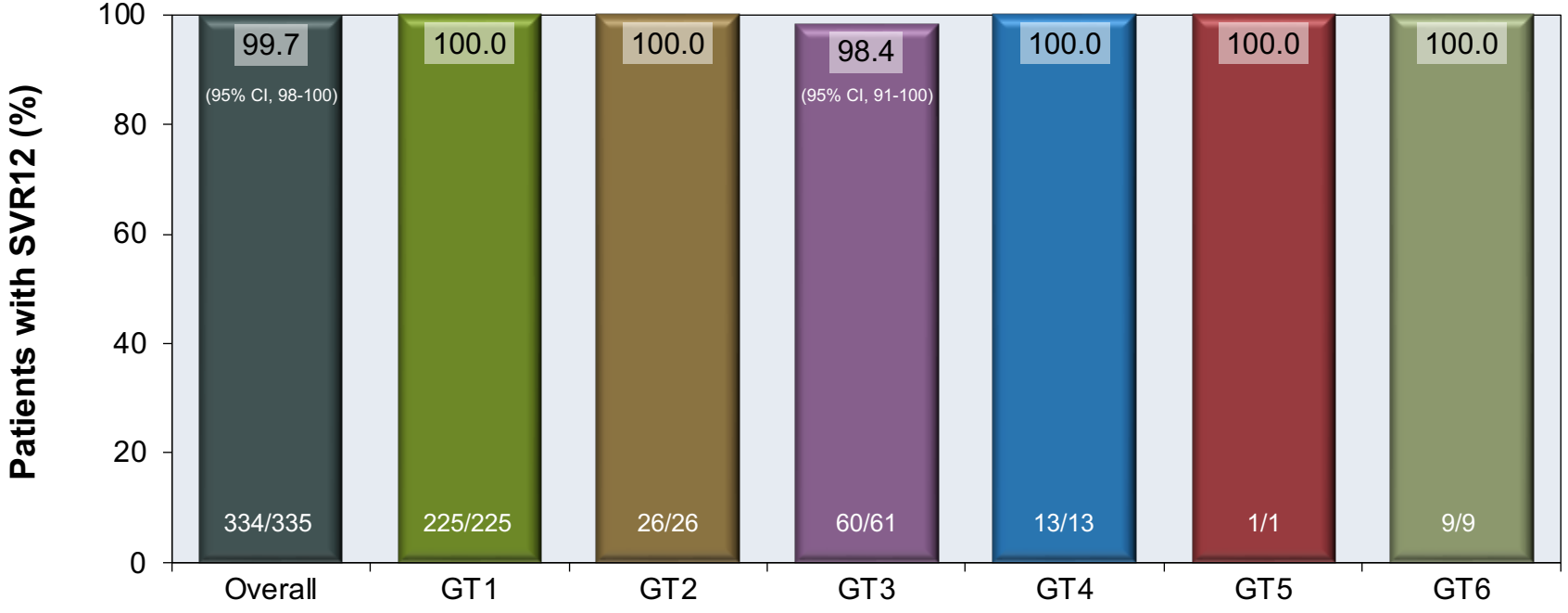
Glecaprevir-Pibrentasvir in GT 1-6 & Compensated Cirrhosis
EXPEDITION-8: Results (Per Protocol Analysis)

Sustained Virologic Response Rates (SVR): Per Protocol Analysis



Source: Brown RS, et al. J Hepatol. 2020;72:441-8.

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Glecaprevir-Pibrentasvir in GT 1-6 & Compensated Cirrhosis
EXPEDITION-8: Adverse Events

Adverse Event (AE), n (%)	Glecaprevir-Pibrentasvir (n = 343)
Any serious adverse event	6 (2)
Any drug-related serious adverse event	0
Adverse event leading to treatment discontinuation	0
AEs occurring in ≥5% of patients Fatigue Pruritus Headache Nausea	 30 (9) 29 (8) 28 (8) 19 (6)
Alanine aminotransferase >5x ULN, grade ≥3	1/342 (<1)
Total bilirubin >3x ULN, grade ≥3	0/342 (0)
Hemoglobin <8 g/dL, grade ≥3	0/342 (0)
Neutrophil count (<1.0 x 10^9/L)	2/342 (≤1)

Source: Brown RS, et al. J Hepatol. 2020;72:441-8.

Glecaprevir-Pibrentasvir in GT 1-6 & Compensated Cirrhosis
EXPEDITION-8: Conclusions

Conclusions: “Eight-week glecaprevir/pibrentasvir was well tolerated and led to a similarly high SVR12 rate as the 12-week regimen in treatment-naïve patients with chronic HCV GT1-6 infection and compensated cirrhosis.”

Source: Brown RS, et al. J Hepatol. 2020;72:441-8.

Glecaprevir-Pibrentasvir in HCV GT 1 & Prior DAA Treatment

MAGELLAN-1 (Part 1)

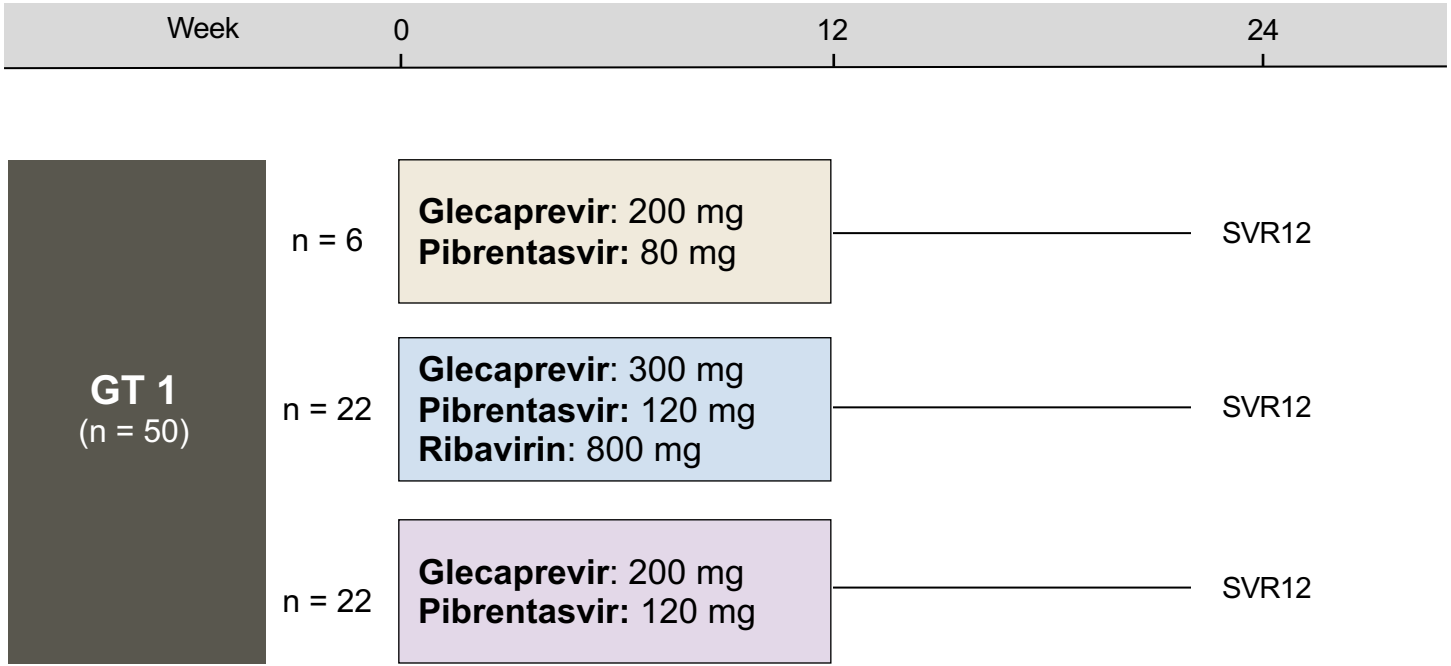
Source: Poordad F, et al. Hepatology. 2017;66:389-97.

Glecaprevir-Pibrentasvir in HCV GT 1 & Prior DAA Treatment
MAGELLAN-1 (Part 1): Study Features

- **Design**: Randomized, open-label, multicenter, phase 2 trial to evaluate the safety and efficacy of glecaprevir-pibrentasvir with or without ribavirin for 12 weeks in patients with genotype 1 chronic HCV (with or without cirrhosis) who previously experienced virologic failure with direct-acting antiviral (DAA) therapy.
- **Setting**: United States
- **Key Eligibility Criteria**
  - Chronic HCV GT 1
  - HCV RNA >1,000 IU/mL at screening
  - Adults 18-70 years of age
  - Prior failure with DAA-containing therapy (NS5A inhibitor and/or NS3/4A PI +/- NS5B inhibitors)
  - Patients without cirrhosis excluded
  - Patients with HIV or HBV coinfection excluded
- **Primary End Point**: SVR12

Source: Poordad F, et al. Hepatology. 2017;66:389-97.

Glecaprevir-Pibrentasvir in HCV GT 1 & Prior DAA Treatment
MAGELLAN-1 (Part 1): Treatment Regimens



Source: Poordad F, et al. Hepatology. 2017;66:389-97.

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Glecaprevir-Pibrentasvir in HCV GT 1 & Prior DAA Treatment
MAGELLAN-1 (Part 1): Baseline Characteristics

Characteristics	GLE 200 mg + PIB 80 mg (n = 6)	GLE 300 + PIB 120 mg + RBV 800 mg (n = 22)	GLE 200 mg + PIB 120 mg (n = 22)
Age, median years (range)	59 (39-61)	56 (39-64)	59 (46-70)
Male sex, n (%)	3 (50)	20 (91)	18 (82)
Black race, n (%)	2 (33)	5 (23)	10 (45)
BMI, median kg/m^2 (range)	27 (25-37)	28 (22-34)	28 (19-37)
IL28B non-CC genotype, n (%)	4 (67)	16 (73)	19 (86)
HCV RNA level, median $\log_{10}$ IU/mL (range)	6.1 (5.6-6.7)	6.7 (5.0-7.3)	6.6 (5.5-7.2)
Fibrosis stage, n (%) F0-F1 F2 F3	 4 (67) 1 (17) 1 (17)	 17 (77) 0 5 (23)	 11 (50) 6 (27) 5 (23)
HCV subtype 1a, n/N (%)	4 (67)	20 (91)	19 (82)

GLE-PIB = glecaprevir-pibrentasvir; RBV = ribavirin; BMI = body mass index

Source: Poordad F, et al. Hepatology. 2017;66:389-97.

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Glecaprevir-Pibrentasvir in HCV GT 1 & Prior DAA Treatment
MAGELLAN-1 (Part 1): Baseline Characteristics

Characteristics	GLE 200 + PIB 80 mg (n = 6)	GLE 300 + PIB 120 mg + RBV 800 mg (n = 22)	GLE 200 + PIB 120 mg (n = 22)
Prior DAA class, n (%)			
NS5A-experienced/PI-naïve	0	4 (18)	4 (18)
NS5A-naïve/PI-experienced	3 (50)	11 (50)	11 (50)
NS5A-experienced/PI-experienced	3 (50)	7 (32)	7 (32)
Baseline polymorphisms, n (%)			
Any (NS3 or NS5A)	5 (83)	18 (82)	17 (77)
NS3 only	2 (33)	7 (32)	5 (23)
NS5A only	3 (50)	5 (23)	3 (14)
Both NS3 and NS5A	0	6 (27)	9 (41)

GLE-PIB = glecaprevir-pibrentasvir

Source: Poordad F, et al. Hepatology. 2017;66:389-97.

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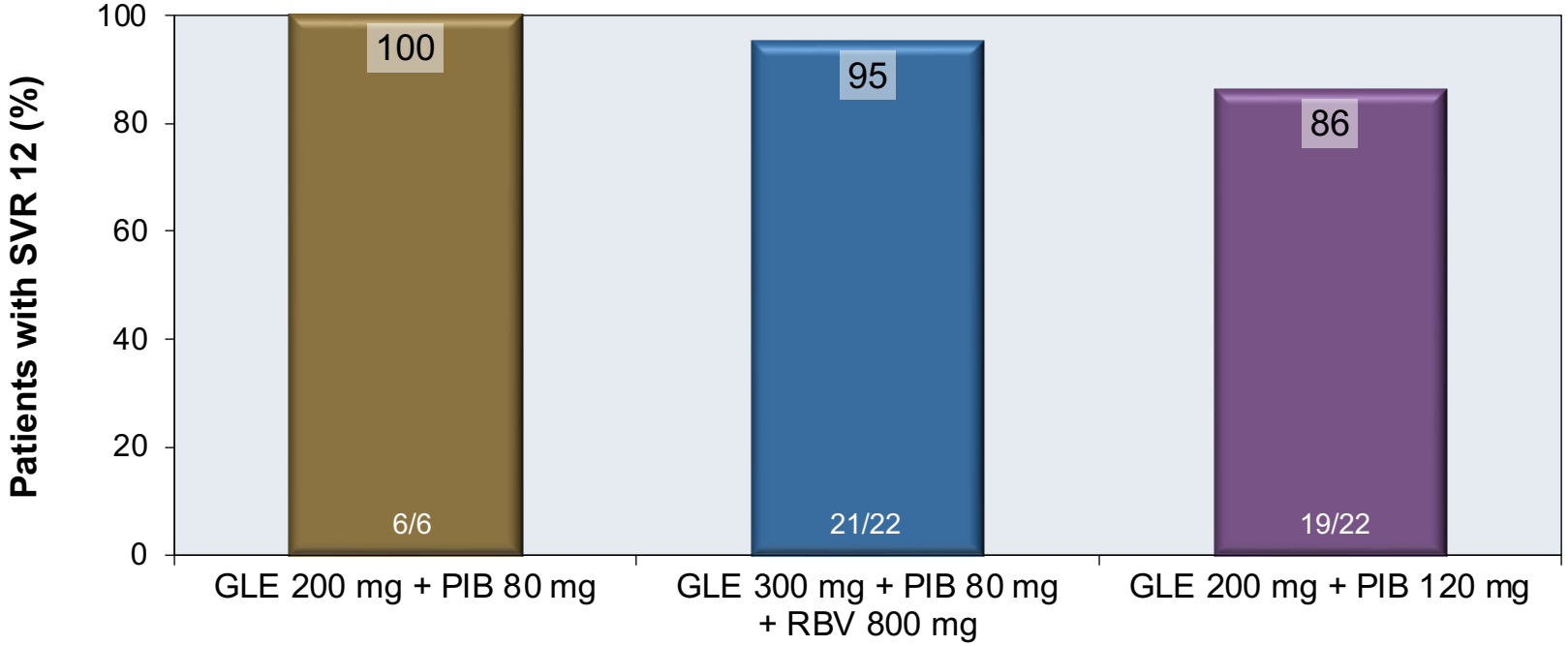
Glecaprevir-Pibrentasvir in HCV GT 1 & Prior DAA Treatment
MAGELLAN-1 (Part 1): Study Design

Intent-to-Treat Analysis



Source: Poordad F, et al. Hepatology. 2017;66:389-97.

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Glecaprevir-Pibrentasvir in HCV GT 1 & Prior DAA Treatment
MAGELLAN-1 (Part 1): Conclusions

Conclusions: “The combination of glecaprevir and pibrentasvir was highly efficacious and well tolerated in patients with HCV genotype 1 infection and prior failure of DAA-containing therapy; ribavirin coadministration did not improve efficacy.”

Source: Poordad F, et al. Hepatology. 2017;66:389-97.

Glecaprevir-Pibrentasvir in Patients with and without Cirrhosis

Pooled Analysis

Source: Gane E, et al. Clin Infect Dis. 2019;69:1657-64.

Glecaprevir-Pibrentasvir in Patients with and without Cirrhosis Pooled Analysis: Study Features

- **Design**: Integrated analysis of pooled data from nine phase 2 & 3 trials to evaluate the safety and efficacy of the fixed-dose combination of glecaprevir-pibrentasvir for 8, 12 or 16 weeks in treatment-naïve and treatment-experienced adults with GT 1-6 chronic HCV infection with and without cirrhosis
- **Setting:** US, Canada, Europe, Australia, New Zealand and South Africa
- **Key Eligibility Criteria**
  - Chronic HCV GT 1-6
  - HCV RNA ≥1,000 IU/mL at screening
  - Treatment naïve
  - Prior treatment with (1) PEG (or INF) +/- RIB or (2) Sofosbuvir + RIB +/- PEG
  - Patients with compensated cirrhosis permitted in some trials
  - Patients with chronic HBV excluded
- **End Points**: Safety and efficacy, stratified by cirrhosis status

Source: Gane E, et al. Clin Infect Dis. 2019;69:1657-64.

Glecaprevir-Pibrentasvir in Patients +/- Cirrhosis (Pooled Analysis) Baseline Characteristics

Characteristics	Cirrhosis* (n = 308)	No Cirrhosis (n = 2,061)	Overall (n = 2,369)
Age ≥65 years	64 (21)	264 (13)	328 (14)
Male sex, n (%)	199 (65)	1119 (54)	1318 (56)
Race, n (%)			
White	261 (85)	1637 (80)	1898 (80)
Black	25 (8)	124 (6)	149 (6)
Asian	17 (6)	255 (12)	272 (11)
Other	5 (2)	42 (2)	47 (2)
BMI ≥30 kg/m^2, n (%)	115 (37)	387 (19)	502 (21)
HCV genotype, n (%)			
GT 1	123 (40)	864 (42)	987 (42)
GT 2	38 (12)	439 (21)	477 (20)
GT 3	116 (38)	527 (26)	643 (27)
GT 4	22 (7)	160 (8)	182 (8)
GT 5 / 6	2 (<1) / 7 (2)	30 (1)/ 41 (2)	32 (1) / 48 (2)

*All with cirrhosis had compensated cirrhosis
Abbreviations: BMI = body mass index; GT = genotype

Source: Gane E, et al. Clin Infect Dis. 2019;69:1657-64.

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Glecaprevir-Pibrentasvir in Patients +/- Cirrhosis (Pooled Analysis) Baseline Characteristics

Characteristics	Cirrhosis* (n = 308)	No Cirrhosis (n = 2,061)	Overall (n = 2,369)
Treatment experienced, n (%)	126 (41)	603 (29)	729 (31)
PRS experienced**	99 (79)	517 (86)	616 (84)
PI and/or NS5A experienced**	27 (21)	86 (14)	113 (16)
HCV RNA ≥1 million IU/ml, n (%)	183 (59)	1224 (59)	1407 (59)
Fibrosis stage, n (%)			
F0-1	0	1651 (80)	1651 (70)
F2	0	163 (8)	165 (7)
F3	0	243 (12)	245 (10)
F4	307 (99)***	0	307 (13)
Child-Pugh score, n (%)			
5	264 (86)	4 (<1)	268 (11)
6	41 (13)	0	41 (2)
>6	2 (<1)	0	2 (<1)
Platelet count <100 x 10^9 cells/L	70 (23)	7 (<1)	77 (3)

*Compensated
**Percentage out of total number of treatment-experienced
***Missing in n=1
Abbreviations: PRS = pegIFN, ribavirin or sofosbuvir plus ribavirin; PI = protease inhibitor

Source: Gane E, et al. Clin Infect Dis. 2019;69:1657-64.

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Glecaprevir-Pibrentasvir in Patients +/- Cirrhosis (Pooled Analysis) Baseline Characteristics

Characteristics	Cirrhosis* (n = 308)	No Cirrhosis (n = 2,061)	Overall (n = 2,369)
G/P treatment duration, n (%)			
8 weeks	0	828 (40)	828 (35)
12 weeks	245 (80)	1176 (57)	1421 (60)
16 weeks	63 (20)	57 (3)	120 (5)
Albumin <3.5 g/dl, n (%)	23 (7)	5 (<1)	28 (1)
CKD stage 4 or 5 (eGFR <30 ml/min/1.73 m^2)	20 (7)	83 (4)	103 (5)
History of diabetes**	63 (20)	141 (7)	204 (9)
History of cardiovascular disease**	154 (50)	622 (30)	776 (33)

*Compensated
**Statistically significant difference between those with versus without cirrhosis at p-value <0.05 level

Abbreviation: CKD = chronic kidney disease

Source: Gane E, et al. Clin Infect Dis. 2019;69:1657-64.

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Glecaprevir-Pibrentasvir in Patients +/- Cirrhosis (Pooled Analysis) Adverse Events (without chronic kidney disease stage 4-5)

Adverse Event (AE), n (%)	Cirrhosis[1] (n = 288)	No Cirrhosis (n = 1,977)	Overall (n = 2,265)
Any AE	213 (74)	1316 (67)	1529 (68)
Any grade ≥3 AE	20 (7)	45 (2)	65 (3)
Serious AE	17 (6)	31 (2)	48 (2)
DAA-related serious AE	0	1 (<1)	1 (<1)
AE leading to drug discontinuation	0	8 (<1)[2]	8 (<1)
AEs in 10% patients			
Headache	47 (16)	363 (18)	410 (18)
Fatigue	58 (20)	272 (14)	330 (15)
Nausea	27 (9)	181 (9)	208 (9)
Pruritus	18 (6)	85 (4)	103 (5)
Deaths	1 (<1)[3]	5 (<1)[4]	6 (<1)

[1]Compensated. [2] Of these 8 patients, 3 experienced a total of 9 DAA-related AEs that led to study drug discontinuation, including abdominal pain, diarrhea, nausea, fatigue, malaise, dizziness, headache, and transient ischemic attacks.
[3]Due to cerebral hemorrhage. [4]Due to pneumonia, accidental overdose, adenocarcinoma, hepatic cancer metastatic, and acute ethanol and combined methadone toxicity
Abbreviation: CKD, chronic kidney disease

Source: Gane E, et al. Clin Infect Dis. 2019;69:1657-64.

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Glecaprevir-Pibrentasvir in Patients +/- Cirrhosis (Pooled Analysis) Adverse Events (with CKD stage 4-5)

Adverse Event (AE), n (%)	Cirrhosis[1] (n = 20)	No Cirrhosis (n = 84)	Overall (n = 104)
Any AE	20 (100)	54 (64)	74 (71)
Any grade ≥3 AE	11 (55)	14 (17)	25 (24)
Serious AE	11 (55)	14 (17)	25 (24)
DAA-related serious AE	0	0	0
AE leading to drug discontinuation	2 (10)	2 (2)	4 (4)[2]
AEs in 10% patients			
Headache	1 (5)	8 (10)	9 (9)
Fatigue	1 (5)	14 (17)	15 (14)
Nausea	4 (20)	8 (10)	12 (12)
Pruritus	6 (30)	15 (18)	21 (20)
Deaths	1 (5)[3]	0	1 (<1)

[1]Compensated cirrhosis
[2]Of these 4 patients, 2 with compensated cirrhosis experienced a DAA-related AE: 1 had Grade 2 diarrhea, and 1 had Grade 3 pruritus.
[3]Cause of death was cerebral hemorrhage.
Abbreviation: CKD, chronic kidney disease

Source: Gane E, et al. Clin Infect Dis. 2019;69:1657-64.

Hepatitis C Online

Glecaprevir-Pibrentasvir in Patients +/- Cirrhosis (Pooled Analysis) Laboratory Abnormalities

Grade ≥3, n (%)	Cirrhosis* (n = 308)	No Cirrhosis (n = 2,061)	Overall (n = 2,369)
ALT >5 x ULN	0	2 (<1)	2 (<1)
AST >5 x ULN	0	6 (<1)	6 (<1)
Total bilirubin >3 x ULN	3 (1)	6 (<1)	9 (<1)
Platelets <50 x 10^9/L	4 (1)	0	4 (<1)

*All with cirrhosis had compensated cirrhosis

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase, ULN = upper limit of normal

Source: Gane E, et al. Clin Infect Dis. 2019;69:1657-64.

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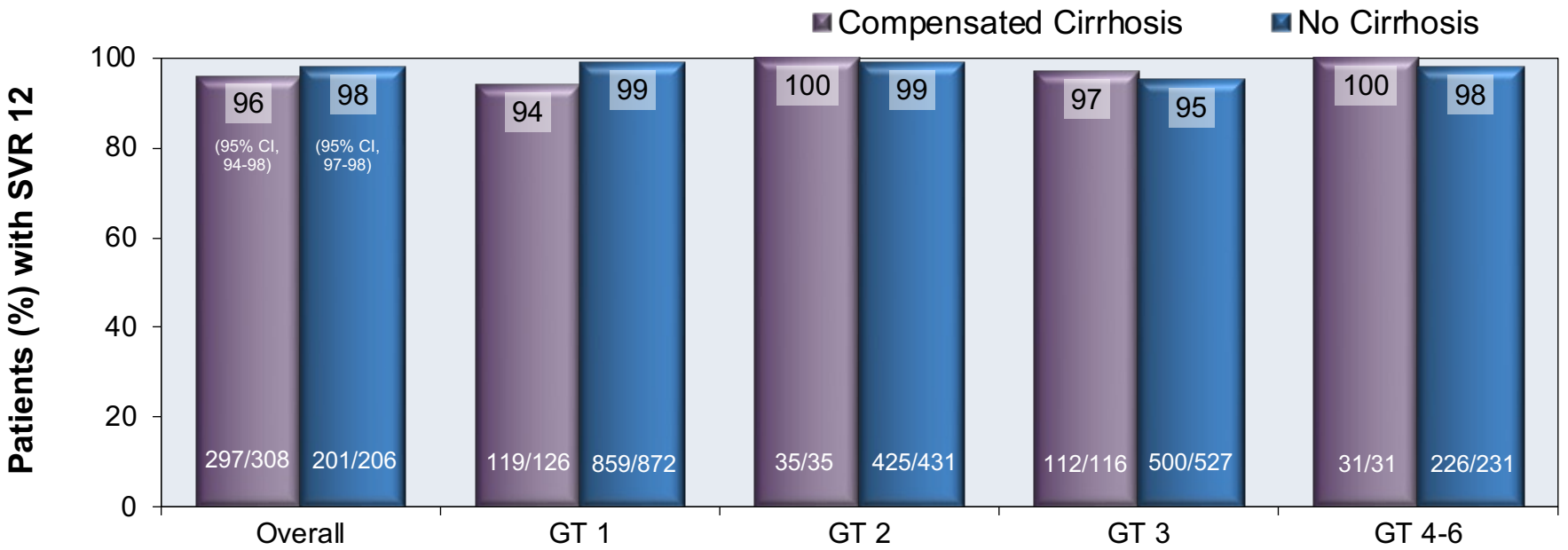
Glecaprevir-Pibrentasvir in Patients +/- Cirrhosis (Pooled Analysis) Results

Overall SVR by Intention-to-Treat Analysis



Note – duration of treatment 12 (80%) or 16 (20%) weeks for cirrhosis.

Source: Gane E, et al. Clin Infect Dis. 2019;69:1657-64.

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Glecaprevir-Pibrentasvir in Patients +/- Cirrhosis (Pooled Analysis) Outcomes

Outcome	Cirrhosis* (n = 308)	No Cirrhosis (n = 2,061)
SVR12, n (%, [95% CI])	297 (96.4 [93.7-98.0])	2010 (97.5 [96.8-98.1])
Non-response, n (%)		
On-treatment virologic failure	5**	6
Viral relapse	3	19
Premature drug discontinuation	1	11
Missing SVR12 data	2	15

*Compensated. Abbreviation: SVR12, sustained virologic response 12 weeks post-treatment; CI, confidence interval.
**2 patients had prior treatment experience with both a NS5A inhibitor and NS3/4A protease inhibitor. Glecaprevir-pibrentasvir not recommended for treatment in this dual DAA-experienced patient population.

Source: Gane E, et al. Clin Infect Dis. 2019;69:1657-64.

Glecaprevir-Pibrentasvir in Patients +/- Cirrhosis (Pooled Analysis) Conclusions

Conclusions: “Glecaprevir-pibrentasvir was safe and efficacious in patients with compensated liver disease, including those with CKD 4/5.”

Source: Gane E, et al. Clin Infect Dis. 2019;69:1657-64.

Glecaprevir-Pibrentasvir in HCV GT 1 or 4 & Prior DAA Treatment

MAGELLAN-1 (Part 2)

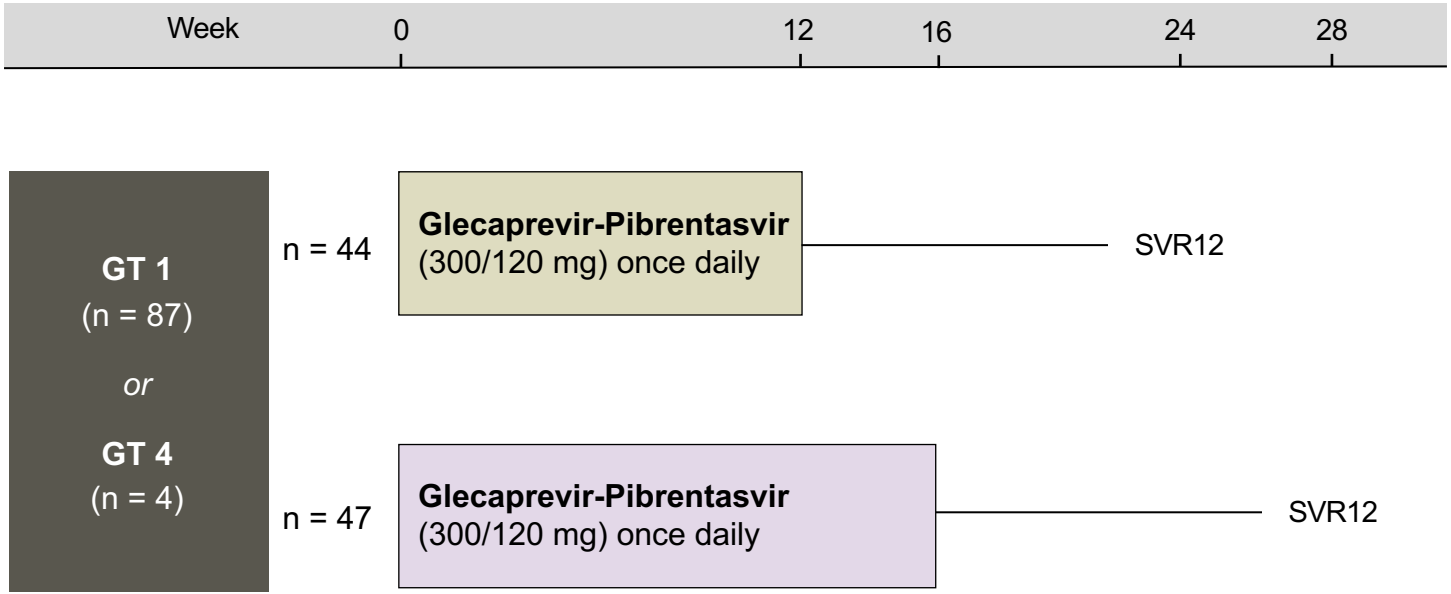
Source: Poordad F, et al. Hepatology. 2018;67:1253-60.

Glecaprevir-Pibrentasvir in HCV GT 1 or 4 & Prior DAA Treatment MAGELLAN-1 (Part 2): Study Features

- **Design**: Randomized, open-label, multicenter, phase 3 trial to evaluate the safety and efficacy of glecaprevir-pibrentasvir for 12 or 16 weeks in patients with genotype 1 or 4 chronic HCV (with or without cirrhosis) who previously experienced virologic failure with direct-acting antiviral (DAA) therapy.
- **Setting**: 31 sites in Australia, France, Spain, UK, and United States
- **Key Eligibility Requirements**
  - Chronic HCV GT 1, 4, 5, or 6
  - HCV RNA >1,000 IU/mL at screening
  - At least 18 years of age (no upper limit)
  - Prior failure with ≥1 NS3/4A protease and/or NS5A inhibitor-based regimen
  - Patients without cirrhosis or with compensated cirrhosis
  - Patients with HIV or HBV coinfection excluded
- **Primary End Point**: SVR12

Source: Poordad F, et al. Hepatology. 2018;67:1253-60.

Glecaprevir-Pibrentasvir in HCV GT 1 or 4 & Prior DAA Treatment MAGELLAN-1 (Part 2): Regimens



Randomized 1:1 ratio to 12 or 16 weeks; stratified by genotype and past NS5A experience

Source: Poordad F, et al. Hepatology. 2018;67:1253-60.

Glecaprevir-Pibrentasvir in HCV GT 1 or 4 & Prior DAA Treatment MAGELLAN-1 (Part 2): Baseline Characteristics

Characteristics	Glecaprevir-Pibrentasvir 12 weeks (n = 44)	Glecaprevir-Pibrentasvir 16 weeks (n = 47)
Age, median years (range)	57 (22-67)	56 (36-70)
Male sex, n (%)	31 (70)	33 (70)
Black race, n (%)	9 (20)	11 (23)
BMI, median kg/m^2 (range)	28 (21-41)	29 (20-52)
IL28B non-CC genotype, n (%)	38 (86)	42 (89)
HCV RNA, median $\log_{10}$ IU/mL (range)	6.1 (4.7-7.2)	6.3 (4.7-7.1)
HCV Subtype, n (%) 1a 1b 1c 4	 35 (80) 8 (18) - 1 (2)	 32 (71) 11 (23) 1 (2) 3 (6)
Compensated cirrhosis, n (%)	15 (34)	12 (26)

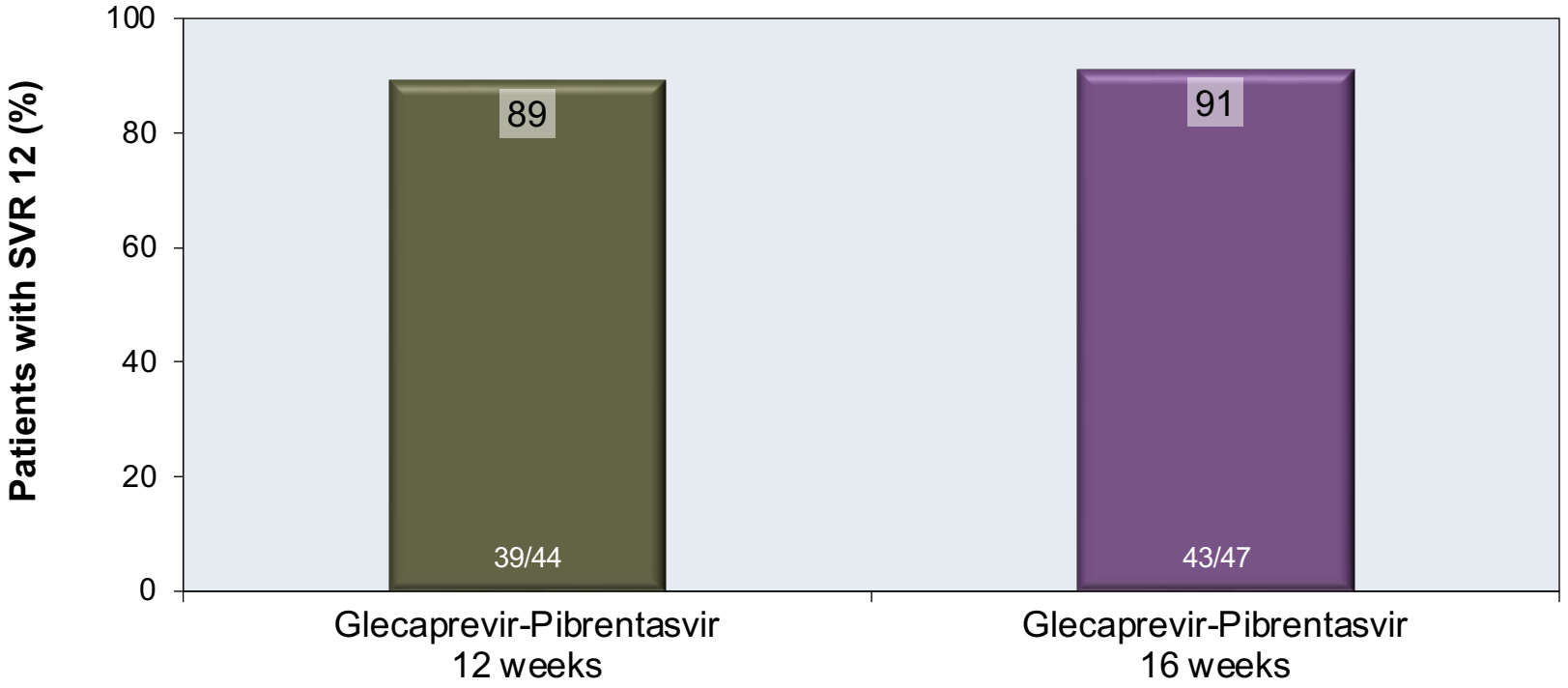
Source: Poordad F, et al. Hepatology. 2018;67:1253-60.

Glecaprevir-Pibrentasvir in HCV GT 1 or 4 & Prior DAA Treatment
MAGELLAN-1 (Part 2): Baseline Characteristics

Characteristics	Glecaprevir-Pibrentasvir 12 weeks (n = 44)	Glecaprevir-Pibrentasvir 16 weeks (n = 47)
Prior DAA class, n (%)		
NS3/4A PI only (NS5A inhibitor naïve)	14 (32)	13 (28)
NS5A inhibitor only (PI-naïve)	16 (36)	18 (30)
N3/4A PI + NS5A inhibitor	14 (32)	16 (34)
Past DAA response, n (%)		
On-treatment failure	14 (32)	13 (28)
Virologic relapse	30 (68)	34 (72)
Key baseline substitutions, n (%)		
None	13 (30)	13 (30)
NS3 only	2 (5)	4 (9)
NS5A only	24 (55)	23 (52)
NS3 and NS5A	5 (11)	4 (9)

Source: Poordad F, et al. Hepatology. 2018;67:1253-60.

Glecaprevir-Pibrentasvir in HCV GT 1 or 4 & Prior DAA Treatment
MAGELLAN-1 (Part 2): Results



Source: Poordad F, et al. Hepatology. 2018;67:1253-60.

Glecaprevir-Pibrentasvir in HCV GT 1 or 4 & Prior DAA Treatment
MAGELLAN-1 (Part 2): Results by Prior DAA Class

Sustained Virologic Response		
Response	Glecaprevir-Pibrentasvir 12 weeks (n = 44)	Glecaprevir-Pibrentasvir 16 weeks (n = 47)
Overall	39/44 (89)	43/47 (91)
On-treatment virologic failure	1/44 (2)	4/47 (9)
Virologic relapse	4/44 (9)	0/47 (0)

Source: Poordad F, et al. Hepatology. 2018;67:1253-60.

Glecaprevir-Pibrentasvir in HCV GT 1 or 4 & Prior DAA Treatment
MAGELLAN-1 (Part 2): Results by Prior DAA Class

Sustained Virologic Response Based on Prior DAA Class		
Prior DAA Class	Glecaprevir-Pibrentasvir 12 weeks (n = 44)	Glecaprevir-Pibrentasvir 16 weeks (n = 47)
NS3/4A PI only	14/14 (100)	13/13 (100)
NS5A inhibitor only	14/16 (88)	17/18 (94)
NS3/4A PI + NS5A inhibitor	11/14 (79)	13/16 (81)

Source: Poordad F, et al. Hepatology. 2018;67:1253-60.

Glecaprevir-Pibrentasvir in HCV GT 1 or 4 & Prior DAA Treatment MAGELLAN-1 (Part 2): Results by Baseline Substitutions

Sustained Virologic Response Based on Baseline Substitutions		
Baseline Substitutions	Glecaprevir-Pibrentasvir 12 weeks (n = 44)	Glecaprevir-Pibrentasvir 16 weeks (n = 47)
None	13/13 (100)	13/13 (100)
NS3 only	2/2 (100)	4/4 (100)
NS5A only	20/24 (83)	22/23 (96)
NS3 and NS5A	4/5 (80)	1/4 (25)

Source: Poordad F, et al. Hepatology. 2018;67:1253-60.

Glecaprevir-Pibrentasvir in HCV GT 1 or 4 & Prior DAA Treatment MAGELLAN-1 (Part 2): Conclusions

Conclusions: “Patients with hepatitis C virus (HCV) who have virologic failure after treatment containing an NS5A inhibitor have limited retreatment options.”

Source: Poordad F, et al. Hepatology. 2018;67:1253-60.

Glecaprevir-Pibrentasvir + Sofosbuvir + Ribavirin for Retreatment in G/P-Experienced

MAGELLAN-3

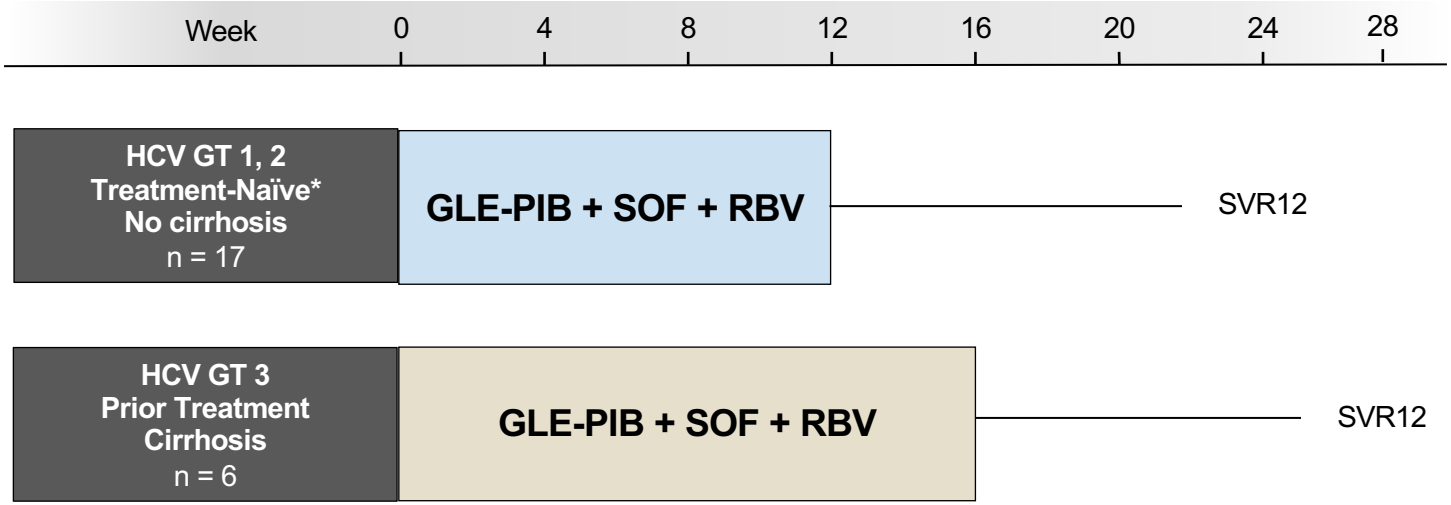
Source: Wyles D, et al. J Hepatol;2019;70:1019-38.

Glecaprevir-Pibrentasvir + SOF + RBV for Retreatment of HCV GT 1-3 MAGELLAN-3: Study Features

- **Design**: Phase 3b, open-label study that assessed the safety and efficacy of glecaprevir-pibrentasvir plus sofosbuvir with ribavirin for 12 or 16 weeks in patients with a history of failure after glecaprevir-pibrentasvir and GT 1, 2 or 3.
- **Setting:** United States, Australia, Canada, Europe, New Zealand, South Korea, & China
- **Key Eligibility Criteria**
  - Chronic HCV GT 1-3
  - Age 18 years or older or adolescents weighing at least 35 kg
  - HCV RNA >1,000 IU/mL at screening
  - Prior treatment with glecaprevir-pibrentasvir
  - Compensated cirrhosis permitted
  - Patients with HIV or chronic HBV excluded
- **Primary End Point**: SVR12, by intent-to-treat analysis

Source: Wyles D, et al. J Hepatol;2019;70:1019-38.

Glecaprevir-Pibrentasvir + SOF + RBV for Retreatment of HCV GT 1-3
MAGELLAN-3: Study Design



Abbreviations: GLE-PIB = glecaprevir-pibrentasvir; SOF = sofosbuvir; RBV = Ribavirin

Naïve* defined as treatment-naïve to NS5A inhibitor or protease inhibitor prior to 1st GLE-PIB treatment

Drug Dosing: Glecaprevir-pibrentasvir (100/40 mg) fixed-dose combination; three pills (300/120 mg) 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. J Hepatol;2019;70:1019-38.

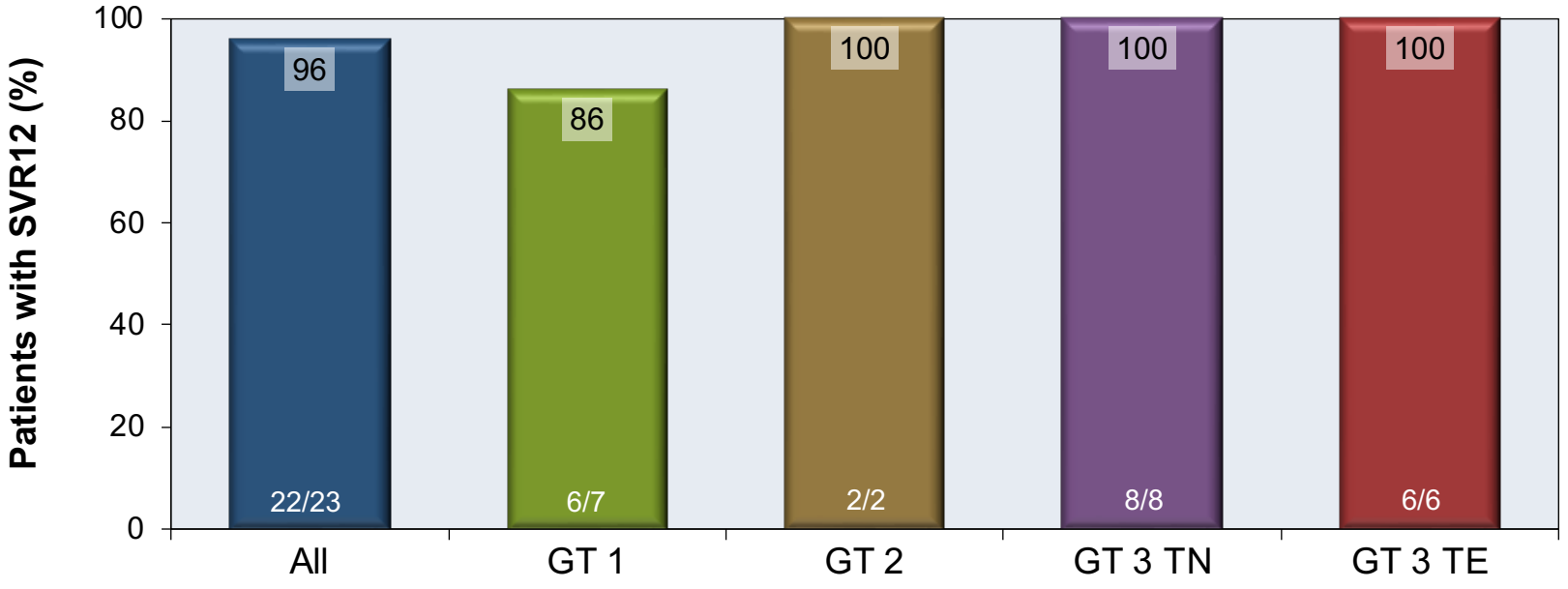
Glecaprevir-Pibrentasvir + SOF + RBV for Retreatment of HCV GT 1-3
MAGELLAN-3: Baseline Characteristics

Baseline Characteristic	12 weeks			16 weeks
	GT 1 (n = 7)	GT 2 (n = 2)	GT 3 naive (n = 8)	GT 3 experienced (n = 6)
Age, median (range)	59 (48-67)	56 (56-56)	50 (38-60)	58 (53-65)
Male, n (%)	4 (57)	1 (50)	7 (88)	6 (100)
Race				
White, n (%)	6 (86)	2 (100)	6 (75)	6 (100)
Asian, n (%)	0	0	2 (25)	0
Black, n (%)	1 (14)	0	0	0
BMI, kg/m^2 mean (range)	34 (20-36)	35 (30-41)	25 (22-30)	27 (22-32)
HCV RNA, $\log_{10}$ IU/ml (median)	6.3 (6.0-6.8)	6.6 (6.6-6.6)	6.2 (3.7-7.4)	6.6 (5.9-7.0)
Cirrhosis, n (%)	4 (57)	0	2 (25)	1 (17)
Presence of baseline RAS, n (%)				
None	0	2 (100)	0	0
NS3 only	0	0	0	0
NS5A only	5 (71)	0	5 (62)	6 (100)
NS3 and NS5A	2 (29)	0	3 (38)	0

Source: Wyles D, et al. J Hepatol;2019;70:1019-38.

Glecaprevir-Pibrentasvir + SOF + RBV for Retreatment of HCV GT 1-3
MAGELLAN-3: Results

MAGELLAN-3: SVR12 Results by Prior Treatment Status and Genotype



Abbreviations: TN = treatment-naïve; TE = treatment-experienced

Source: Wyles D, et al. J Hepatol;2019;70:1019-38.

Glecaprevir-Pibrentasvir + SOF + RBV for Retreatment of HCV GT 1-3
MAGELLAN-3: Conclusions

Conclusions: “Retreatment of glecaprevir-pibrentasvir virologic failures with glecaprevir-pibrentasvir plus sofosbuvir plus ribavirin for 12 or 16 weeks was well-tolerated and high.”

Source: Gane E, et al. Clin Infect Dis. 2019;69:1657-64.

Glecaprevir-Pibrentasvir in HCV GT 3, +/- Cirrhosis

SURVEYOR-II (Part 3)

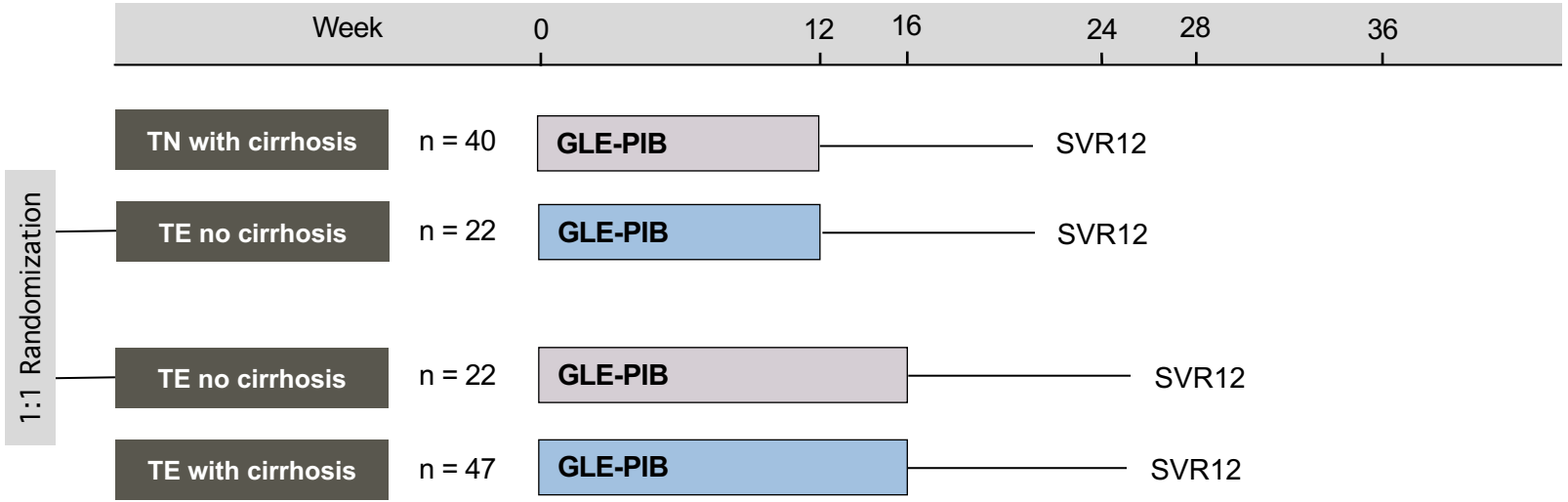
Source: Wyles D, et al. Hepatology. 2018;67:514-23.

Glecaprevir-Pibrentasvir for Retreatment in Patients with GT3 SURVEYOR-II, part 3: Study Features

- **Design**: Phase 3 partly randomized, open-label trial that assessed the safety and efficacy of glecaprevir-pibrentasvir for 12 or 16 weeks in patients with GT3, including those with prior treatment experience with sofosbuvir and/or compensated cirrhosis.
- **Setting:** United States, Australia, Canada, France, New Zealand and United Kingdom
- **Key Eligibility Criteria**
  - Chronic HCV GT 3
  - HCV RNA >1,000 IU/mL at screening
  - Treatment naïve or
  - Prior treatment with (1) PEG (or INF) +/- RIB or (2) Sofosbuvir + RIB +/- PEG
  - Patients with compensated cirrhosis included
  - Patients with HIV or chronic HBV excluded
- **End Points**: Safety and efficacy, stratified by cirrhosis status

Source: Wyles D, et al. Hepatology;2018;67:514-523.

Glecaprevir-Pibrentasvir for Retreatment in Patients with GT3 SURVEYOR-II, part 3: Study Design



Abbreviations: GLE-PIB = glecaprevir-pibrentasvir; GT, genotype; TN = treatment-naïve; TE = treatment-experienced

Drug Dosing: Glecaprevir-pibrentasvir (300/120 mg), once daily

Source: Wyles D, et al. Hepatology;2018;67:514-23.

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Glecaprevir-Pibrentasvir for Retreatment in Patients with GT3 SURVEYOR-II, part 3: Baseline Characteristics

Baseline Characteristic	12-Week GLE-PIB		16-Week GLE-PIB	
	TN w/ cirrhosis (n = 40)	TE no cirrhosis (n = 22)	TE no cirrhosis (n = 22)	TE w/ cirrhosis (n = 47)
Median age, y (range)	56 (36-70)	56 (35-68)	59 (29-66)	59 (47-70)
Male sex, n (%)	24 (60)	14 (64)	14 (64)	36 (77)
White race, n (%)	24 (60)	17 (77)	20 (91)	42 (89)
Cirrhosis, n (%) Child-Pugh score 5 Child-Pugh score 6	 35 (88) 5 (13)	 0	 0	 37 (79) 10 (21)
BMI, kg/m^2 median (range)	29 (21-51)	26 (19-42)	28 (22-48)	27 (21-42)
HCV RNA, $\log_{10}$ IU/mL median (range)	6.2 (4.2-7.1)	6.6 (5.1-7.5)	6.1 (4.7-7.3)	6.5 (4.6-7.2)
Prior treatment history, n (%) IFN/pegIFN ± RBV SOF + RBV ± pegIFN	 0 0	 14 (64) 8 (36)	 13 (59) 9 (41)	 22 (47) 25 (53)
Baseline polymorphisms, n (%) Any NS3 only NS5A only Both NS3 + NS5A	 10 (26) 1 (3) 9 (23) 0	 6 (27) 0 6 (27) 0	 3 (14) 0 3 (14) 0	 7 (15) 1 (2) 6 (13) 0

Source: Wyles D, et al. Hepatology;2018;67:514-23.

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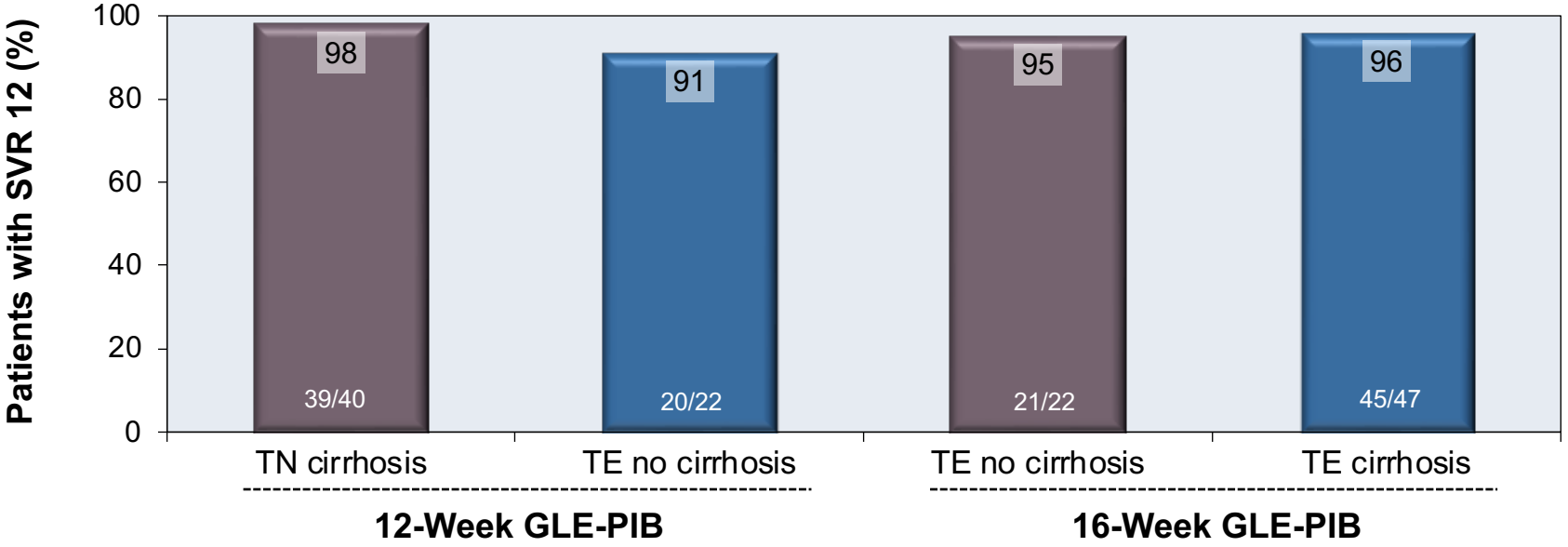
Glecaprevir-Pibrentasvir for Retreatment in Patients with GT3 SURVEYOR-II, part 3: Results

SURVEYOR-II, part 3: SVR 12* by Treatment Duration and Subgroup



Abbreviations: GLE-PIB, glecaprevir-pibrentasvir
* Primary end-point by intention-to-treat analysis

Source: Wyles D, et al. Hepatology;2018;67:514-523.

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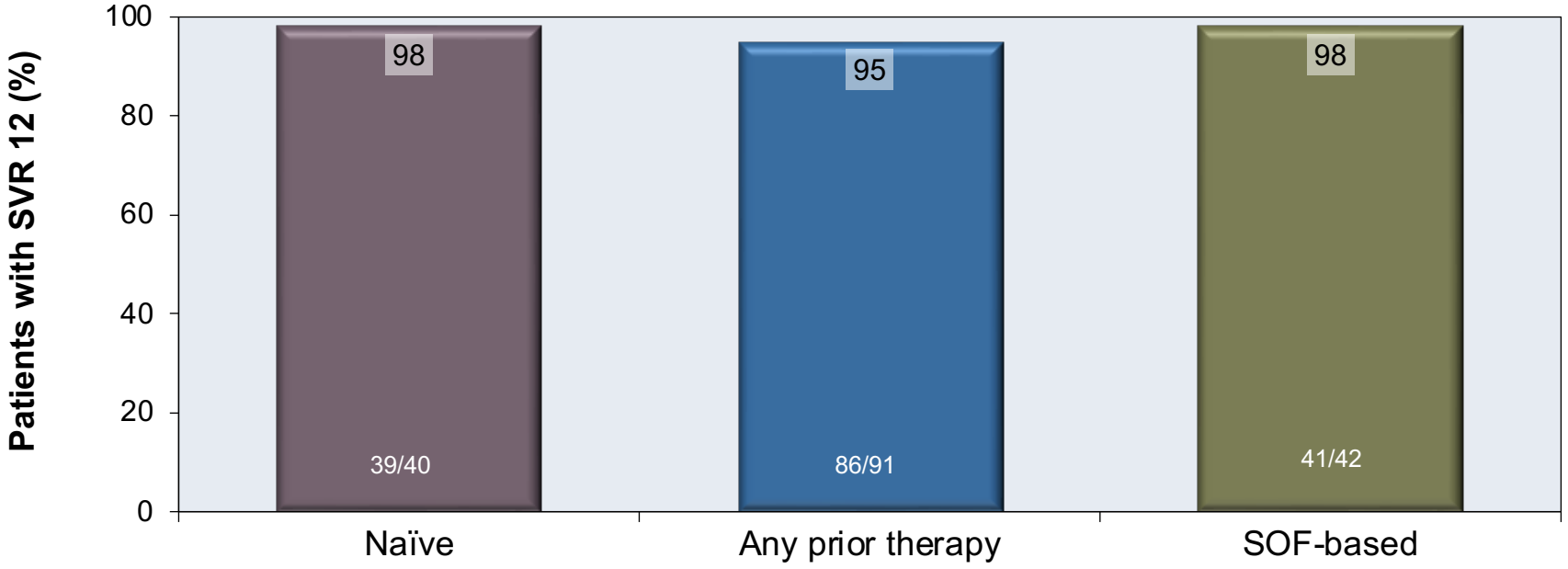
Glecaprevir-Pibrentasvir for Retreatment in Patients with GT3 SURVEYOR-II, part 3: Results

SURVEYOR-II, part 3: SVR12 by Treatment Experience



Source: Wyles D, et al. Hepatology;2018;67:514-523.

Glecaprevir-Pibrentasvir in HCV GT 3, with Cirrhosis and Prior Treatment SURVEYOR-II (Part 3): Results

Conclusion: “Patients with HCV GT3 infection with prior treatment experience and/or compensated cirrhosis achieved high SVR12 rates following 12 or 16 weeks of treatment with G/P. The regimen was well tolerated.”

Source: Wyles D, et al. Hepatology. 2018;67:514-23.

Glecaprevir-Pibrentasvir in Patients with GT 1 and Prior NS5A + Sofosbuvir

HCV-TARGET

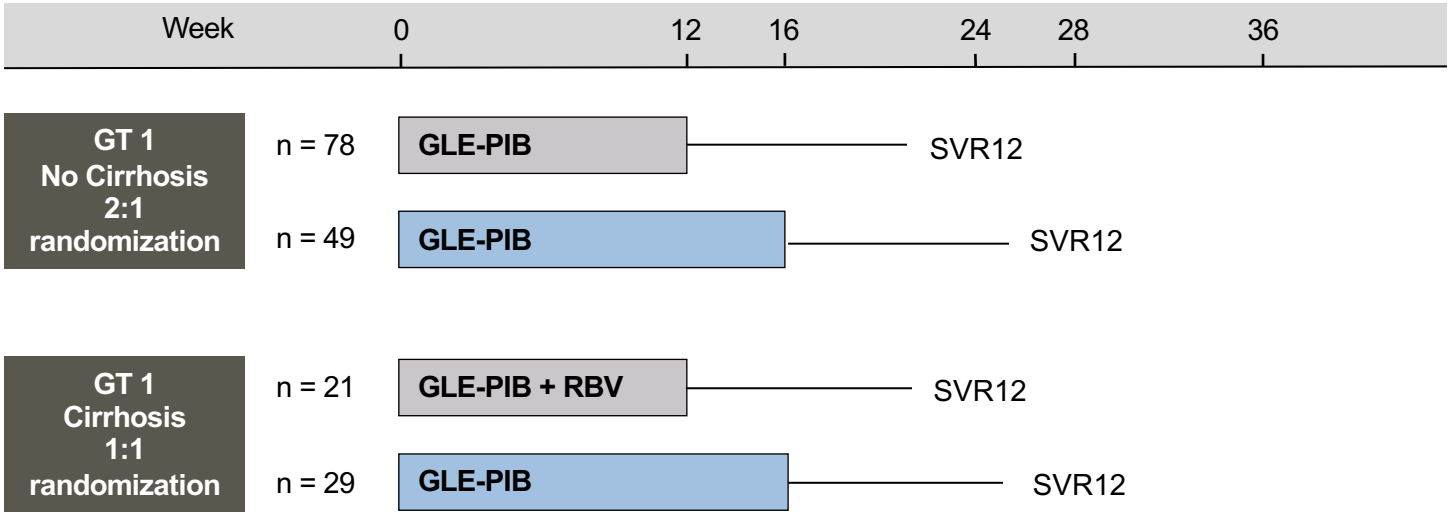
Source: Lok A, et al. Gastroenterology;2019;157:1506-17.

Glecaprevir-Pibrentasvir for Retreatment in Patients with GT 1 HCV-TARGET: Study Features

- **Design**: Phase 3b, randomized, open-label study that assessed the safety and efficacy of glecaprevir-pibrentasvir with or without ribavirin for 12 or 16 weeks in patients with genotype 1 and a history of treatment with NS5A inhibitor (ledipasvir, velpatasvir, daclatasvir) and NS5B inhibitor (sofosbuvir).
- **Setting:** 30 centers in the United States (HCV TARGET network)
- **Key Eligibility Criteria**
  - Chronic HCV GT 1
  - Prior treatment: NS5A inhibitor (ledipasvir, velpatasvir, daclatasvir) + sofosbuvir ± ribavirin
  - Compensated cirrhosis permitted
  - Patients with HIV or chronic HBV excluded
- **Primary End Point**: SVR12, by intent-to-treat analysis

Source: Lok A, et al. Gastroenterology;2019;157:1506-17.

Glecaprevir-Pibrentasvir for Retreatment in Patients with GT 1 HCV-TARGET: Study Design



Abbreviations: GLE-PIB = glecaprevir-pibrentasvir; RBV = ribavirin

Drug Dosing

Glecaprevir-pibrentasvir (100/40 mg) fixed-dose combination; three pills (300/120 mg) once daily.
Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg.

Source: Lok A, et al. Gastroenterology;2019;157:1506-17.

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Glecaprevir-Pibrentasvir for Retreatment in Patients with GT 1 HCV-TARGET: Baseline Characteristics

Baseline Characteristic	GT 1 no cirrhosis		GT 1 with cirrhosis	
	GLE-PIB 12 wk (n = 78)	GLE-PIB 16 wk (n = 49)	GLE-PIB + RBV 12 wk (n = 21)	GLE-PIB 16 wk (n = 29)
Male, n (%)	64 (82)	40 (82)	16 (76)	23 (79)
Race, black, n (%)	32 (41)	25 (51)	8 (38)	12 (41)
Age, years, median (range)	62 (40-77)	62 (45-75)	60 (38-70)	64 (42-81)
BMI, kg/m^2 mean (range)	28 (19-45)	30 (19-50)	30 (19-53)	27 (23-38)
HCV Genotype 1A, n (%)	60 (77)	39 (80)	17 (81)	26 (90)
HCV RNA, $\log_{10}$ IU/ml, median (range)	6.4 (1.9-7.7)	6.4 (4.0-7.7)	6.3 (5.1-7.0)	6.4 (3.7-7.1)
Prior DAA treatment, n (%) SOF + LDV SOF + VEL SOF + DCV	 74 (95) 4 (5) 0	 45 (92) 3 (6) 1 (2)	 21 (100) 0 0	 26 (90) 3 (10) 0
Prior PI exposure, n(%)	0	5 (10)	0	3 (10)
History of HCC, n (%)	4 (5)	3 (6)	0	3 (10)
Post-liver transplantation, n (%)	5 (6)	10 (20)	0	0
HIV coinfection, n (%)	5 (6)	2 (4)	1 (5)	1 (3)

Source: Lok A, et al. Gastroenterology;2019;157:1506-17.

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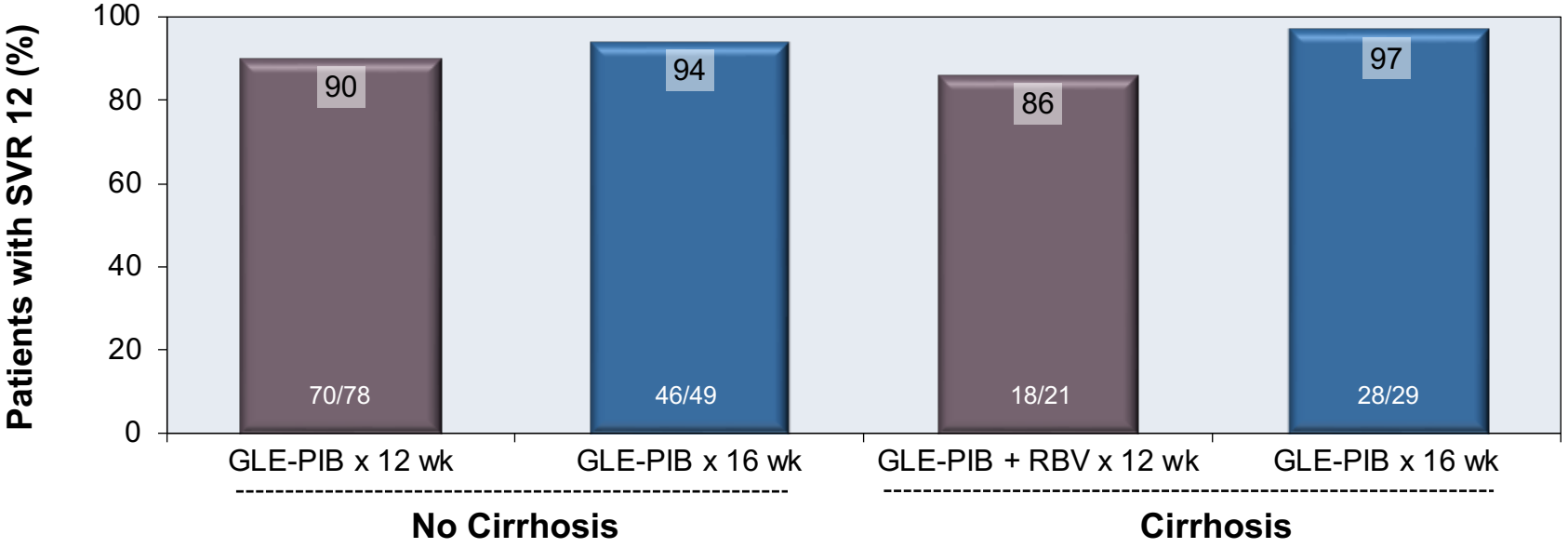
Glecaprevir-Pibrentasvir for Retreatment in Patients with GT 1 HCV-TARGET: Results

HCV-TARGET: SVR 12* by Cirrhosis Status and Regimen



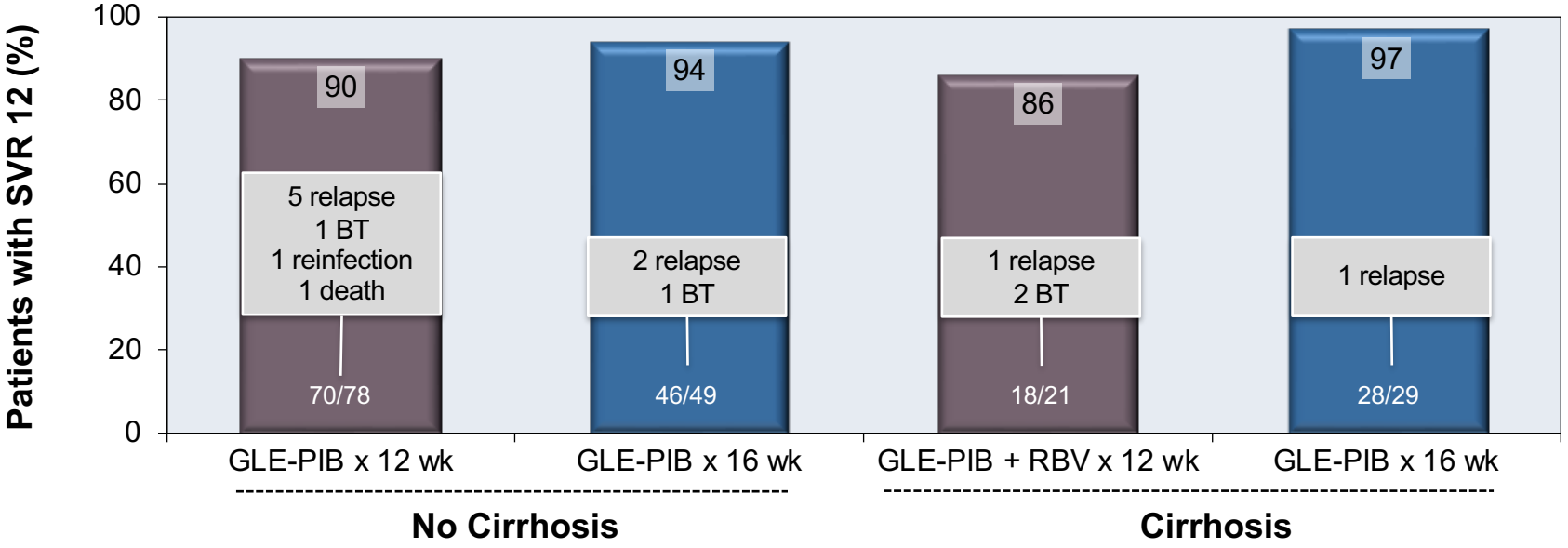
Abbreviations: GLE-PIB = glecaprevir-pibrentasvir; RBV = ribavirin; BT = (virologic) breakthrough
*Primary end point by intention-to-treat analysis

Source: Lok A, et al. Gastroenterology;2019;157:1506-17.

Hepatitis C Online

Glecaprevir-Pibrentasvir for Retreatment in Patients with GT 1 HCV-TARGET: Results

HCV-TARGET: SVR 12* by Cirrhosis Status and Regimen



Abbreviations: GLE-PIB = glecaprevir-pibrentasvir; RBV = ribavirin; BT = (virologic) breakthrough
*Primary end point by intention-to-treat analysis

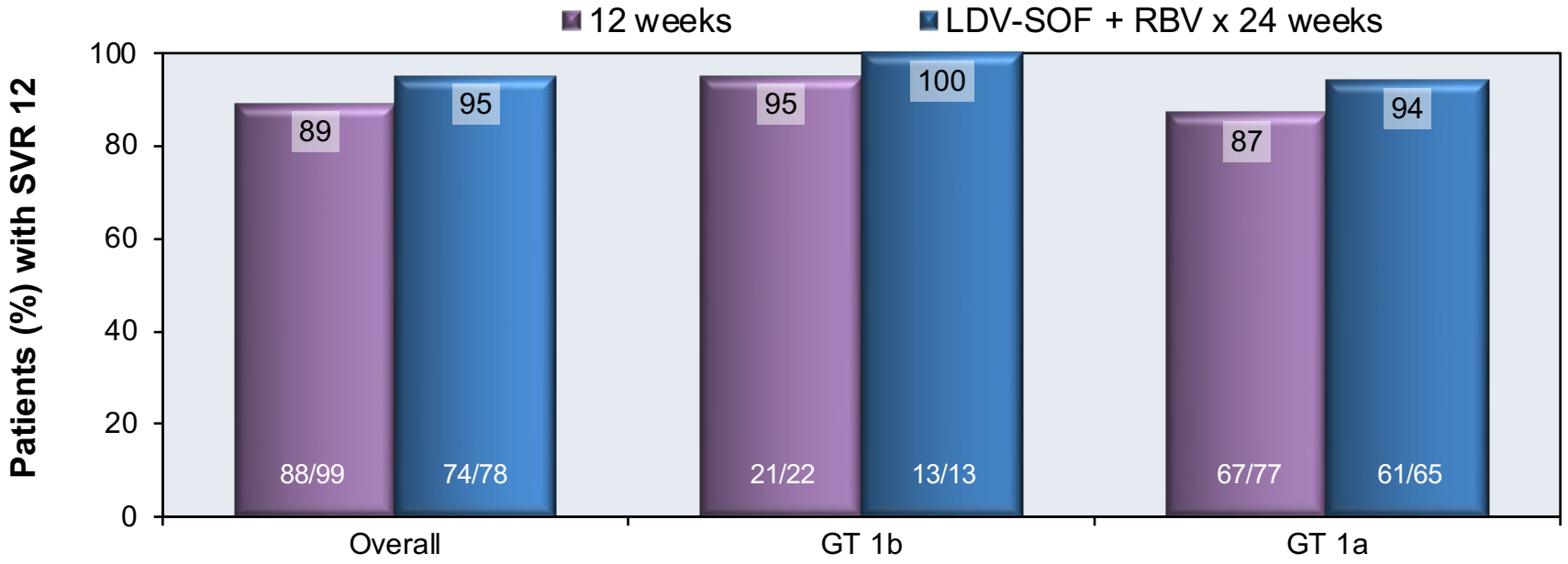
Source: Lok A, et al. Gastroenterology;2019;157:1506-17.

Hepatitis C Online

Glecaprevir-Pibrentasvir for Retreatment in Patients with GT 1 HCV-TARGET: Results

Please correct legend – I couldn't do it for blue (16 weeks)

HCV-TARGET: SVR12 Results by Subtype and Duration



Source: Lok A, et al. Gastroenterology;2019;157:1506-17.

Hepatitis C Online

Glecaprevir-Pibrentasvir for Retreatment in Patients with GT 1 HCV-TARGET: Conclusions

Conclusions: “In a randomized study of patients with chronic HCV genotype 1 infection who received previous treatment with sofosbuvir plus an NS5A inhibitor, 16 weeks treatment with G/P produced sustained virologic response 12 weeks after treatment in >90% of patients, including those with compensated cirrhosis.”

Source: Lok A, et al. Gastroenterology;2019;157:1506-17.

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HEPATITIS B ONLINE

HEPATITIS C ONLINE

IDEA INFECTIOUS DISEASES EDUCATION & ASSESSMENT

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