HEPATITIS WEB STUDY HEPATITIS C ONLINE

Glecaprevir-Pibrentasvir (*Mavyret*)

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Last Updated: October 25, 2017

Hepatitis web study

Glecaprevir-Pibrentasvir (*Mavyret*)

- **Approval Status**: Approval by United States FDA on August 3, 2017
- **Indications and Usage**
  - Treatment-naïve patients with HCV genotypes 1-6 in without cirrhosis and with compensated cirrhosis (Child-Pugh 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
- **Doseage 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*) Indications: Treatment-Naïve Patients

Glecaprevir-Pibrentasvir in HCV Treatment-Naïve Patients		
HCV Genotype	**Treatment Duration**	
	No Cirrhosis	**Compensated Cirrhosis (Child-Pugh Class A)**
Genotype 1	8 weeks	12 weeks
Genotype 2	8 weeks	12 weeks
Genotype 3	8 weeks	12 weeks
Genotype 4	8 weeks	12 weeks
Genotype 5	8 weeks	12 weeks
Genotype 6	8 weeks	12 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 (*Mavyret*)
Estimated Cost of Therapy

Estimated Cost of Glecaprevir-Pibrentasvir Treatments	
Duration of Treatment	Estimated Cost*
8 Weeks	$26,400
12 Weeks	$39,600
16 Weeks	$52,800
*Estimated cost based on Wholesaler Acquisition Cost in United States	

Source: Gilead Sciences

Treatment Naïve or Experienced

Glecaprevir-Pibrentasvir x 8 or 12 Weeks in GT1 Non-cirrhotics

ENDURANCE-1

Source: Zeuzem S, et al. AASLD 2016. Abstract 253.

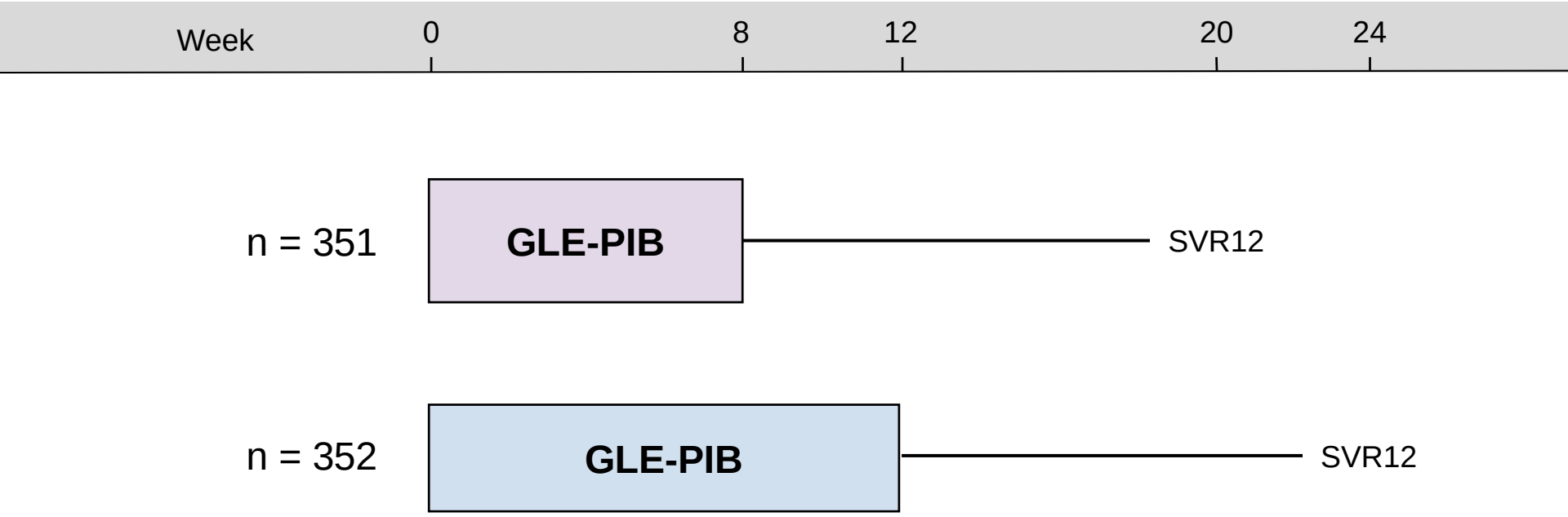
Glecaprevir-Pibrentasvir for 8 or 12 weeks in Non-Cirrhotic GT 1 ENDURANCE-1: Study Features

ENDURANCE-1 Trial

- **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 co-infection allowed; chronic HBV coinfection excluded
- **Primary End-Point**: SVR12

Source: Zeuzem S, et al. AASLD 2016. Abstract 253.

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

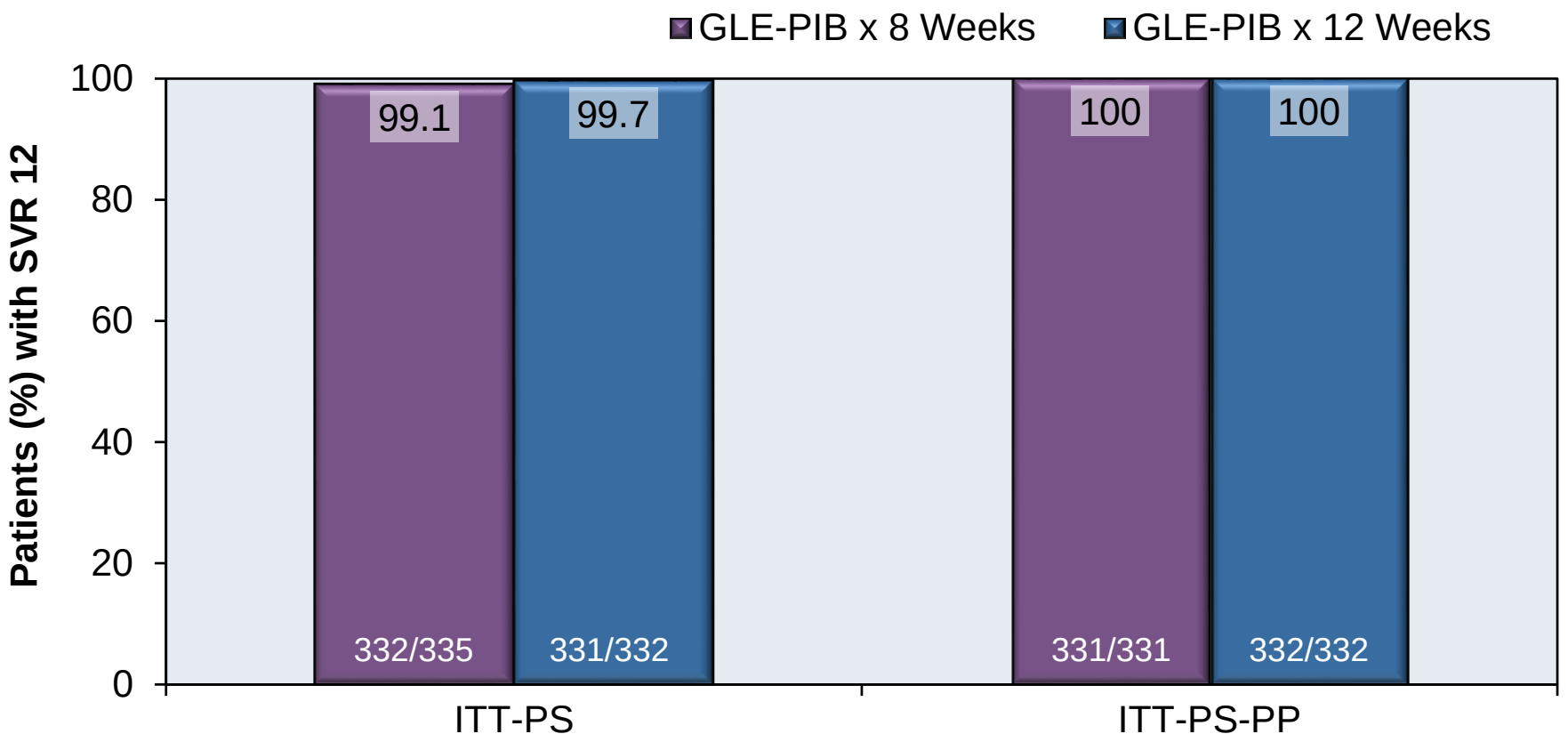
Source: Zeuzem S, et al. AASLD 2016. Abstract 253.

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

Baseline Characteristic	**GLE-PIB** 8 weeks (n = 351)	**GLE-PIB** 12 weeks (n = 352)
Age, mean (range), years	53 (19-84)	52 (21-77)
Male, n (%)	167 (48)	176 (50)
White, n (%)	289 (82)	302 (86)
HCV GT 1A subtype, n (%)	152 (43)	148 (42)
Body mass index, median kg/m^2 (range)	25 (18-41)	25 (18-54)
Median HCV RNA, $\log_{10}$ IU/mL (range)	6.11 (1.18-7.64)	6.14 (3.25-7.39)
IL28B non-CC, n (%)	249 (71)	266 (76)
Fibrosis Stage, n (%) F0-1 F2 F3	 297 (85) 22 (6) 30 (9)	 298 (85) 24 (7) 29 (8)

Source: Zeuzem S, et al. AASLD 2016. Abstract 253.

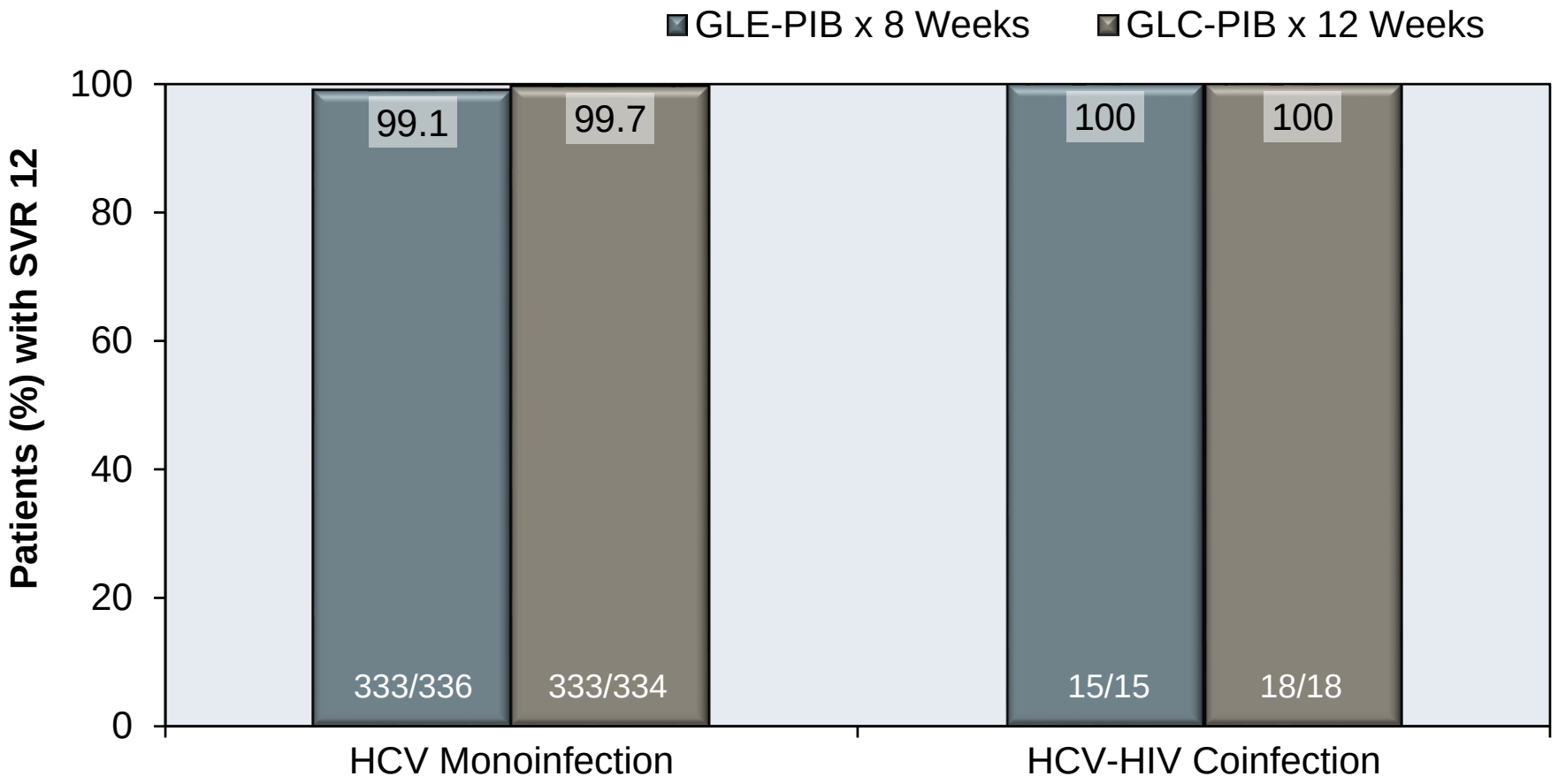
Glecaprevir-Pibrentasvir for 8 or 12 weeks in Non-Cirrhotic GT 1 ENDURANCE-1: Baseline Characteristics



ITT-PS population: ITT excluding patients with HIV coinfection or treatment experience with sofosbuvir
ITT-PS-per protocol (PP) population: ITT-PS excluding patients with premature discontinuation of study drug, virologic failure before Week 8, and missing SVR12 data

Source: Zeuzem S, et al. AASLD 2016.Abstract 253.

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



Source: Zeuzem S, et al. AASLD 2016. Abstract 253.

Treatment Naïve or Experienced

Glecaprevir-Pibrentasvir in Non-Cirrhotic Genotype 2 ENDURANCE-2

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2017 Sep 22. [Epub ahead of print]

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

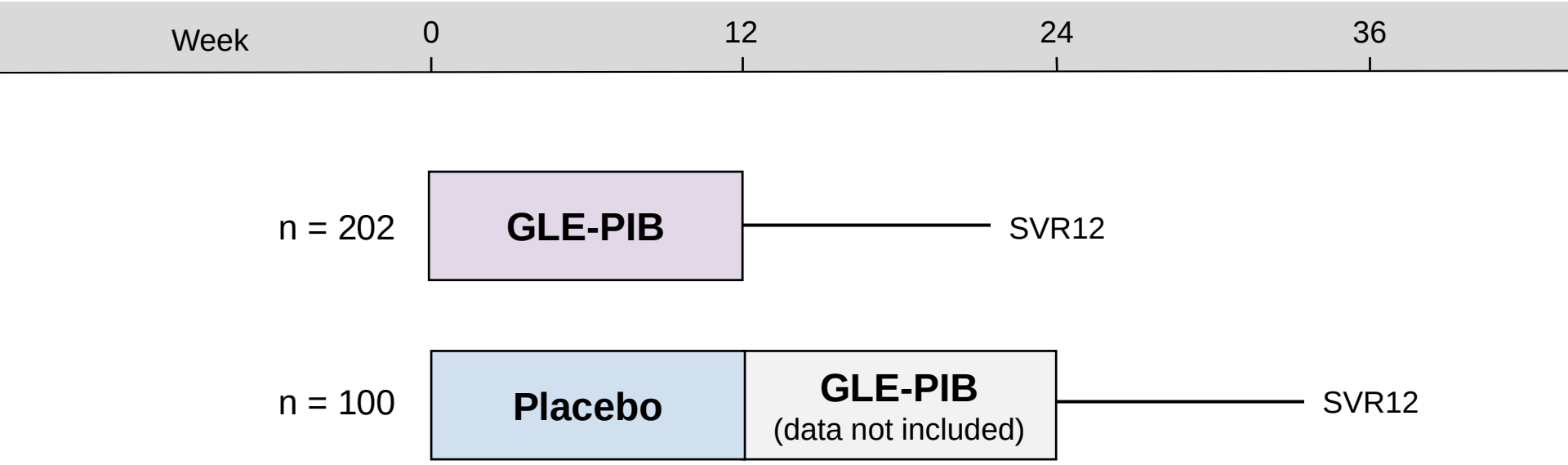
ENDURANCE-2 Trial

- **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 infection without cirrhosis.
- **Setting**: Multiple centers in US, 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

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

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2017 Sep 22. [Epub ahead of print]

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. 2017 Sep 22. [Epub ahead of print]

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. 2017 Sep 22. [Epub ahead of print]

Hepatitis web study

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	154 (76)	85 (85)
F2	18 (9)	9 (9)
F3	30 (15)	6 (6)
Treatment-naïve, n (%)	141 (70)	71 (71)
Treatment-experienced, n (%)	61 (30)	29 (29)
IFN or PEG ± RBV, n (%)	55 (27)	27 (27)
SOF + RBV ± PEG, n (%)	6 (3)	2 (2)
Concomitant PPI use, n (%)	22 (11)	11 (11)

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2017 Sep 22. [Epub ahead of print]

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

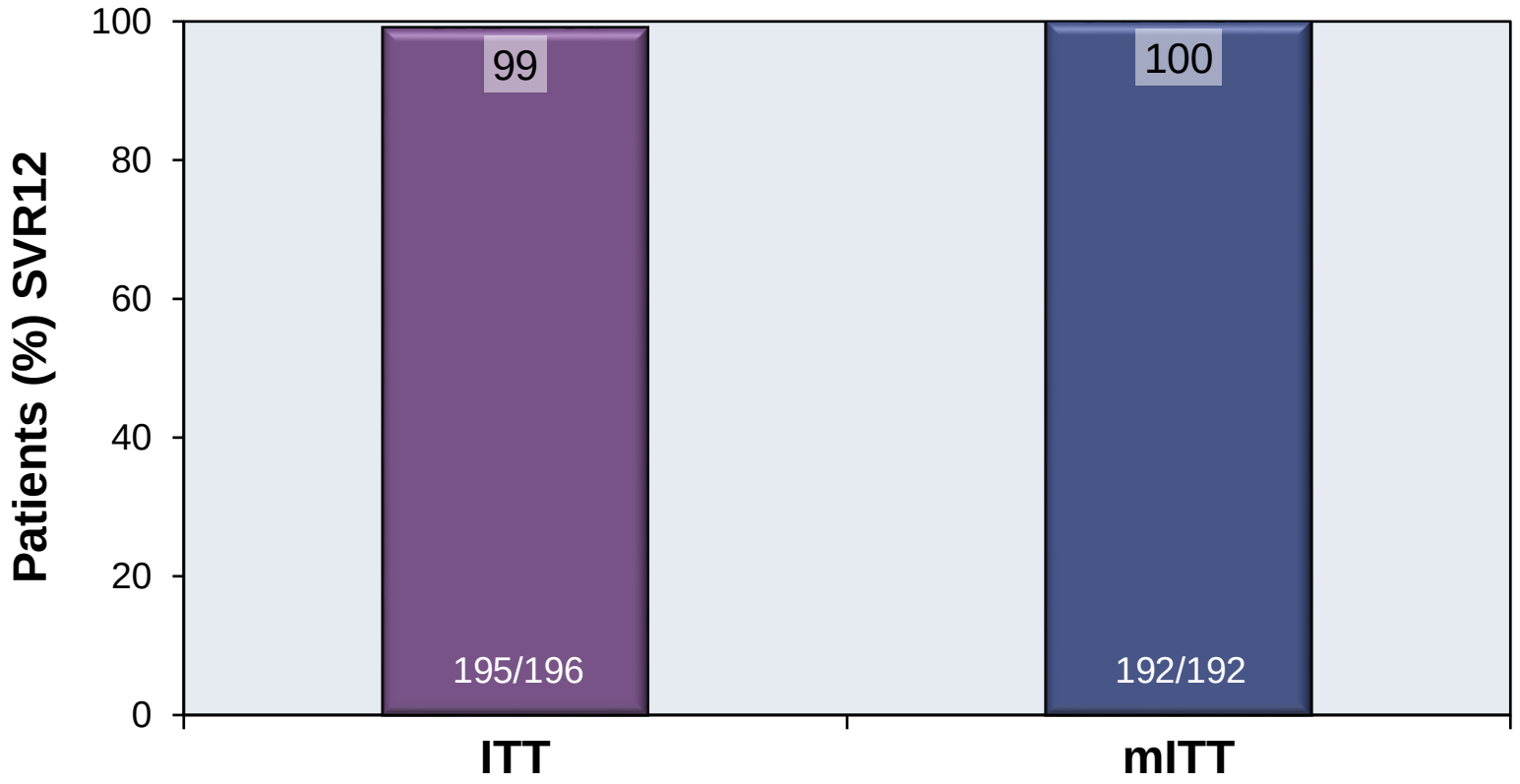
Prevalence of Baseline Polymorphism*, n (%)*	Genotype 2 (n = 160)
None	28 (18)
NS3 only	0
NS5A only	132 (83)
Both NS3 + NS5A	0

*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: 155, 156, 168
- NS5A: 24, 28, 30, 31, 58, 92, 93

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2017 Sep 22. [Epub ahead of print]

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: xcludes patients with non-virologic failure and those with ineligible genotype

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2017 Sep 22. [Epub ahead of print]

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 AEs[§]	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

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit normal

[§] 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.

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2017 Sep 22. [Epub ahead of print]

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. 2017 Sep 22. [Epub ahead of print]

Treatment-Naïve

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

Source: Foster G, et al. EASL 2017. Abstract GS-007.

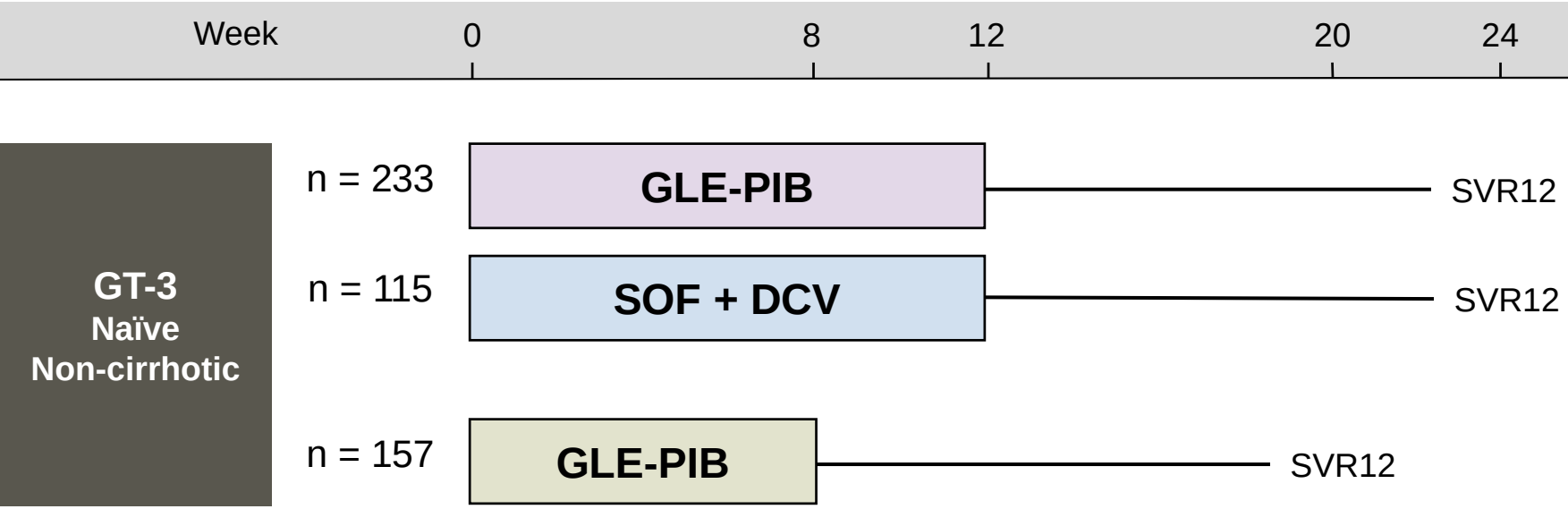
Glecaprevir-Pibrentasvir in Treatment-Naïve, Non-Cirrhotic GT 3
ENDURANCE-3: Study Features

ENDURANCE-3 Trial

- **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: Foster G, et al. EASL 2017. Abstract GS-007.

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
Sofosbuvir 400 mg once daily plus Daclatasvir 60 mg once daily

Source: Foster G, et al. EASL 2017. Abstract GS-007.

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

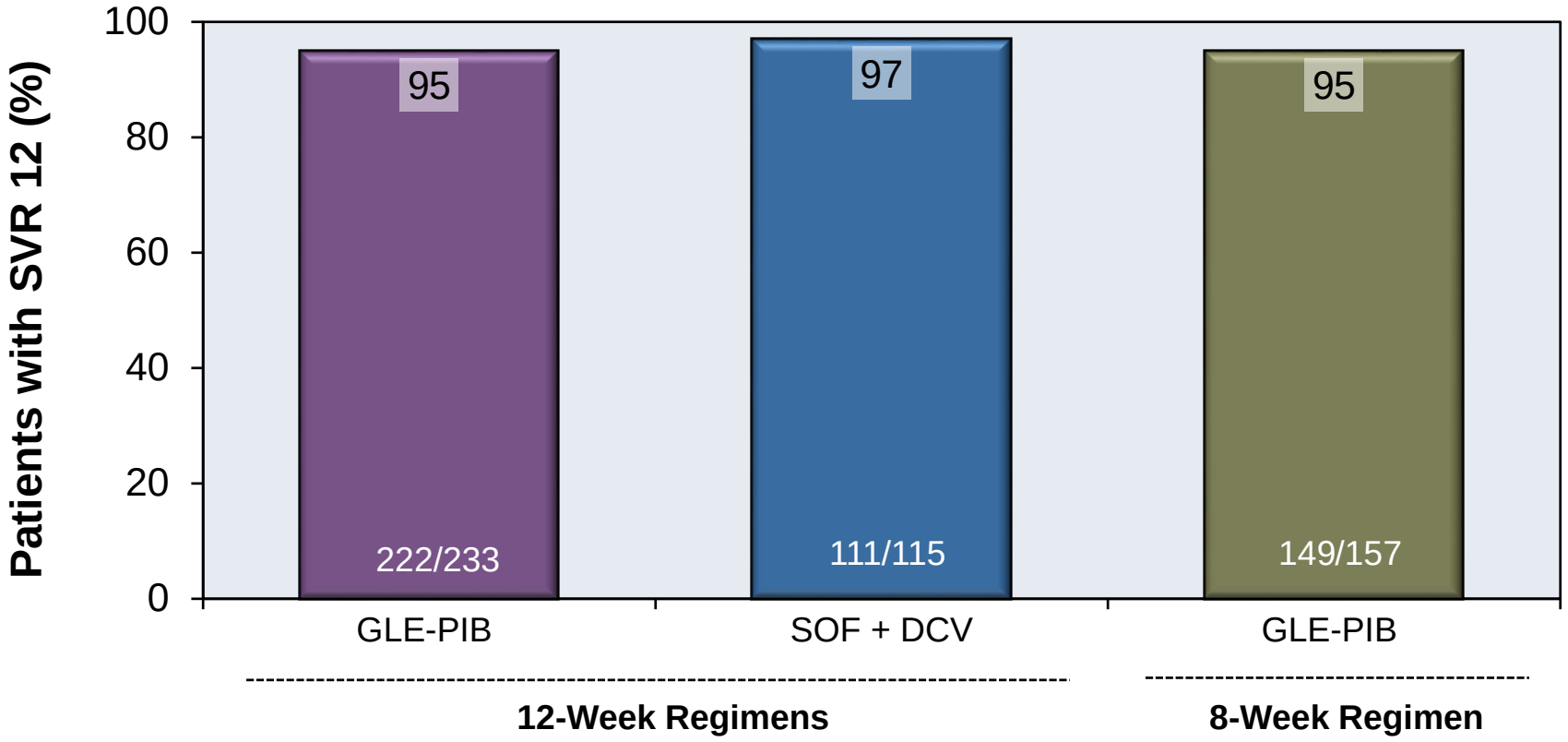
Characteristics	2:1 randomization		Non-randomized
	GLE-PIB 12 wk n = 233	SOF + DCV 12 wk n = 115	GLE-PIB 8 wk n = 157
Age, median years (range)	48 (22-71)	49 (20-70)	47 (20-76)
Male sex, n (%)	121 (52)	52 (45)	92 (59)
White race, n (%)	205 (88)	103 (90)	134 (85)
History of injection drug use, n (%)	149 (64)	73 (63)	104 (66)
BMI, median kg/m^2 (range)	25 (17-49)	25 (18-42)	26 (18-44)
HCV RNA, median $\log_{10}$ IU/ml (range)	6.1 (3.5-7.5)	6.0 (3.8-7.4)	6.1 (1.2-7.6)
Fibrosis stage, n (%) F0-1 F2 F3	 201 (86) 12 (5) 20 (9)	 97 (84) 8 (7) 10 (9)	 122 (78) 8 (5) 27 (17)
HCV subtype 3A, n/N (%)	226/229 (99)	113/113 (100)	154/155 (99)

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

Source: Foster G, et al. EASL 2017. Abstract GS-007.

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

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



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

Source: Foster G, et al. EASL 2017. Abstract GS-007.

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

Outcomes, n (%)	2:1 randomization		Non-randomized
	GLE-PIB 12 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)

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

Source: Foster G, et al. EASL 2017. Abstract GS-007.

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 12 wk	SOF + DCV 12 wk	GLE-PIB 8 wk
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: 36, 55, 56, 80, 155, 156, 166, 168; NS5A at 24, 28, 29, 30, 31, 32, 58, 92, 93

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

Source: Foster G, et al. EASL 2017. Abstract GS-007.

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

Adverse Event (AE), n (%)	Randomized		Non-randomized
	GLE-PIB 12 wk n=233	SOF + DCV 12 wk n=115	GLE-PIB 8 wk n=157
Any AE	177 (76)	80 (70)	98 (62)
AE possibly drug-related	112 (48)	50 (43)	63 (40)
Serious AE	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 (>5 x ULN)	0	1 (1)	0
Grade ≥3 total bilirubin (>3 x ULN)	0	0	1 (1)
Grade ≥3 neutrophil count (< 1 x 10^9/L)	1 (<1)	0	0

Source: Foster G, et al. EASL 2017. Abstract GS-007.

Treatment-Naïve and Treatment-Experienced

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

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2017 Sep 22. [Epub ahead of print]

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

ENDURANCE-4 Trial

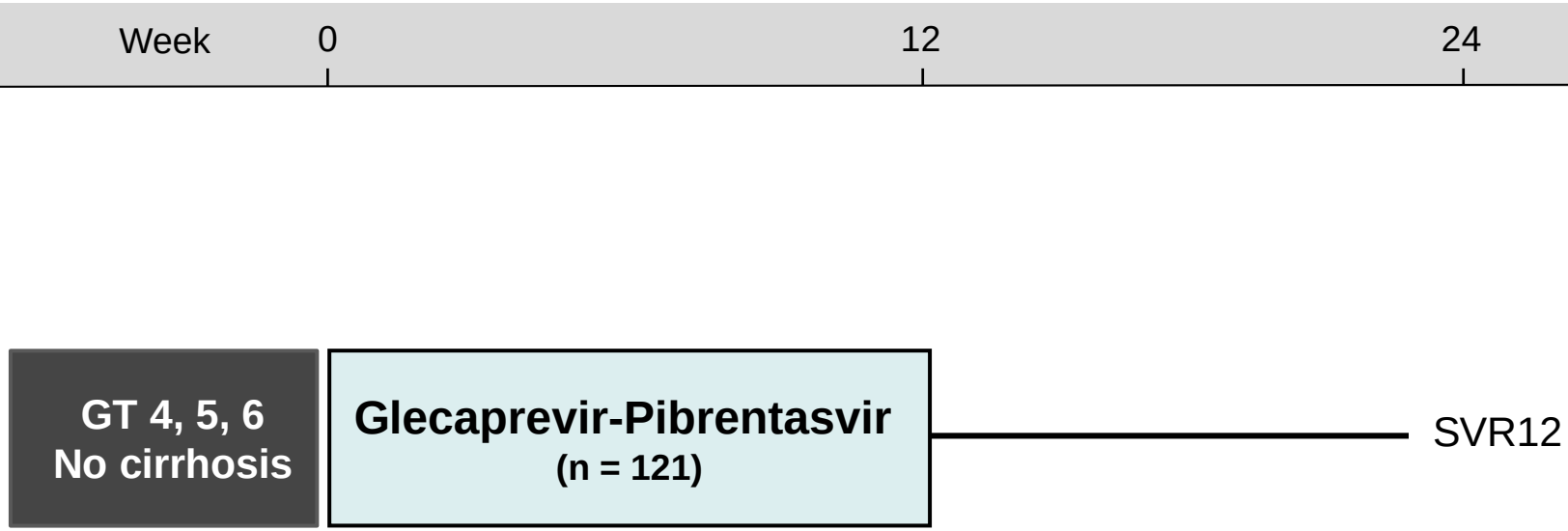
- **Design**: Open-label single-arm phase 3 trial to evaluate the safety and efficacy of the fixed-dose combination of glecaprevir-pibrentasvir for 12 weeks in treatment-naïve and treatment-experienced adults with GT 4, 5 or 6 chronic HCV infection without cirrhosis
- **Setting:** Canada, Europe and 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. 2017 Sep 22. [Epub ahead of print]

Hepatitis web study

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. 2017 Sep 22. [Epub ahead of print]

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 Black Asian	 84 (71) 10 (8) 24 (20)
BMI, mean, ± SD kg/m^2	25.7 ± 4.8
IL28B genotype non-CC, n (%)	91 (75)
HCV Genotype, n (%) 4 5 6	 76 (63) 26 (21) 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. 2017 Sep 22. [Epub ahead of print]

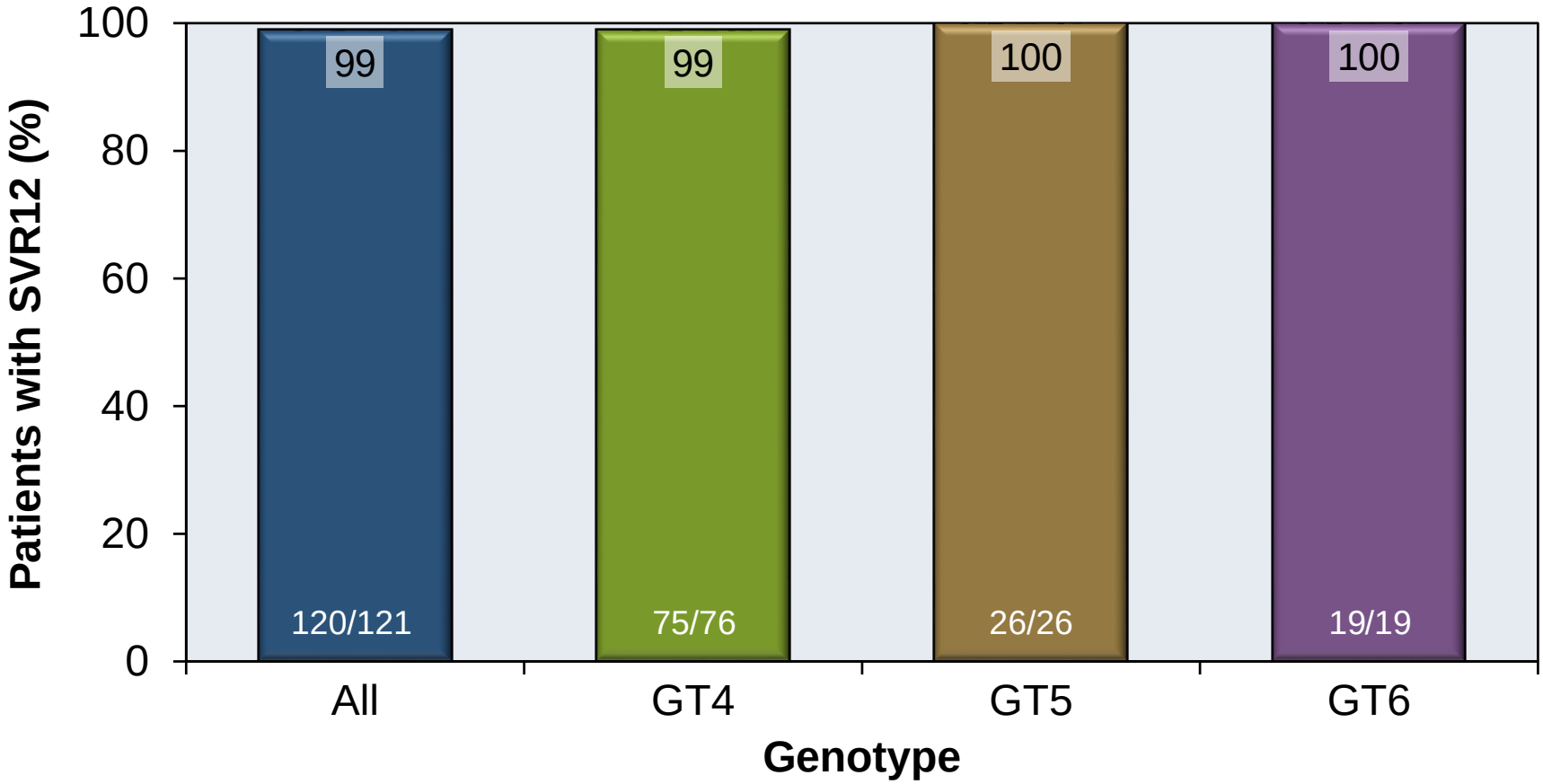
Glecaprevir-Pibrentasvir in Non-Cirrhotic Genotype 4, 5, or 6
ENDURANCE-4: Baseline Characteristics

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

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2017 Sep 22. [Epub ahead of print]

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

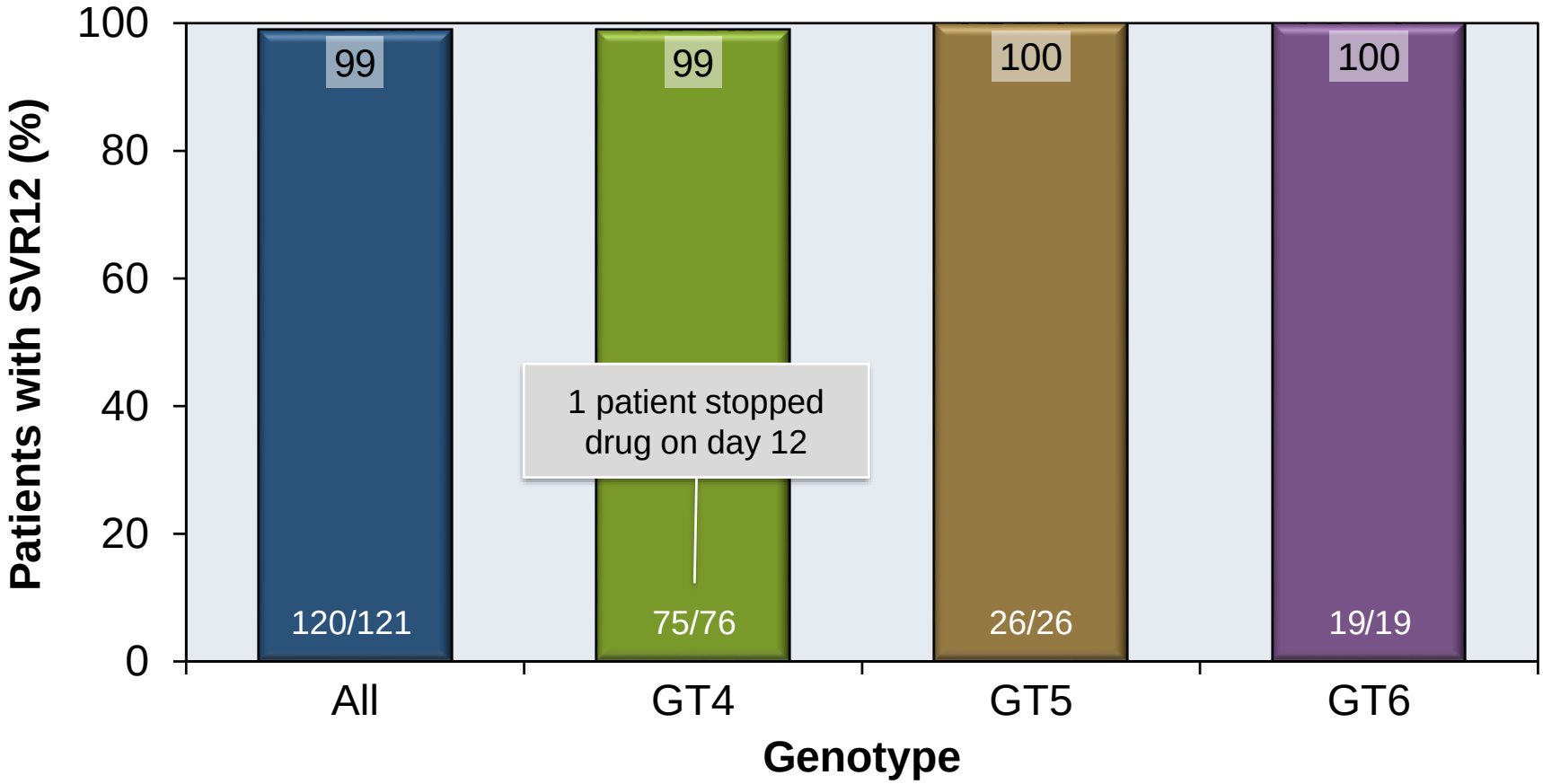
SVR12 (ITT analysis), Overall and by Genotype



Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2017 Sep 22. [Epub ahead of print]

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

SVR12 (ITT analysis), Overall and by Genotype



Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2017 Sep 22. [Epub ahead of print]

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 (>3 x ULN)	0
ALT grade ≥2 (>3 x ULN)	0
Total bilirubin grade ≥3 (>3 x 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. 2017 Sep 22. [Epub ahead of print]

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. 2017 Sep 22. [Epub ahead of print]

Treatment-Naïve and Treatment-Experienced

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.

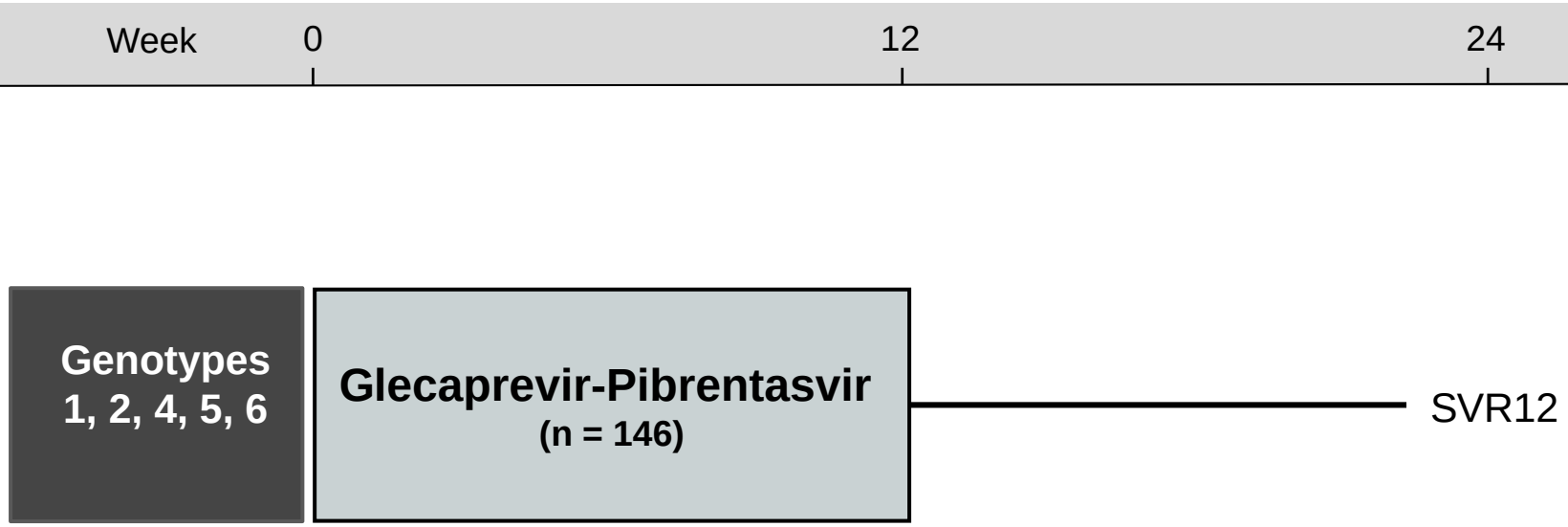
Glecaprevir-Pibrentasvir in Cirrhotic Genotype 1, 2, 4, 5, and 6 EXPEDITION-1: Study Features

EXPEDITION-1 Trial

- **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.

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 (%) 1b, n (%) 2, n (%) 4 / 5 / 6, n (%)	 48 (33) 39 (27) 34 (23) 16 (11) / 2 (1) / 7 (5)
Treatment experienced, n (%) Interferon-based, n/N (%) Sofosbuvir-based, n/N (%)	36 (25) 25/36 (69) 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.

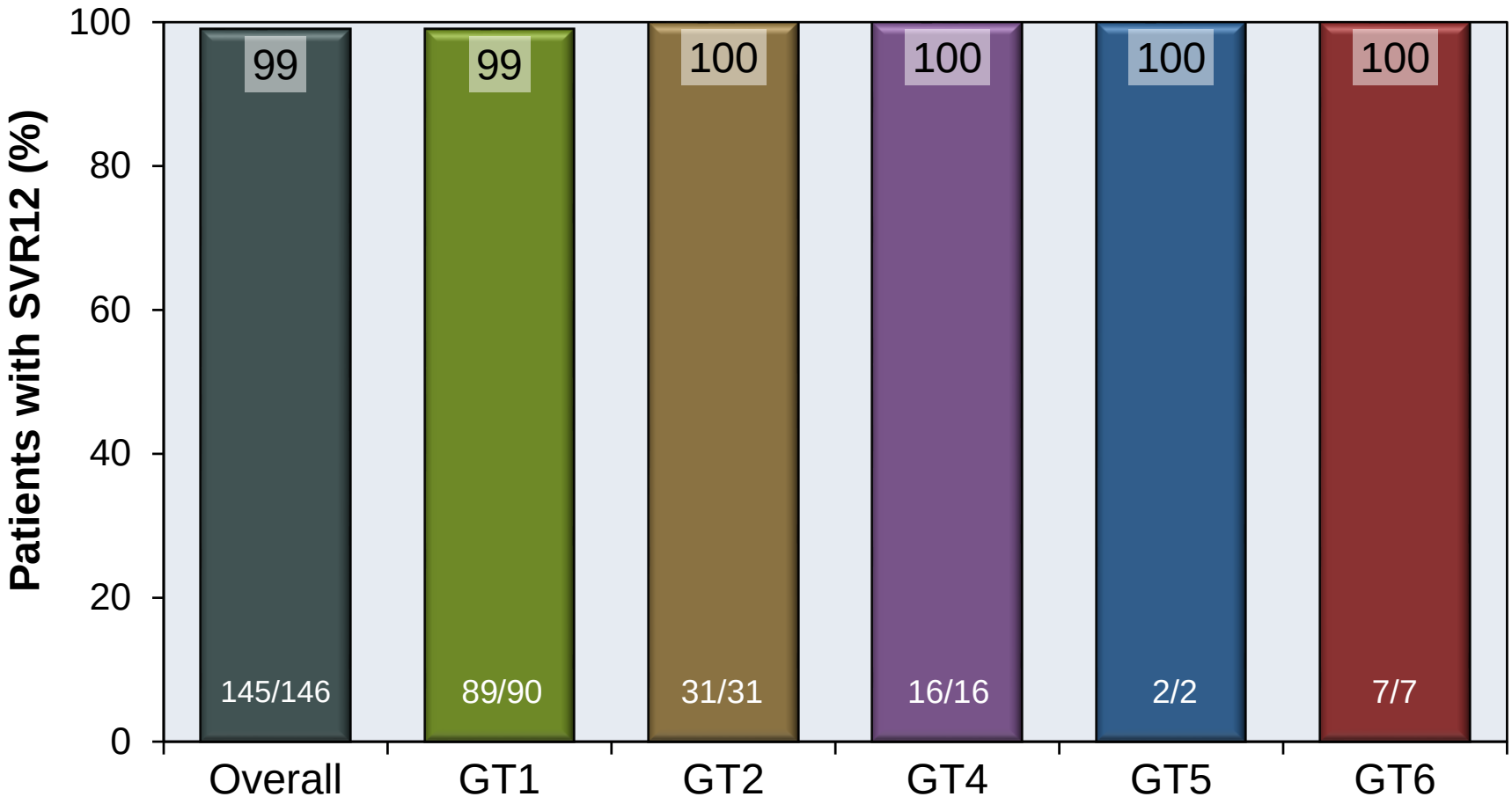
Glecaprevir-Pibrentasvir in Cirrhotic Genotype 1, 2, 4, 5, and 6
EXPEDITION-1: Baseline Characteristics

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 positions 155, 156, 168
- NS5 positions 24, 28, 30, 31, 58, 92, 93

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: 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.

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.

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.

Treatment-Naïve and Treatment-Experienced

Glecaprevir-Pibrentasvir in Patients with HIV-HCV Coinfection
EXPEDITION-2

Source: Rockstroh J, et al. IAS 2017. Abstract 918.

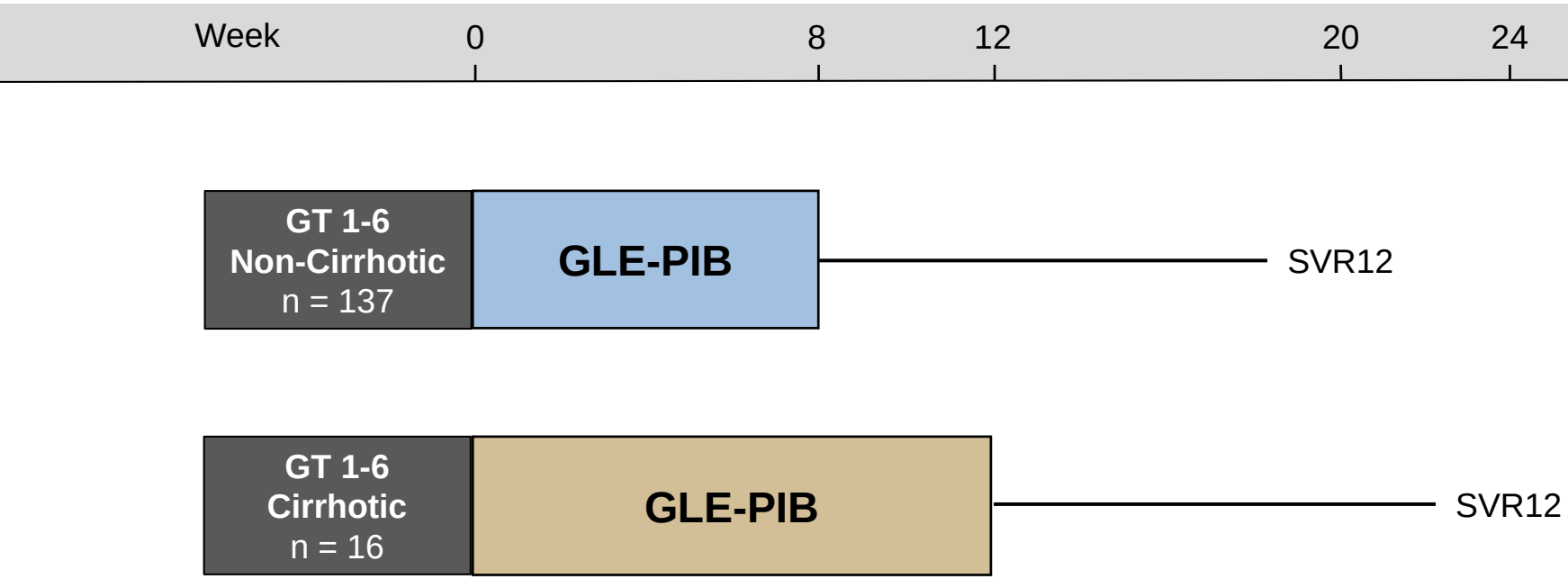
Glecaprevir-Pibrentasvir in HIV-HCV Coinfected Patients
EXPEDITION-2: Study Features

EXPEDITION-2 Trial

- **Design**: Open-label two-arm phase 3 trial to evaluate the safety and efficacy of the fixed-dose combination of glecaprevir-pibrentasvir for 8 or 12 weeks in HIV-HCV coinfected patients without or with compensated cirrhosis, respectively
- **Setting:** Australia, Europe, Russian Federation, UK, US
- **Key Eligibility Criteria**
  - 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 J, et al. IAS 2017. Abstract 918.

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 J, et al. IAS 2017. Abstract 918.

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

Baseline Characteristic	**GLE-PIB** 8 weeks (N=137)	**GLE-PIB** 12 weeks (N=16)
Age, mean (range), years	45 (23-74)	50 (35-62)
Male, n (%)	113 (83)	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 (%) F0-2 F3 F4	 122 (89) 15 (11) 0	 0 0 16 (100)

Source: Rockstroh J, et al. IAS 2017. Abstract 918.

Hepatitis web study

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

Baseline Characteristic	**GLE-PIB** 8 weeks (n = 137)	**GLE-PIB** 12 weeks (n = 16)
Treatment-experienced, n (%) IFN-based, n/N (%) SOF-based, n/N (%)	26 (19) 23 (17) 3 (2)	2 (13) 2 (13) 0
IDU within 12 months, n (%) On opiate substitution therapy, n (%)	12 (9) 11 (8)	1 (6) 2 (13)
N(t)RTI backbone, n (%) Tenofovir disoproxil fumarate Tenofovir alafenamide Abacavir	 74 (54) 6 (4) 49 (36)	 13 (81) 0 3 (19)
ART anchor agent, n (%) Raltegravir Dolutegravir Rilpivirine Elvitegravir/cobicistat	 39 (29) 62 (45) 27 (20) 1 (<1)	 6 (38) 5 (31) 5 (31) 0
ART naïve, n (%)	9 (7)	0
CD4 cell count, median (range), cells/mm^3	588 (154-2103)	545 (222-1806)

Source: Rockstroh J, et al. IAS 2017. Abstract 918.

Hepatitis web study

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

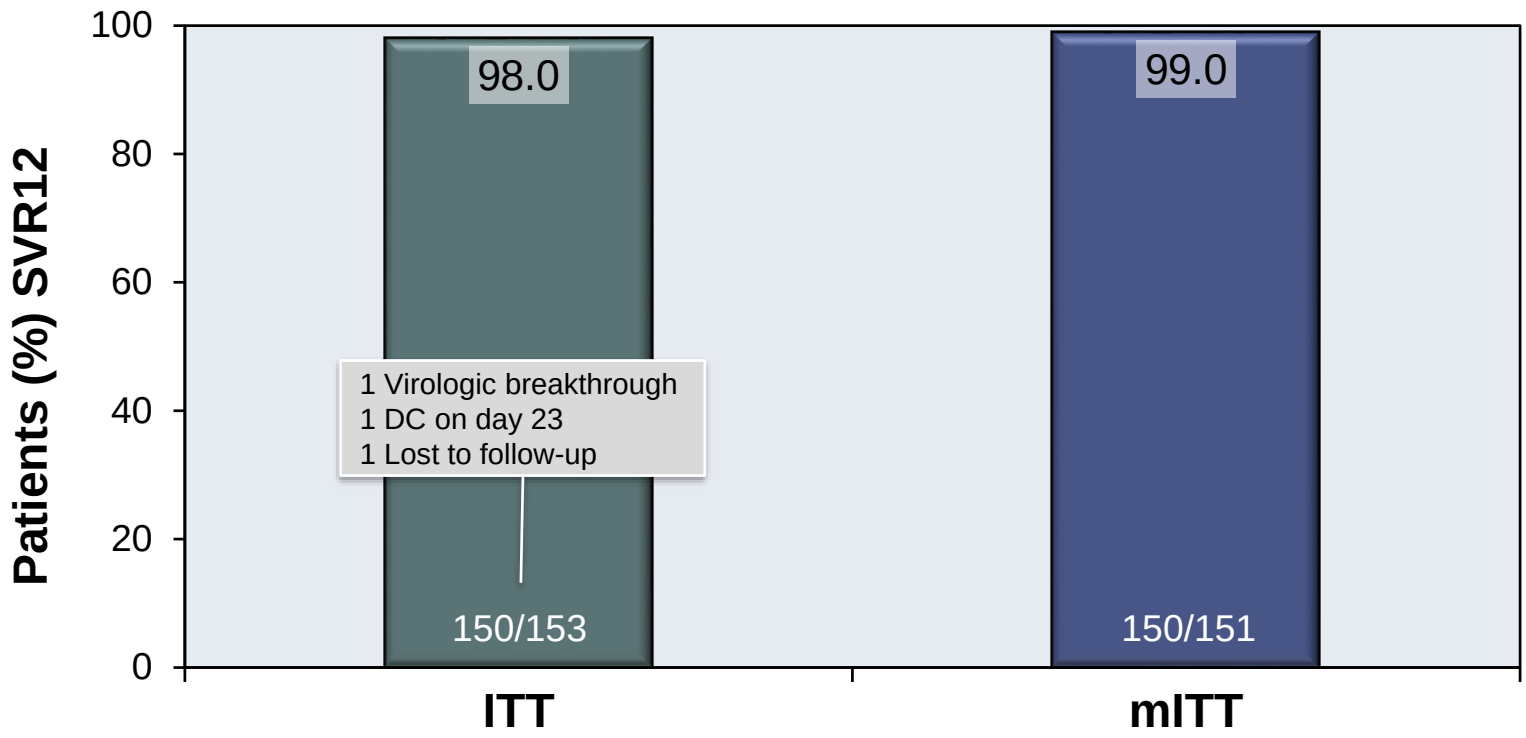
Baseline Polymorphisms*	**GLE-PIB** 8 weeks (n = 130)	**GLE-PIB** 12 weeks (n =16)
None, n (%)	92 (71)	9 (56)
NS3 only, n (%)	1 (<1)	1 (6)
NS5A only, n (%)	36 (28)	6 (38)
Both NS3 + NS5A, n (%)	1 (<1)	0

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

Source: Rockstroh J, et al. IAS 2017. Abstract 918.

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

EXPEDITION-2: Overall SVR by Analysis



ITT = Intent-to-treat; mITT = modified intent-to-treat
One GT3 patient with cirrhosis and 85% compliance had on-treatment virologic failure

Source: Rockstroh J, et al. IAS 2017. Abstract 918.

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

Adverse Event (AE), n (%)	8 weeks (n=137)	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		
AST elevation, grade 3-4 (>5x ULN)	0	0
ALT elevation, grade 3-4 (>5x ULN)	0	0
Total bilirubin, grade 3 (3-10x ULN)	1 (0.7)[#]	0
Failure to maintain HIV suppression	0	0

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit normal
[§] 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.
[#] Grade 3 bilirubin elevation on day 10-31, normalized by day 59 without drug interruption.

Source: Rockstroh J, et al. IAS 2017. Abstract 918.

Treatment-Naïve and Treatment-Experienced

Renal Disease

Glecaprevir-Pibrentasvir in GT 1-6 with Renal Disease
EXPEDITION-4

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

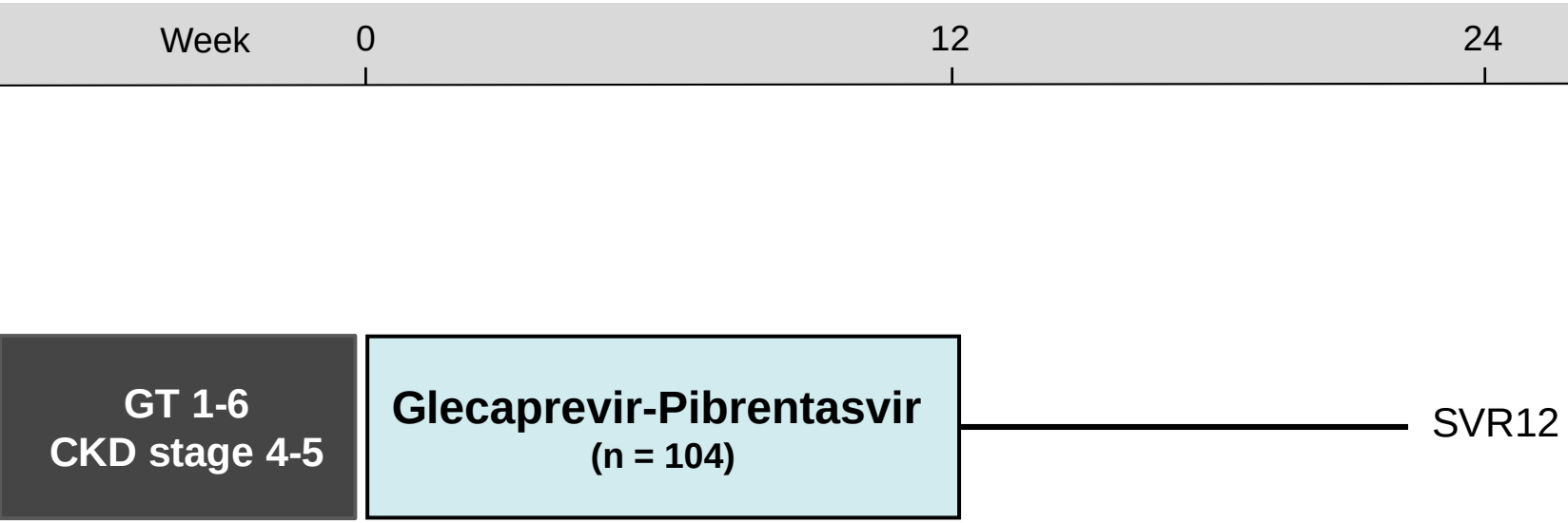
Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease
EXPEDITION-4: Study Features

EXPEDITION-4 Trial

- **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/1.73m^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: Study Design



Abbreviations: CKD = chronic kidney disease
Drug Dosing: Glecaprevir-pibrentasvir (100/40 mg) fixed dose combination; three pills once 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)
Age, mean (range), years	57 (28-83)
Male, n (%)	79 (76)
Race, n (%)	
White	64 (62)
Black	25 (24)
Asian	9 (9)
Other	6 (6)
Median BMI kg/m^2, n (%)	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)
IFN/PEG ± RBV	42 (40)
SOF and RBV ± PEG	2 (2)

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

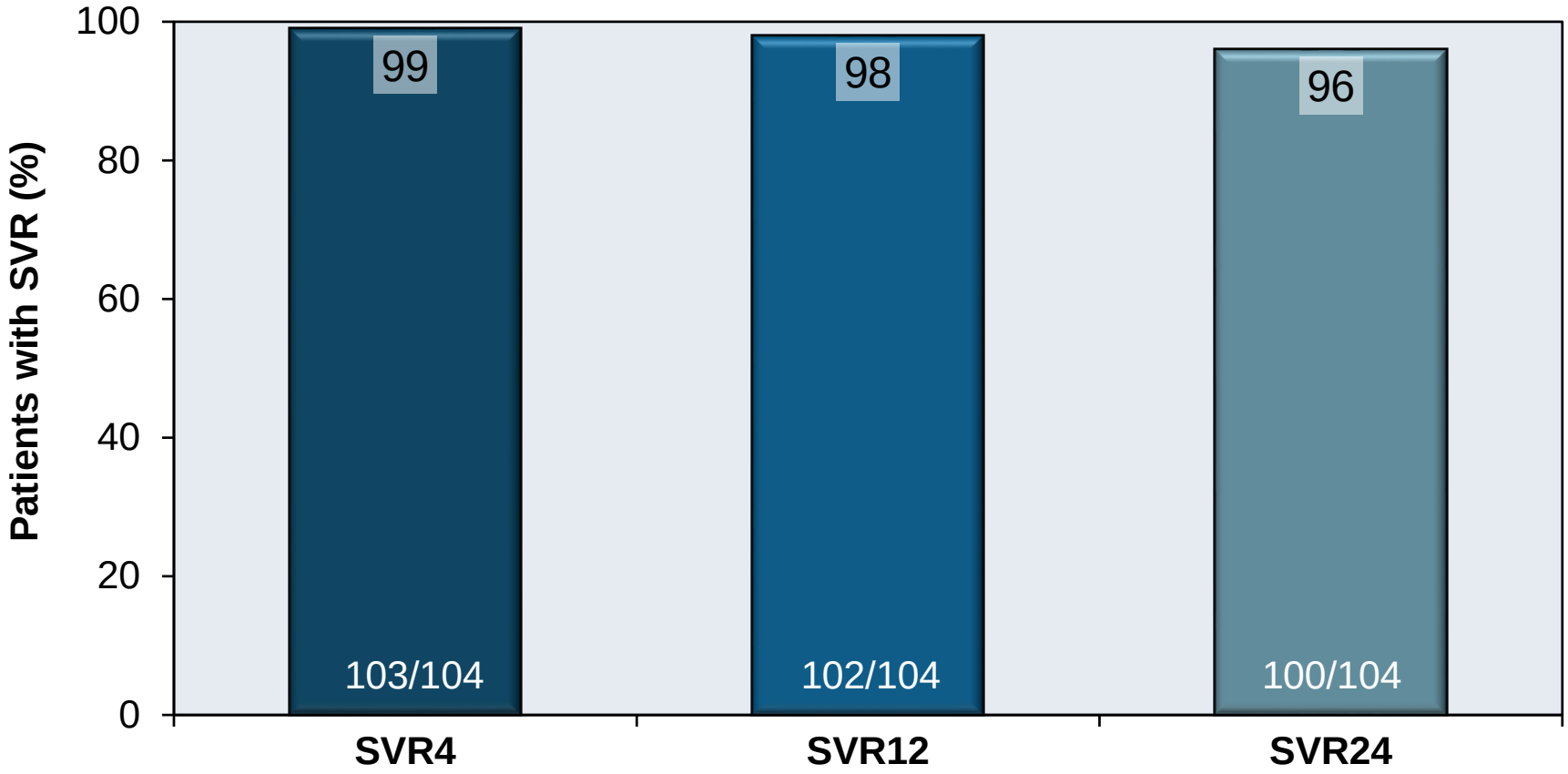
Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease EXPEDITION-4: Baseline Characteristics

Baseline Characteristic	Glecaprevir-Pibrentasvir (n = 104)
IL28B non-CC genotype, n (%)	80 (77)
Concomitant PPI use, n (%)	43 (41)
eGFR in patients not undergoing hemodialysis, ml/min/1.73 m2	20.6 ± 8.0
CKD stage, n (%) Stage 4 Stage 5	 13 (12) 91 (88)
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)

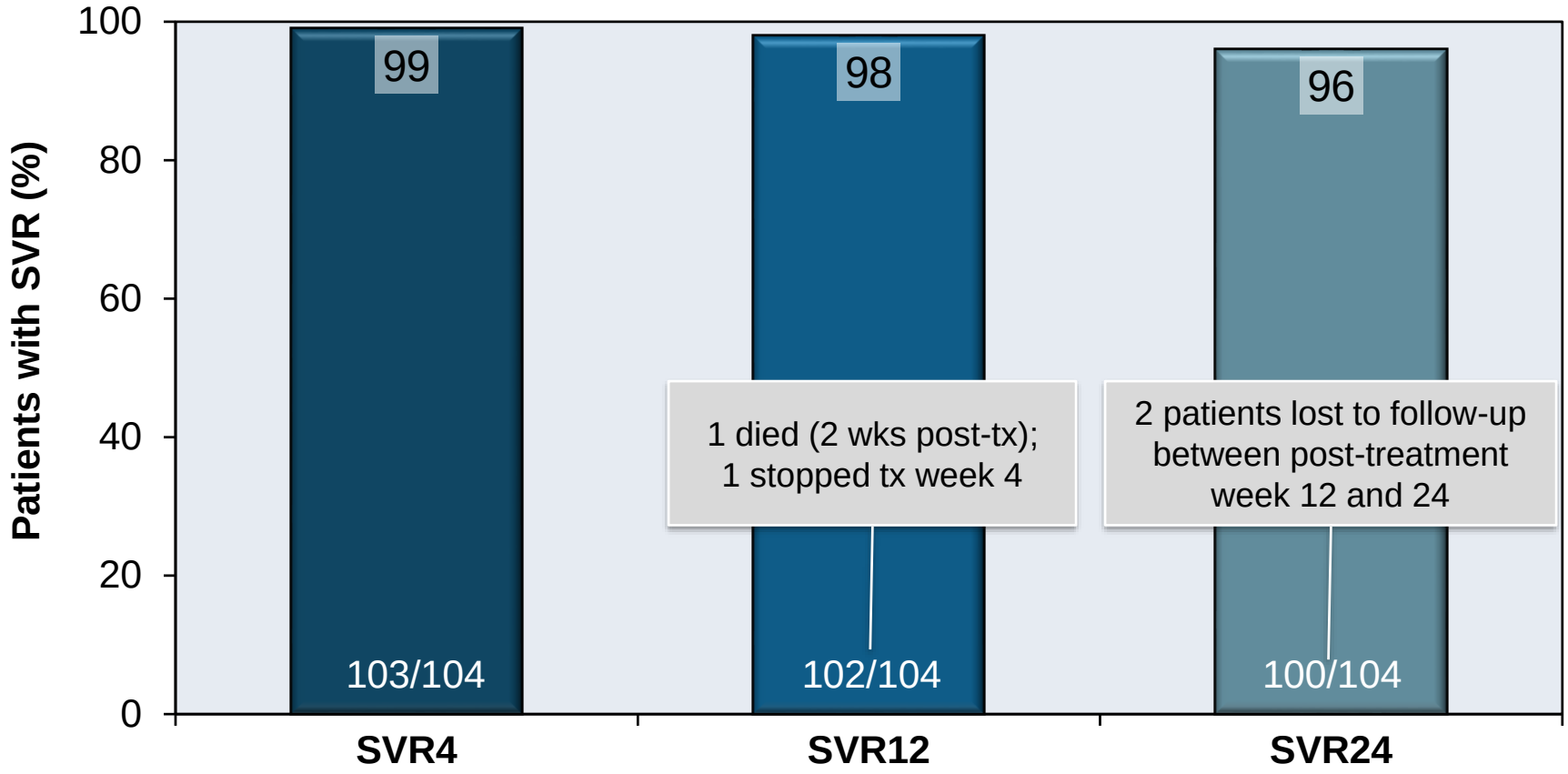


ITT, intent-to-treat analysis; mITT, modified intent-to-treat analysis

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)



ITT, intent-to-treat analysis; mITT, modified intent-to-treat analysis

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

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 >3 x 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: Adverse Events Conclusions

Conclusions: “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.

Treatment-Experienced

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

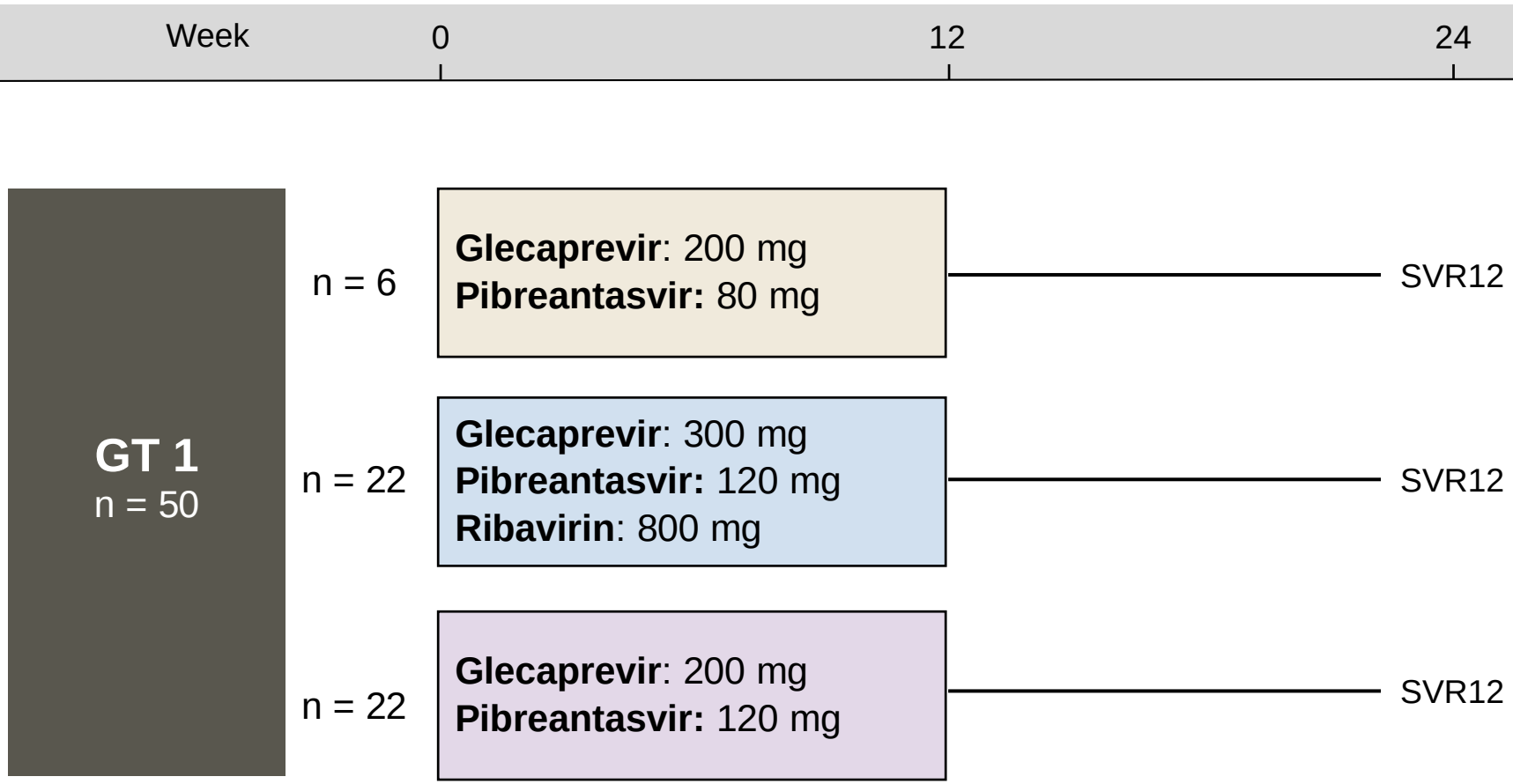
MAGELLAN-1 Trial

- **Design**: Randomized, open-label, multicenter, phase 2 trial to evaluate the safety and efficacy of the glecaprevir plus pibrentasvir, with or without ribavirin, for 12 weeks in patients with GT 1 chronic HCV (without cirrhosis) who previously experienced virologic failure with direct-acting antiviral (DAA) therapy.
- **Setting**: Multiple centers in United States
- **Key Eligibility Criteria**
  - Chronic HCV GT 1
  - Age 18-70
  - Prior treatment failure with DAA regimen
  - Patients with 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): Study Design



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

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 (%) F0-1 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: Foster G, et al. EASL 2017, Abstract GS-007.

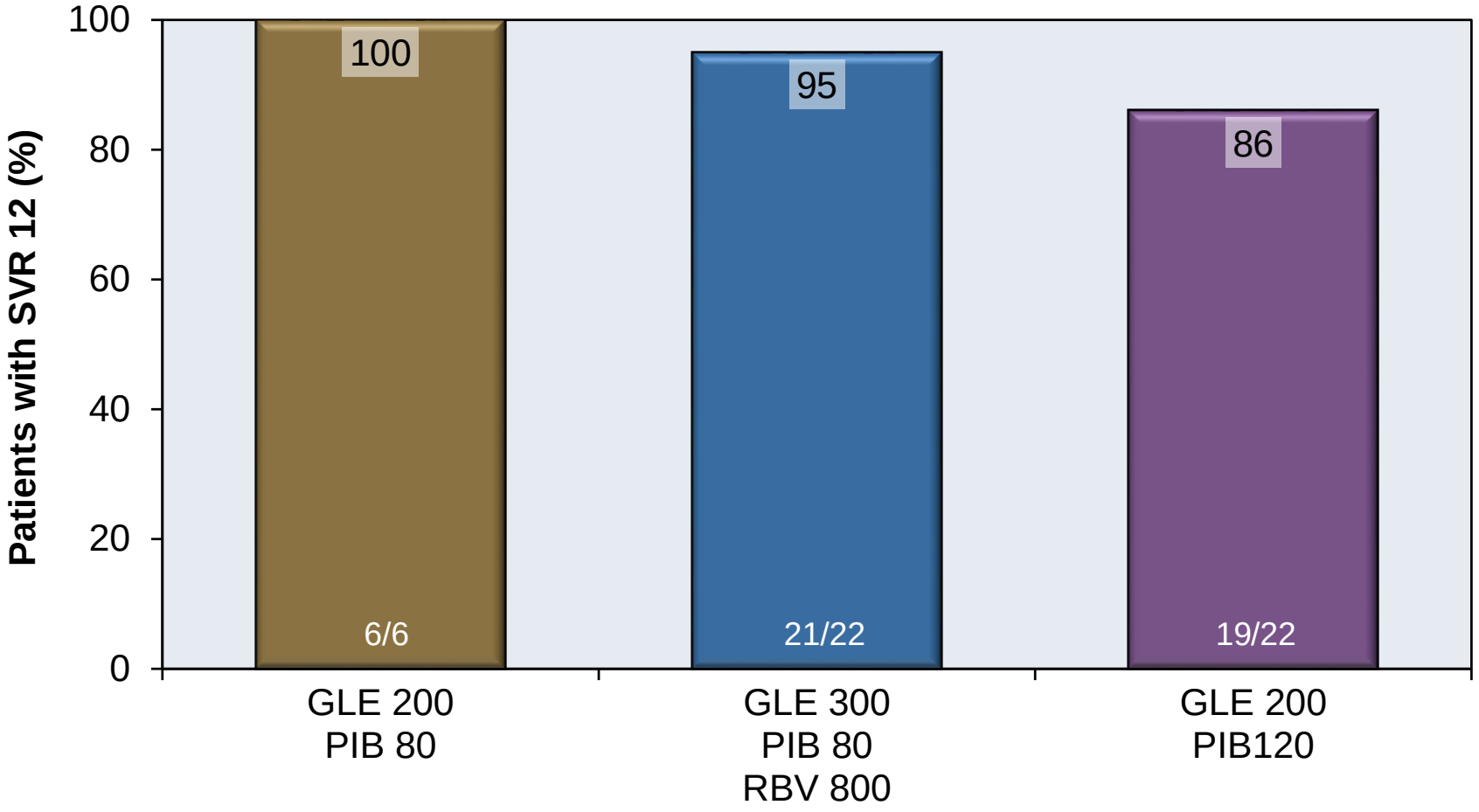
Glecaprevir-Pibrentasvir in HCV GT 1 & Prior DAA Treatment
MAGELLAN-1 (Part 1): Baseline Characteristics

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	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: Foster G, et al. EASL 2017, Abstract GS-007.

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



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

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

Conclusion: “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.

Treatment-Naïve and Treatment-Experienced

Glecaprevir and Pibrentasvir in HCV GT 1-6 without Cirrhosis

SURVEYOR-I and SURVEYOR-II

Source: Kwo PY, et al. J Hepatol 2017;67:263-71.

Glecaprevir and Pibrentasvir in HCV GT 1-6 without Cirrhosis
SURVEYOR-I and SURVEYOR-II: Study Features

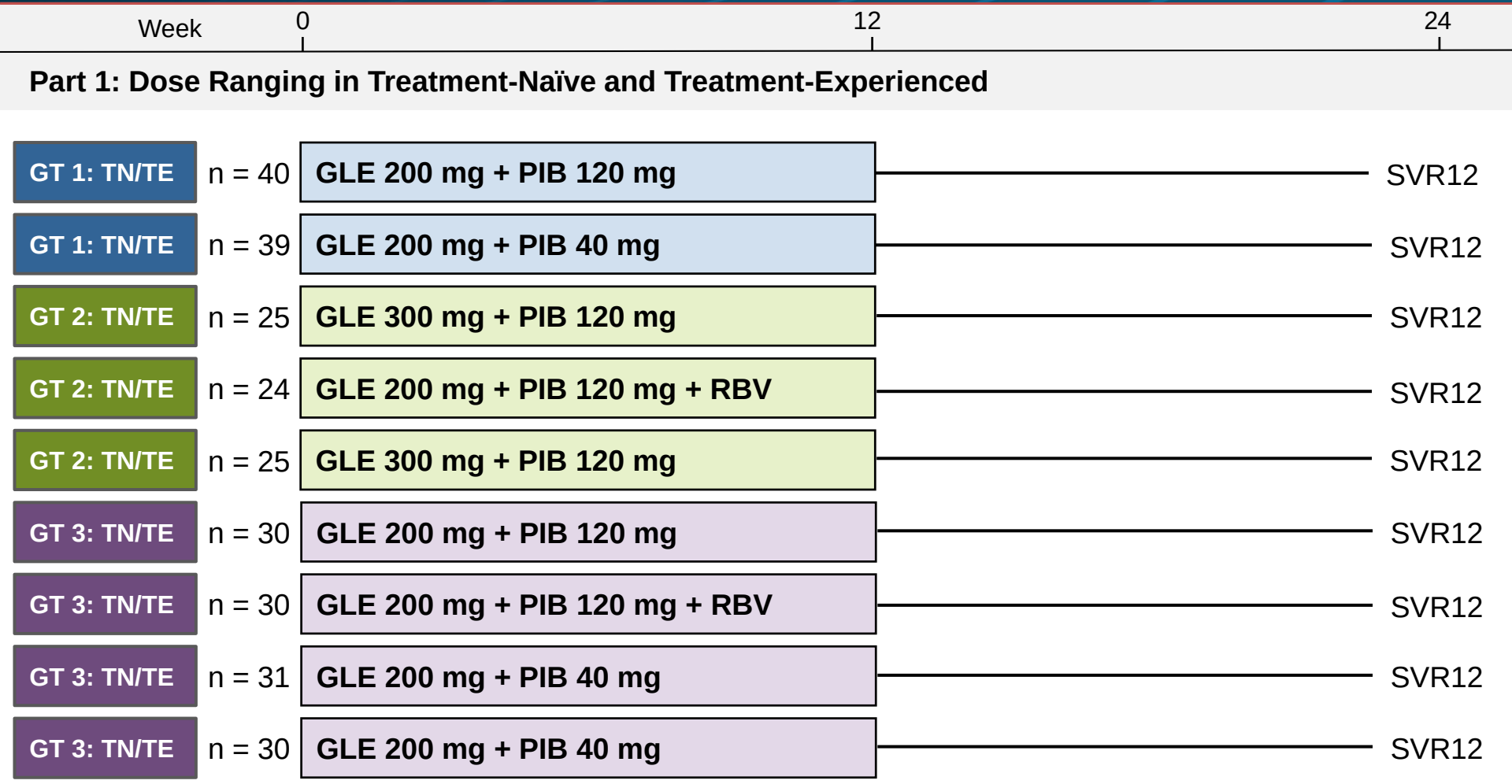
SURVEYOR-I and SURVEYOR-II

- **Design**: Open-label single-arm phase 2, multicenter trial to evaluate the safety and efficacy of various doses of glecaprevir and pibrentasvir, with or without ribavirin, for 8 or 12 weeks in treatment-naïve and treatment-experienced, non-cirrrhotic patients with chronic HCV GT 1, 2, 3, 4, 5, or 6
- **Setting**: 80 sites in U.S., Canada, Europe, Australia, and New Zealand
- **Key Eligibility Criteria**
  - SURVEYOR I = Chronic HCV GT 1, 4, 5, or 6
  - SURVEYOR 2 = Chronic HCV GT 2 or 3
  - Age 18-70
  - HCV RNA >10,000 IU/mL at screening
  - Naïve or treated with peginterferon plus ribavirin
  - Absence of cirrhosis
- **Primary End-Point**: SVR12

Source: Kwo PY, et al. J Hepatol 2017;67:263-71.

Glecaprevir and Pibrentasvir in HCV GT 1-6 without Cirrhosis

SURVEYOR-I and SURVEYOR-II: Study Design (Part 1)

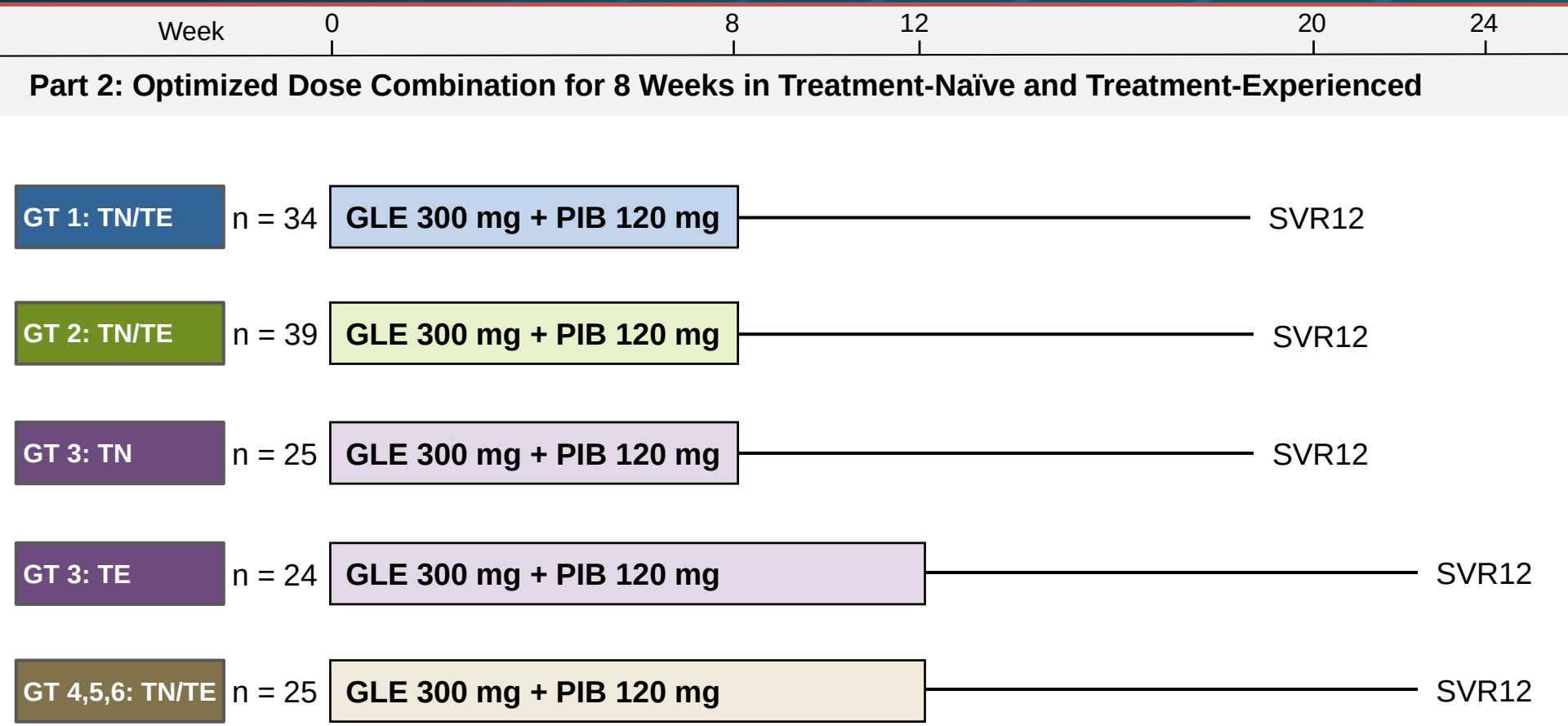


Abbreviations: TN = Treatment Naïve; TE = Treatment Experienced; GLE = glecaprevir; PIB = pibrentasvir; RBV = ribavirin

Source: Kwo PY, et al. J Hepatol 2017;67:263-71.

Glecaprevir and Pibrentasvir in HCV GT 1-6 without Cirrhosis

SURVEYOR-I and SURVEYOR-II: Study Design (Part 2)



Abbreviations: TN = Treatment Naïve; TE = Treatment Experienced; GLE = glecaprevir; PIB = pibrentasvir

Source: Kwo PY, et al. J Hepatol 2017;67:263-71.

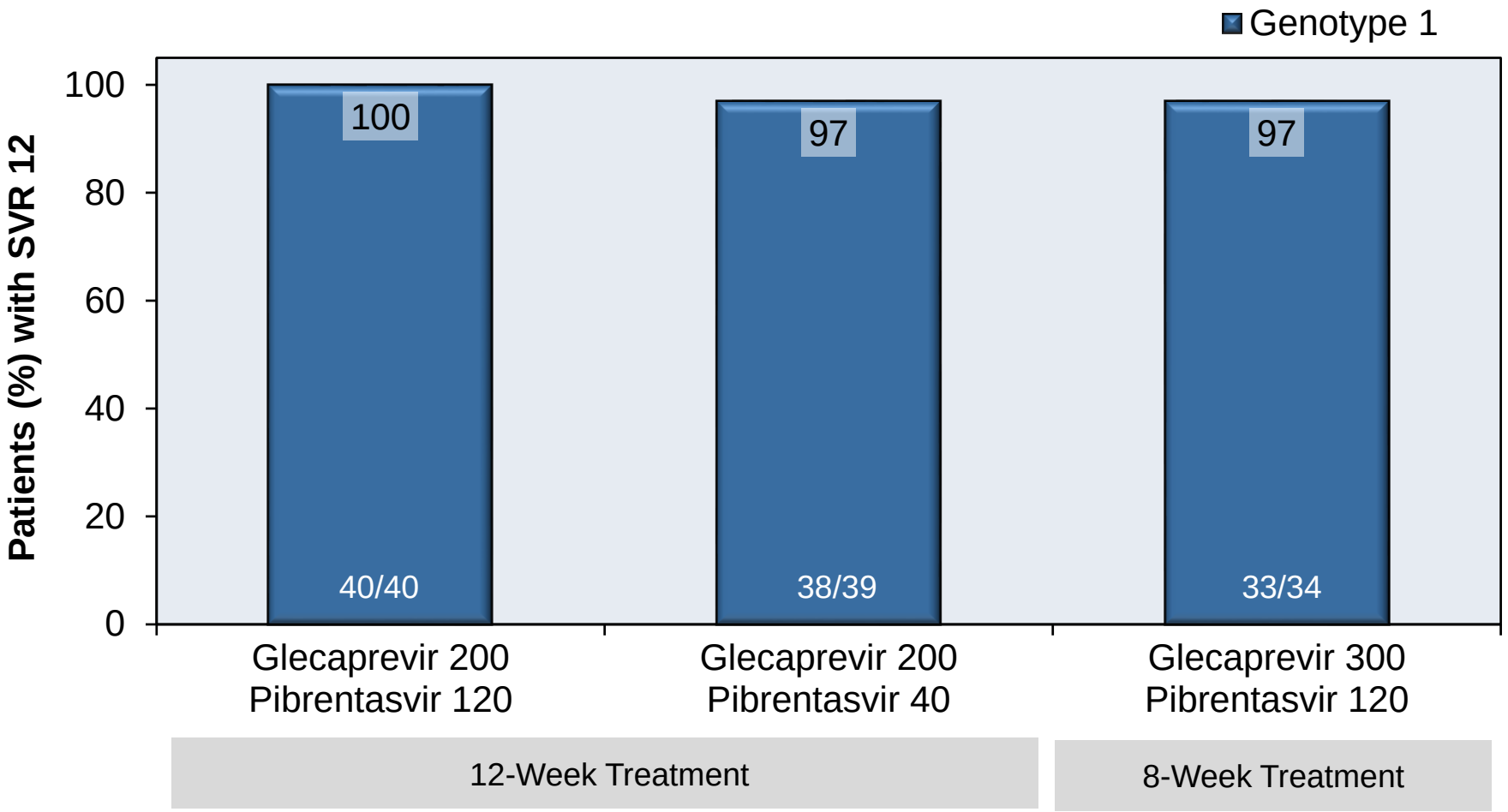
Glecaprevir and Pibrentasvir in HCV GT 1-6 without Cirrhosis SURVEYOR-I and SURVEYOR-II: Baseline Characteristics

Prevalence of Baseline Amino Acid Polymorphisms			
Genotype	**Amino Acid Polymorphisms, n/N %**		
	NS3 Only	NS5A Only	NS3 + NS5A
1a	40/87 (46)	9/87 (10)	12/87 (14)
1b	10/24 (42)	4/24 (17)	4/24 (17)
2	3/124 (2)	79/124 (64)	11/124 (9)
3	22/174 (13)	33/174 (19)	7/174 (4)
4	1/22 (5)	7/22 (32)	0/22 (0)
5	0/1 (0)	0/1 (0)	0/1 (0)
6	2/11 (18)	4/11 (36)	14/11 (9)

Source: Kwo PY, et al. J Hepatol 2017;67:263-71.

Glecaprevir and Pibrentasvir in HCV GT 1-6 without Cirrhosis
SURVEYOR-I and SURVEYOR-II: Results

Genotype 1: SVR12 ITT



Source: Kwo PY, et al. J Hepatol 2017;67:263-71.

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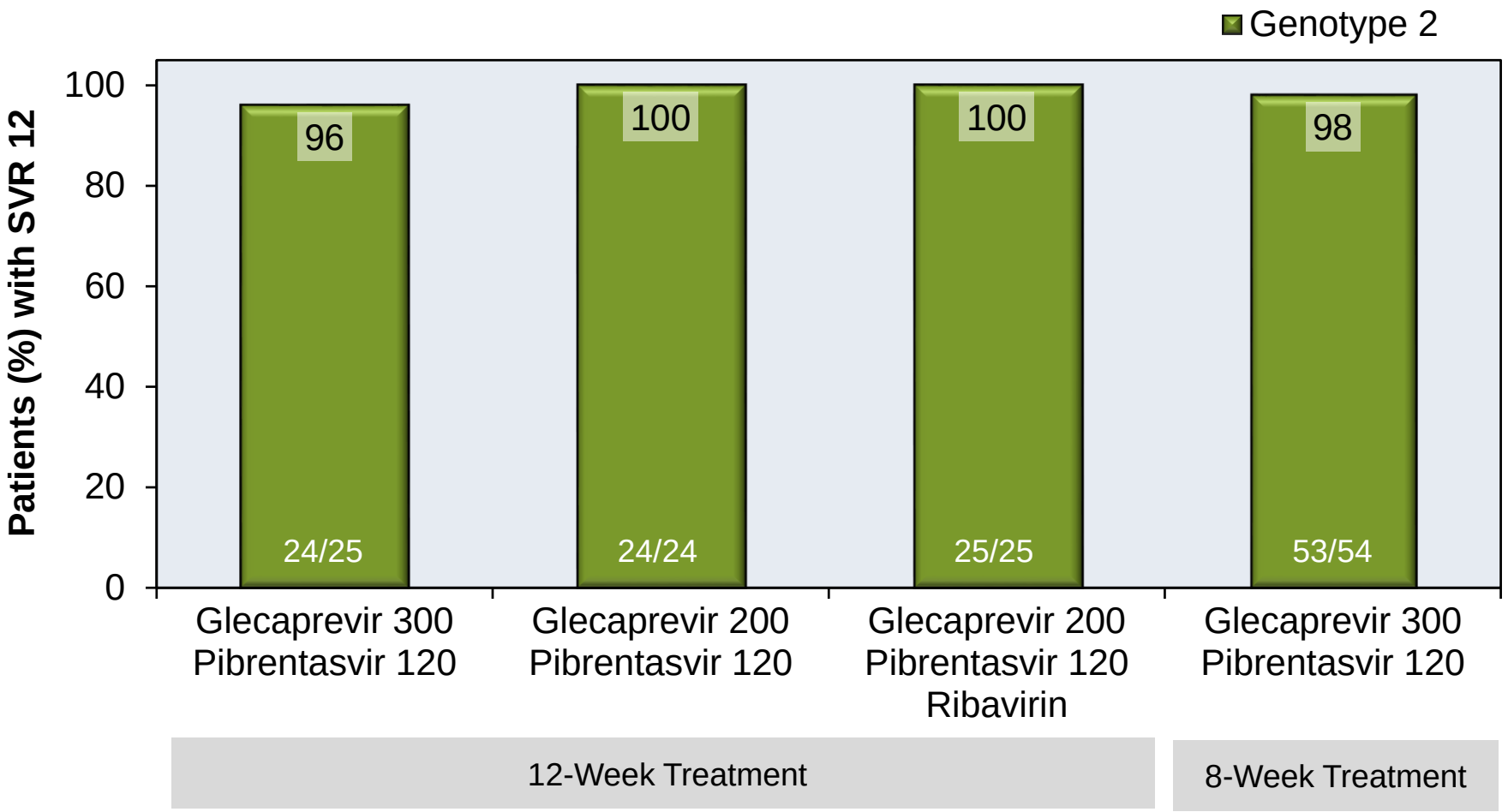
Glecaprevir and Pibrentasvir in HCV GT 1-6 without Cirrhosis
SURVEYOR-I and SURVEYOR-II: Results

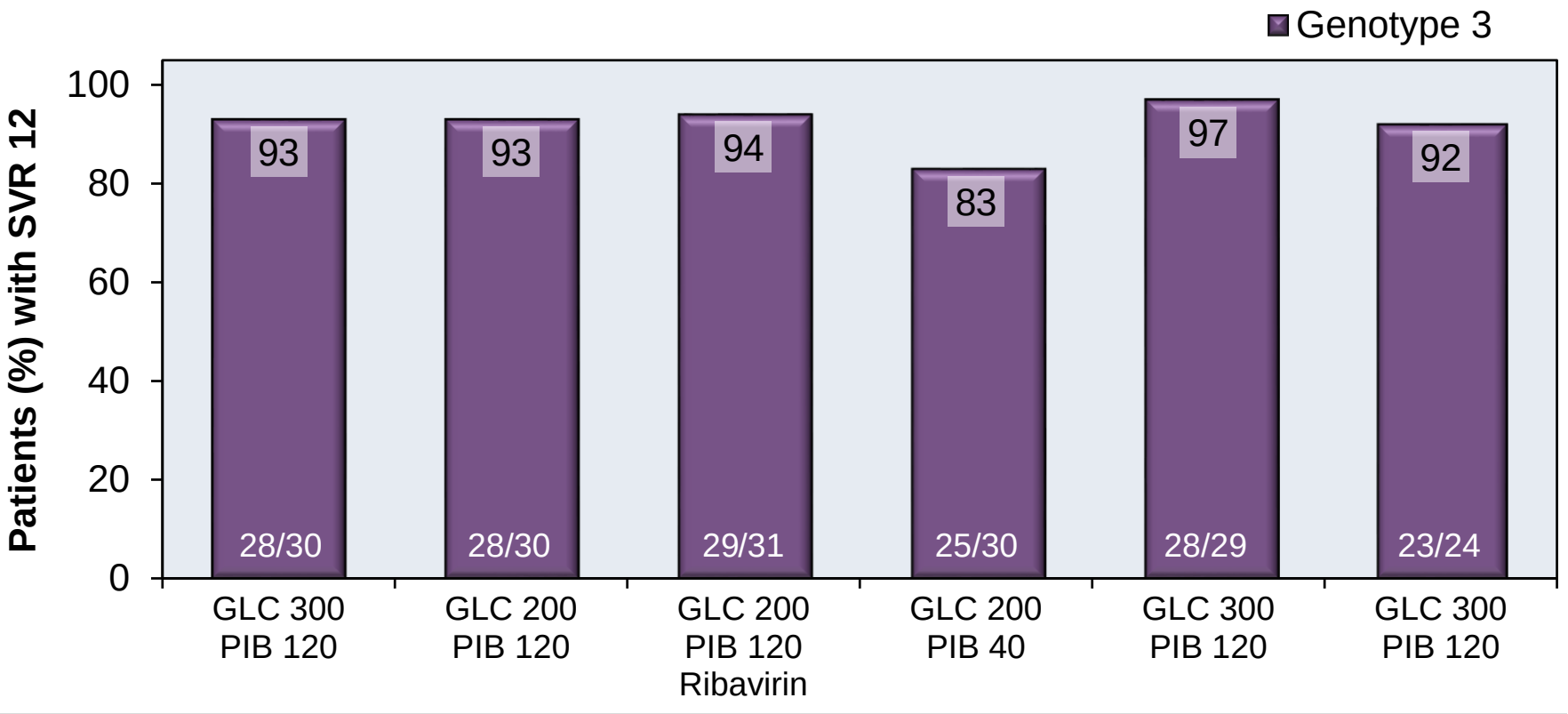
Genotype 2: SVR12 ITT



Source: Kwo PY, et al. J Hepatol 2017;67:263-71.

Glecaprevir and Pibrentasvir in HCV GT 1-6 without Cirrhosis
SURVEYOR-I and SURVEYOR-II: Results

Genotype 3: SVR12 ITT



Source: Kwo PY, et al. J Hepatol 2017;67:263-71.

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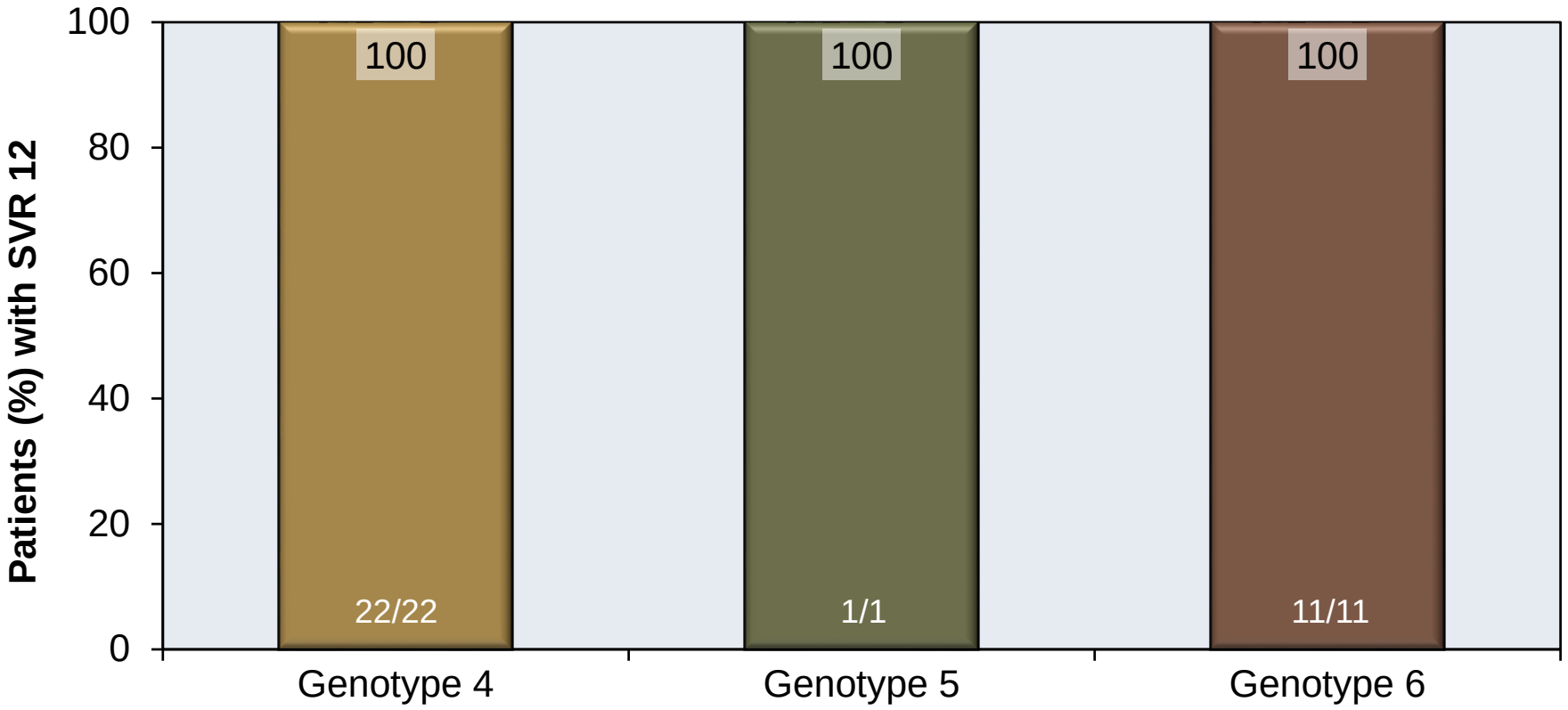
Glecaprevir and Pibrentasvir in HCV GT 1-6 without Cirrhosis
SURVEYOR-I and SURVEYOR-II: Results

Genotype 4, 5, and 6: SVR12 ITT



12-Week Treatment with Glecaprevir 300 mg and Pibrentasvir 120 mg*
Includes 2 patients who received Glecaprevir 200 mg and Pibrentasvir 120 mg)

Source: Kwo PY, et al. J Hepatol 2017;67:263-71.

Glecaprevir and Pibrentasvir in HCV GT 1-6 without Cirrhosis
SURVEYOR-I and SURVEYOR-II: Conclusions

Conclusions: “Glecaprevir plus pibrentasvir was well tolerated and achieved high sustained virologic response rates in HCV genotypes 1-6-infected patients without cirrhosis following 8- or 12-week treatment durations.”

Source: Kwo PY, et al. J Hepatol 2017;67:263-71.

Treatment-Naïve and Treatment-Experienced

Glecaprevir-Pibrentasvir in HCV GT 3, Without Cirrhosis
SURVEYOR-II (Part 3)

Source: Wyles D, et al. Hepatology. 2017 Sep 19. [Epub ahead of print]

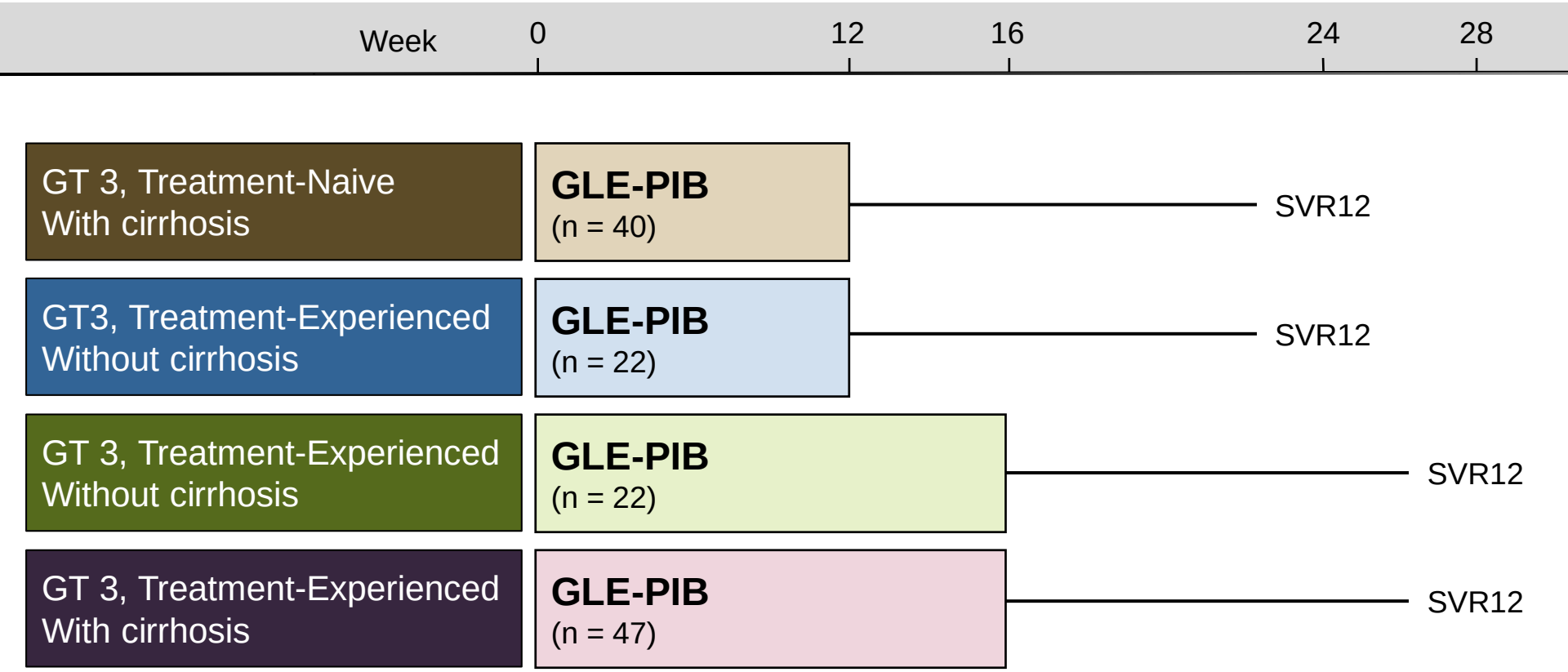
Glecaprevir-Pibrentasvir in HCV GT 3, with Cirrhosis and Prior Treatment
SURVEYOR-II (Part 3): Study Features

SURVEYOR-II (Part 3) Trial

- **Design**: Open-label single-arm phase 3 trial to evaluate the safety and efficacy of the fixed-dose combination of glecaprevir-pibrentasvir for 8 weeks in treatment-naïve and treatment-experienced adults with GT 3 chronic HCV infection, without cirrhosis and with compensated cirrhosis
- **Setting**: U.S., 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
  - 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
- **Primary End-Point**: SVR12

Source: Wyles D, et al. Hepatology. 2017 Sep 19. [Epub ahead of print]

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



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

Source: Wyles D, et al. Hepatology. 2017 Sep 19. [Epub ahead of print]

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

Baseline Characteristic	Arm A: 12 weeks GLE-PIB		Arm B: 16 weeks GLE-PIB	
	Naive (+) Cirrhosis (n = 40)	Experienced (-) Cirrhosis (n = 22)	Experienced (-) Cirrhosis (n = 22)	Experienced (+) Cirrhosis (n = 47)
Age, median years (range)	56 (36-70)	56 (35-68)	59 (29-66)	59 (47-70)
Male, n (%)	24 (60)	14 (64)	14 (64)	36 (77)
White race, n (%)	37 (93)	17 (77)	20 (91)	42 (89)
HCV RNA, median $\log_{10}$ IU/mL (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)
BMI, median SD, kg/m^2	29 (21-51)	26 (19-42)	28 (22-48)	27 (21-42)
Prior Treatment History, n (%)				
Naïve	40 (100)	0	0	0
IFN/PEG ± RBV, n (%)	0	14 (64)	13 (59)	22 (47)
SOF + RBV ± PEG, n (%)	0	8 (36)	9 (41)	25 (53)

Source: Wyles D, et al. Hepatology. 2017 Sep 19. [Epub ahead of print]

Glecaprevir-Pibrentasvir in HCV GT 3, Without Cirrhosis
SURVEYOR-II (Part 3): Baseline Characteristics

Prevalence of Baseline Amino Acid Polymorphisms* in NS3 or NS5A				
Genotype	**Prevalence of Baseline Polymorphism, n (%)**			
	Naive (+) Cirrhosis (n = 40)	Experienced (-) Cirrhosis (n = 22)	Experienced (-) Cirrhosis (n = 22)	Experienced (+) Cirrhosis (n = 47)
Any	10 (26)	6 (27)	3 (14)	7 (15)
NS3 only	1 (3)	0	0	1 (2)
NS5A only	9 (23)	6 (27)	3 (14)	6 (13)
NS3 + NS5A	0	0	0	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: 155, 156, 168
NS5A: 24, 28, 30, 31, 58, 92, 93

Source: Wyles D, et al. Hepatology. 2017 Sep 19. [Epub ahead of print]

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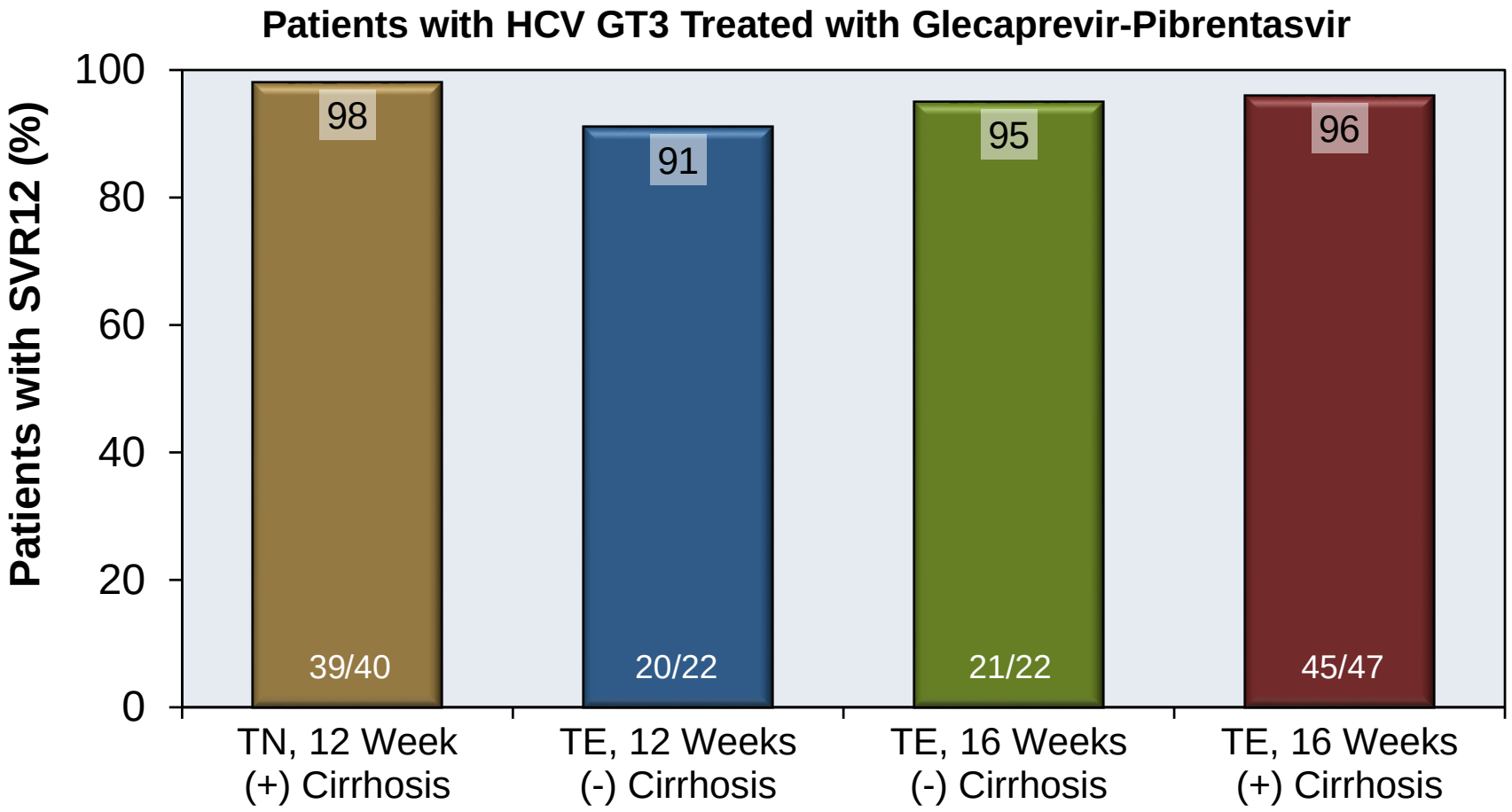
Glecaprevir-Pibrentasvir in HCV GT 3, with Cirrhosis and Prior Treatment
SURVEYOR-II (Part 3): Results



Abbreviations: TN = Treatment Naïve; TE = Treatment Experienced

Source: Wyles D, et al. Hepatology. 2017 Sep 19. [Epub ahead of print]

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

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. 2017 Sep 19. [Epub ahead of print]

Treatment-Naïve and Treatment-Experienced

Glecaprevir-Pibrentasvir for 8 Weeks in HCV GT 2, 4, 5, or 6 without Cirrhosis

SURVEYOR-II (Part 4)

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2017 Sep 22. [Epub ahead of print]

Glecaprevir-Pibrentasvir in HCV GT 2, 4, 5, or 6 without Cirrhosis *SURVEYOR-II (Part 4): Study Features

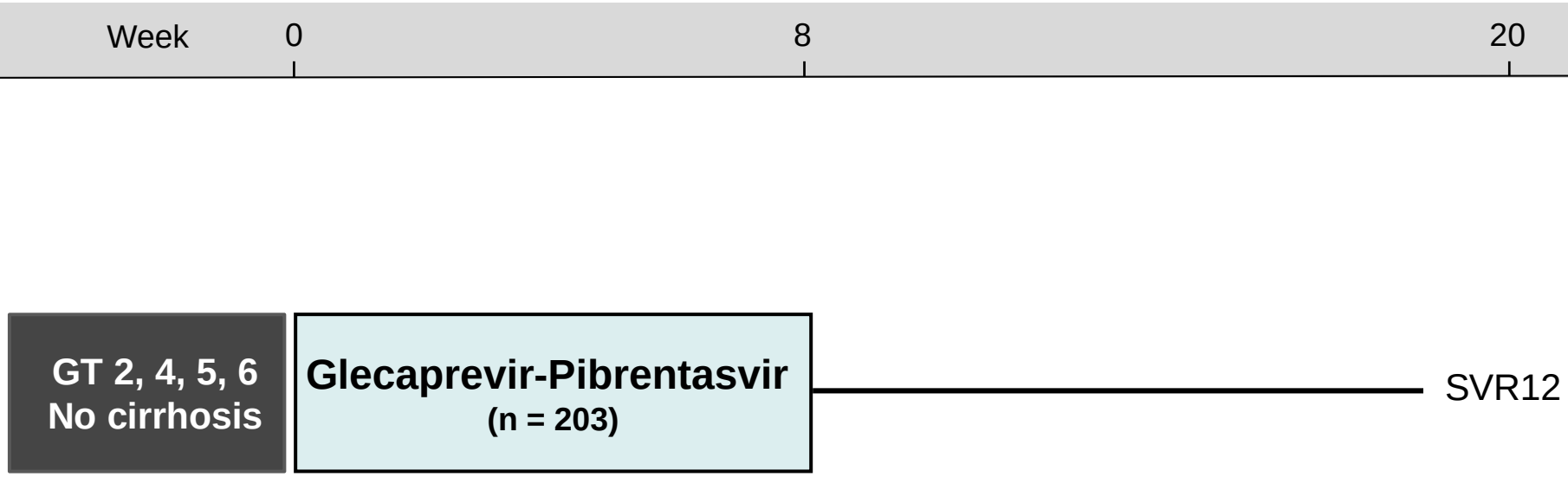
SURVEYOR-II (Part 4) Trial

- **Design**: Open-label single-arm phase 3 trial to evaluate the safety and efficacy of the fixed-dose combination of glecaprevir-pibrentasvir for 8 weeks in treatment-naïve and treatment-experienced adults with GT 2, 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
  - Treatment naïve
  - Prior treatment with (1) PEG (or INF) +/- RIB or (2) Sofosbuvir + RIB +/- PEG
  - Patients with cirrhosis excluded
  - Patients with HIV or chronic HBV excluded
- **Primary End-Point**: SVR12

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

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2017 Sep 22. [Epub ahead of print]

Glecaprevir-Pibrentasvir in HCV GT 2, 4, 5, or 6 without Cirrhosis
SURVEYOR-II (Part 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. 2017 Sep 22. [Epub ahead of print]

Glecaprevir-Pibrentasvir in HCV GT 2, 4, 5, or 6 without Cirrhosis
SURVEYOR-II (Part 4): Baseline Characteristics

Baseline Characteristic	GT2 (n = 145)	GT 4-6 (n = 58)
Age, mean ± SD, years	54 ± 11.8	48 ± 13.8
Male, n (%)	61 (42)	37 (64)
Race, n (%) White Black Asian	 120 (83) 11 (8) 10 (7)	 35 (60) 10 (17) 13 (22)
BMI, mean ± SD, kg/m^2	28.5 ± 6.9	25.9 ± 5.0
HCV RNA, median (range), log_{10} IU/mL	6.67 (0.75-7.6)	5.45 (4.3-7.5)
HCV Treatment experienced, n (%) IFN or PEG ± RBV, n (%) SOF + RBV ± PEG, n (%)	18 (12) 12 (8) 6 (4)	9 (16) 9 (16) 0
Former IDU, n (%)	71 (49%)	21 (36)

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2017 Sep 22. [Epub ahead of print]

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Glecaprevir-Pibrentasvir in HCV GT 2, 4, 5, or 6 without Cirrhosis
SURVEYOR-II (Part 4): Baseline Characteristics

Prevalence of Baseline Amino Acid Polymorphisms* in NS3 or NS5A

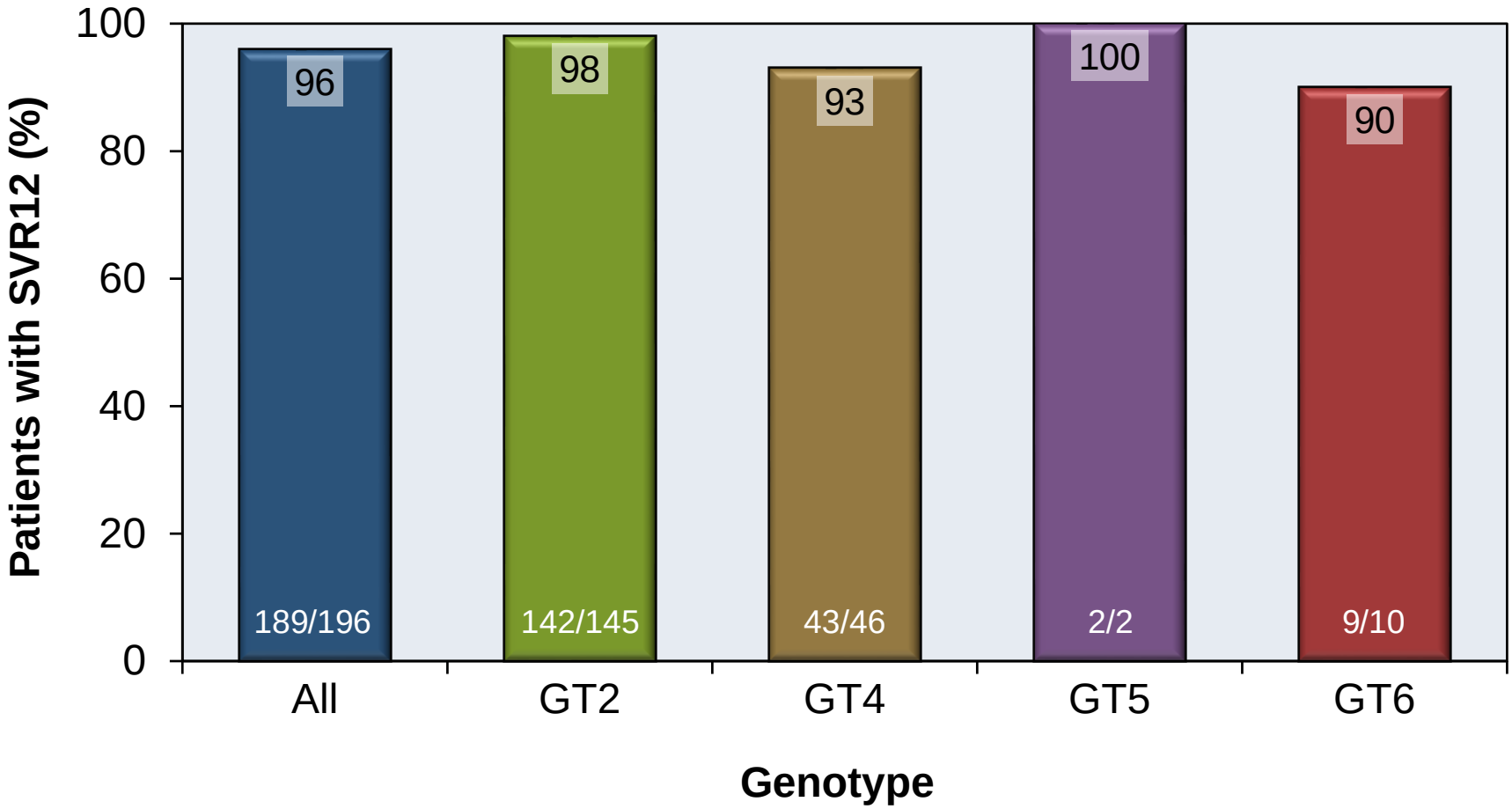
Genotype	Prevalence of Baseline Polymorphism, n (%)			
	GT2 (n = 123)	GT4 (n = 41)	GT5 (n = 1)	GT6 (n = 6)
None	29 (24)	23 (56)	1 (100)	2 (33)
NS3 only	0	0	0	0
NS5A only	93 (76)	17 (41%)	0	4 (67)
NS3 + NS5A	1 (0.8)	1 (2)	0	0 (9)

*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: 155, 156, 168
NS5A: 24, 28, 30, 31, 58, 92, 93

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2017 Sep 22. [Epub ahead of print]

Glecaprevir-Pibrentasvir in HCV GT 2, 4, 5, or 6 without Cirrhosis
SURVEYOR-II (Part 4): Results

SVR12 (ITT analysis), Overall and by Genotype



Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2017 Sep 22. [Epub ahead of print]

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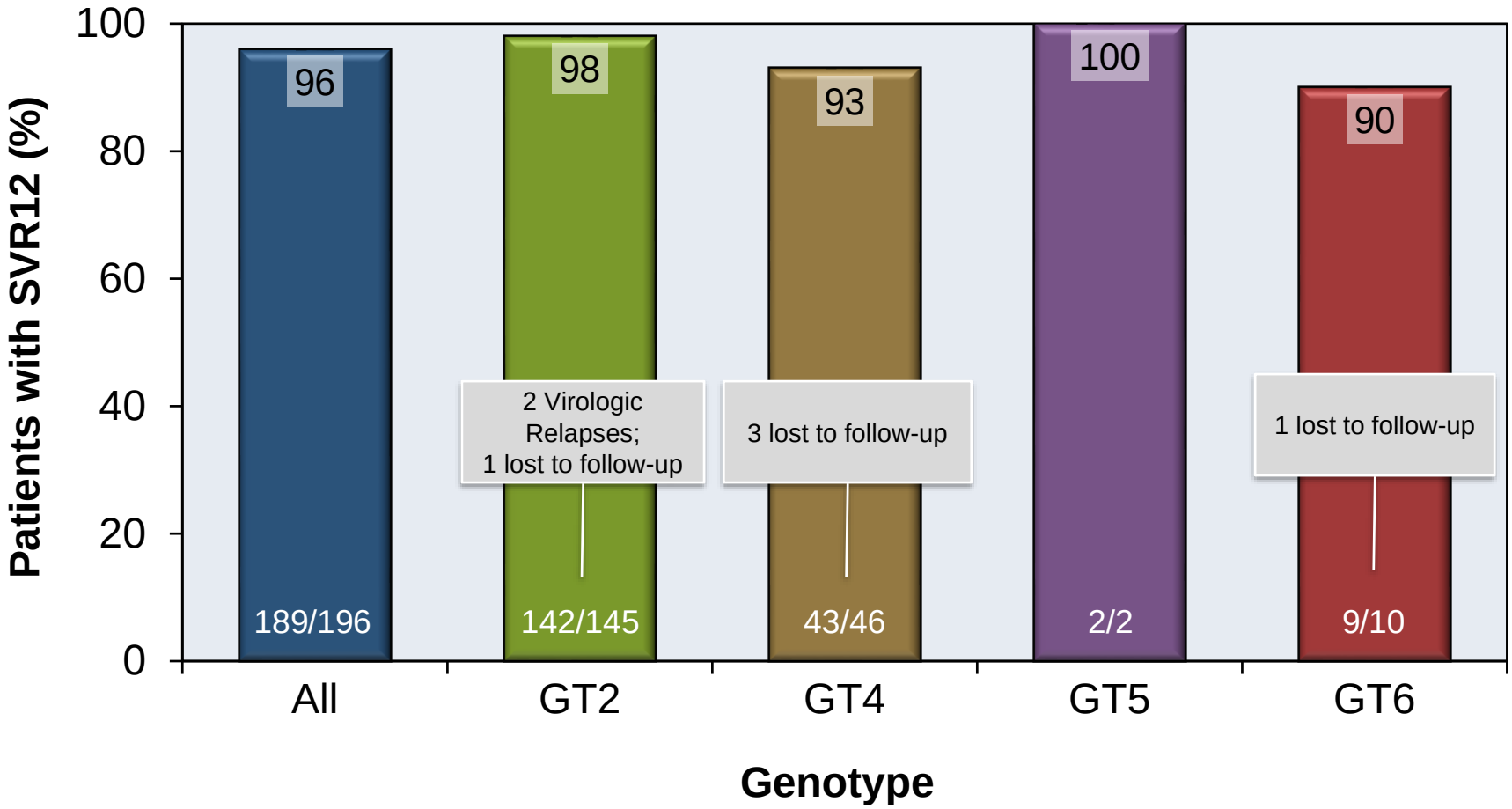
Glecaprevir-Pibrentasvir in HCV GT 2, 4, 5, or 6 without Cirrhosis
SURVEYOR-II (Part 4): Results

SVR12 (ITT analysis), Overall and by Genotype



Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2017 Sep 22. [Epub ahead of print]

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Glecaprevir-Pibrentasvir in HCV GT 2, 4, 5, or 6 without Cirrhosis
SURVEYOR-II (Part 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 (>3 x ULN)	0
ALT grade ≥2 (>3 x ULN)	0
Total bilirubin grade ≥3 (>3 x 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. 2017 Sep 22. [Epub ahead of print]

Glecaprevir-Pibrentasvir in HCV GT 2, 4, 5, or 6 without Cirrhosis *SURVEYOR-II (Part 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**: SURVEYOR-II (Part-4) was published in conjunction with ENDURANCE-2 and ENDURANCE-4

Source: Asselah T, et al. Clin Gastroenterol Hepatol. 2017 Sep 22. [Epub ahead of print]

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