Ledipasvir/Sofosbuvir (LDV/SOF) for 8 Weeks in Genotype 1 (GT1) Treatment-Naïve (TN) Non-Cirrhotic (NC) Patients with HCV Viral load (VL) <6 million IU/ml (6M); A Comparative Analysis of the Phase-3 ION-3 Efficacy Data to Real World Effectiveness (RWE)

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2016 ICVH, San Francisco, CA

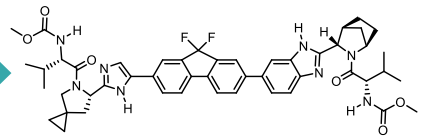
Disclosures

- Dr Terrault's disclosures:
  - Grant Support: Abbvie, Biotest, Eisai, and Gilead
  - Consultant: BMS, CoCrystal Pharmaceuticals, Gilead, Janssen, and Merck

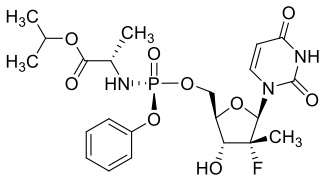
Introduction

- **Ledipasvir (LDV)**
  - Picomolar potency against multiple HCV genotypes
  - Effective against NS5B RAV S282T
  - Once-daily, oral, 90 mg

LDV NS5A inhibitor



- **Sofosbuvir (SOF)**
  - Potent antiviral activity against HCV GT 1–6
  - Effective against NS5A RAVs
  - High barrier to resistance
  - Once-daily, oral, 400-mg tablet



SOF - NS5B nucleotide polymerase inhibitor

- **Ledipasvir/Sofosbuvir STR**
  - Once-daily, oral fixed-dose (90/400 mg) combination tablet, RBV-free

LDV NS5A inhibitor

SOF - NS5B nucleotide polymerase inhibitor

To date, >250,000 patients treated with LDV/SOF Globally.

Lawitz E, et al. EASL 2011, poster 1219; Cheng G, et al. EASL 2012, poster 1172; SOVALDI® [PI]. Gilead Sciences, Inc. Foster City, CA August 2015; HARVONI ® [PI]. Gilead Sciences, Inc. Foster City, CA November 2015; Data on File. Gilead Sciences, Inc.

Background

- ION-3 was a phase 3, randomized, open-label study comparing 8 vs. 12 weeks of LDV/SOF in GT 1 treatment-naïve, non-cirrhotic patients
- SVR rates were non-inferior between the 8 and 12 week LDV/SOF arms (94% vs. 96%, respectively)
- Post-hoc analysis showed that the relapse rates in the 8 week arm were comparable to 12 weeks of LDV/SOF in patients with a baseline HCV RNA of <6M IU/ml
- The FDA, EMA and several treatment guidelines have endorsed the 8 week LDV/SOF regimen as a first line treatment option for TN, NC, GT1 patients with HCV RNA <6M IU/ml

HARVONI ® [PI]. Gilead Sciences, Inc. Foster City, CA November 2015
Kowdley K, et al. *N Engl J Med* 2014;370:1879-1888.

Objectives & Methods

Objectives

- Evaluate the effectiveness of LDV/SOF for 8 weeks in real world datasets
- Compare SVR data from the ION-3 study to several real world cohorts

Methods

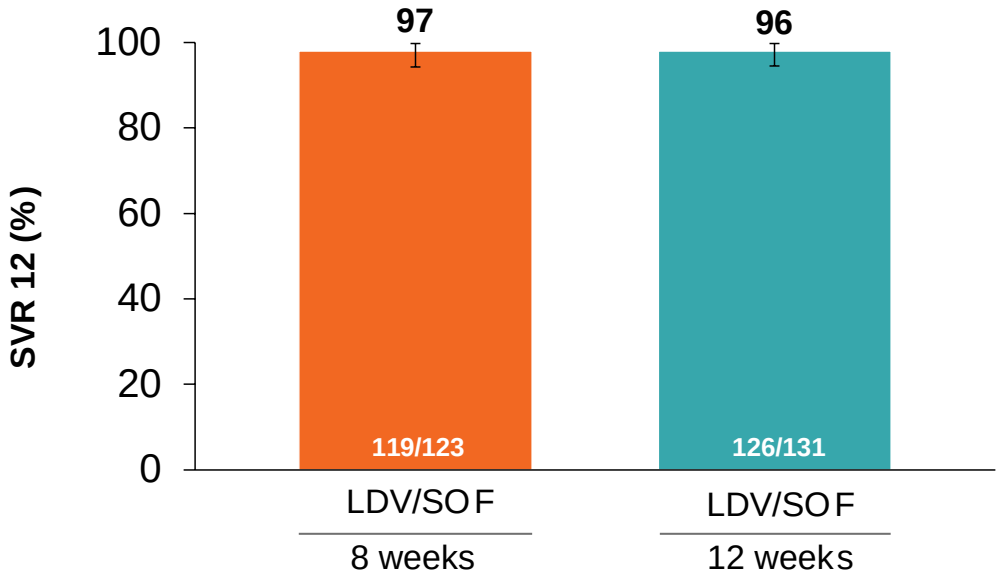
- Three large, prospective, open-label, multicenter real world cohorts and two retrospective single center real world cohort were reviewed
- Cohorts with missing or incomplete baseline demographic data or single center cohorts with less than 50 patients were excluded

Baseline Demographics

Characteristic	ION 3 N=123	TARGET N=154	TRIO N=263	GECCO N=148	IFI N=103	VA- Ohio N= 60
Median age, years (range)	52 (22-73) ^	58 (19-84)	57 (18-84) ^	52 (44-58)	50 (22-77)	61 (32-75) ^
Male, n (%)	67 (54)	70 (46)	121 (46)	79 (42)	43 (42)	56 (93)
Race, n (%)						
Non black	96 (78)	120 (78)	224 (85)	n/a	103 (100)	27 (46)
Black	27 (22)	34 (22)	39 (15)	n/a	0	33 (54)
HCV genotype 1a, n (%)	89 (72)	(66)	180 (68)	71 (48)	49 (46)	36 (59)
HCV GT 4	0	0	0	3	2	0
HIV/HCV	0	1	0	28	3	0
VL >6 M IU/ml	0	n/a	8	13*	2	0
Treatment Experienced	0	8	0	26	3	7
Fibrosis Score (liver biopsy), n (%)						
F0-F2	87 (71)	n/a	205 (78)	n/a	98(95)	n/a
F3	14 (12)	n/a	32 (12)	n/a	5 (5)	n/a
F4	0	n=6	0	n=5 ***	0	0
Unknown/other	22 (17) **	n/a	26 (10)	n/a	0	60^^

* Defined as >6 million with Roche TaQman® v2.0, >2 million with the Abbott Real Time PCR **15% were cirrhotic on FibroTest but confirmed non-cirrhotic with biopsy, 2% had no data, ***FibroScan® >12.5 or APRI >2.0, n/a= not available, ^ mean age used, ^^ All patients had fibroscan <12.5 kPa

ION-3 - Efficacy and Relapse with Baseline HCV RNA <6 Million IU/ml



	LDV/SOF 8 weeks	LDV/SOF 12 weeks
Relapse Rates < 6M	1.6% (2/123)	1.5% (2/131)
Relapse Rates ≥ 6M	9.8% (9/92)	1.2% (1/85)

*2 patients were lost to follow-up after their baseline visit and never achieved HCV RNA < lower limit of quantitation on treatment.

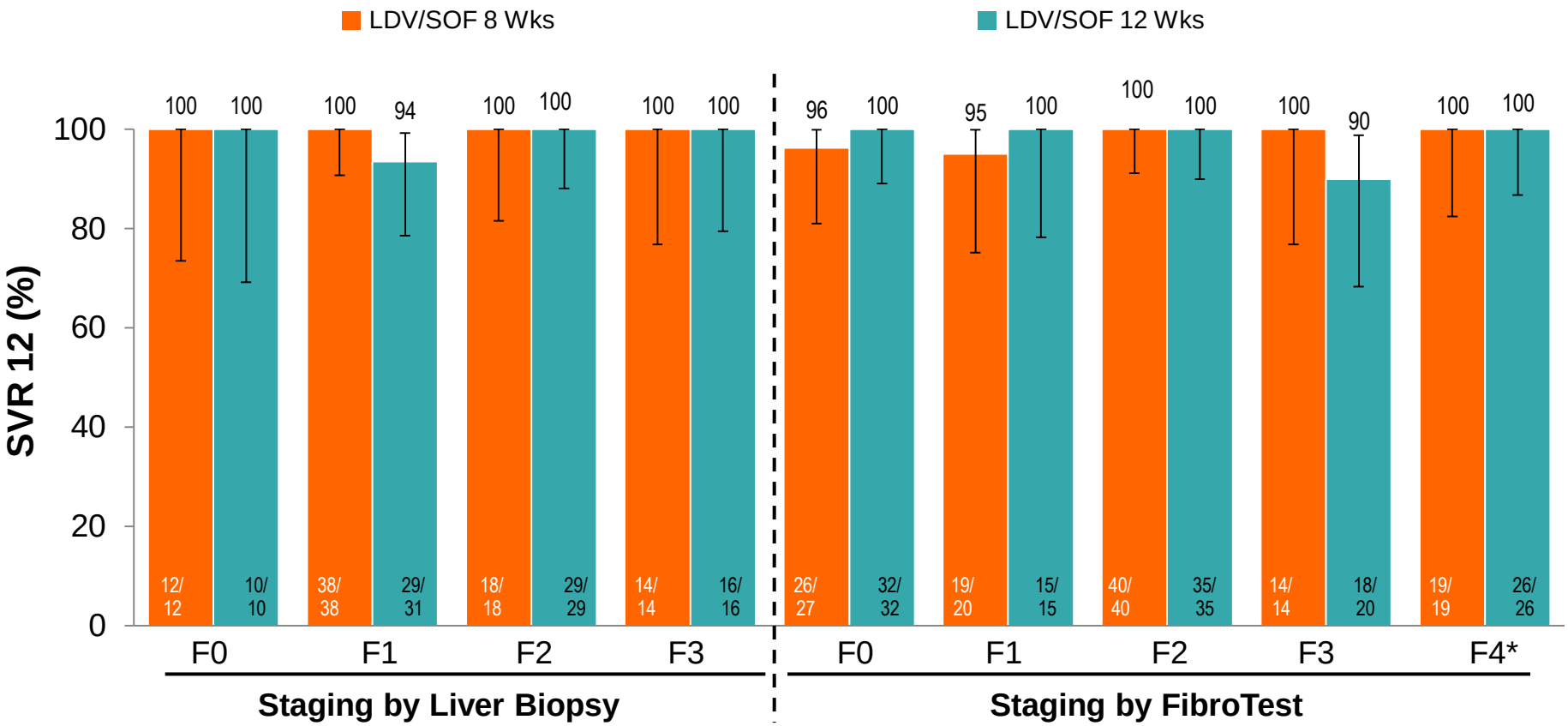
8 weeks of LDV/SOF was non-inferior to 12 weeks LDV/SOF for both SVR12 and relapse rates

Kowdley K, et al. *N Engl J Med* 2014;370:1879-1888.
Jacobson I, et al. AASLD, 2014, Poster #1945.
Gordon S, et al. ACG 2015, Poster 459

ION-3 - SVR12 by Fibrosis Scores in Patients with Baseline HCV RNA <6 Million IU/mL

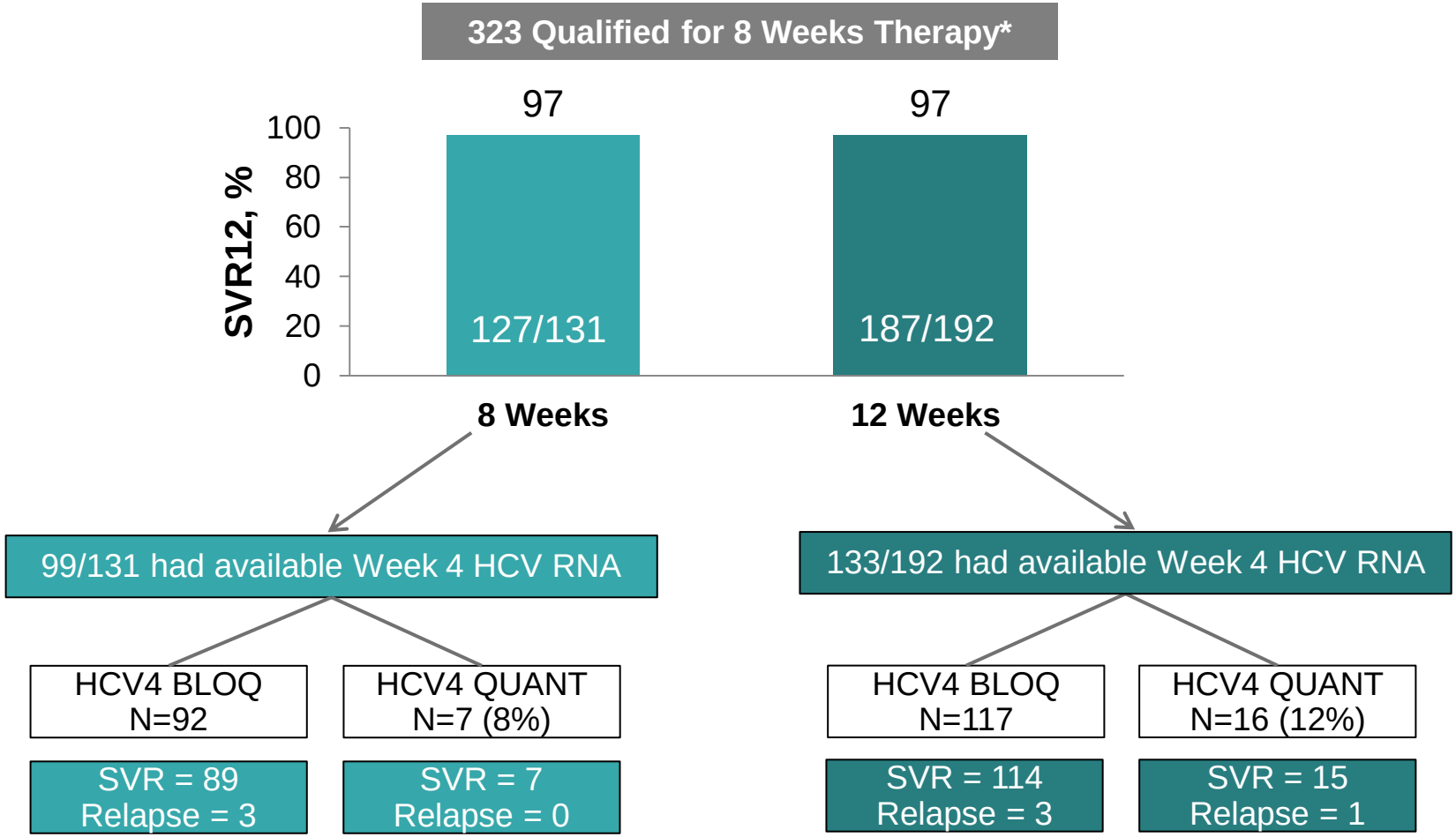
The baseline viral load cut-off of <6 million IU/mL

Demonstrated high efficacy across fibrosis stages



* FibroTest is based on quantitative results of 5 serum biochemical markers (alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, gamma glutamyl transpeptidase (GGT) and bilirubin) – can overestimate stage of fibrosis. If patients had discordant biochemical tests, a liver biopsy was used.

HCV TARGET- SVR12 Among Those Who Qualified for 8 Week Treatment



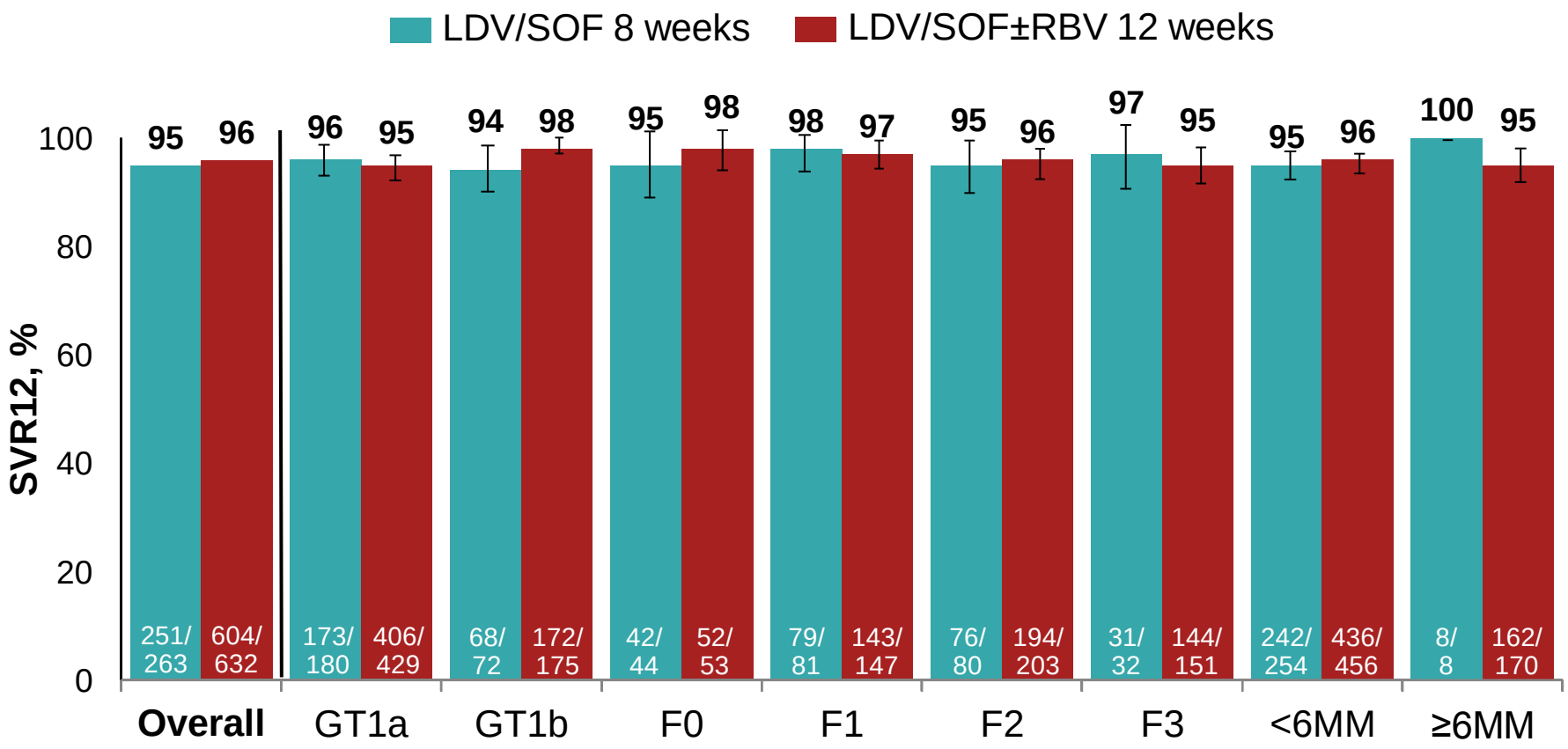
323 subjects qualified for 8 week therapy, but only 41% received an 8 week duration

*Qualified = Treatment-naïve, no cirrhosis, HCV RNA ≤ 6 million IU/mL

Terrault, AASLD, 2015, 94

TRIO Real-World Cohort: LDV/SOF ± RBV for 8 or 12 Weeks in Treatment-Naïve, Non-Cirrhotic GT 1 HCV, non randomized, observational cohort

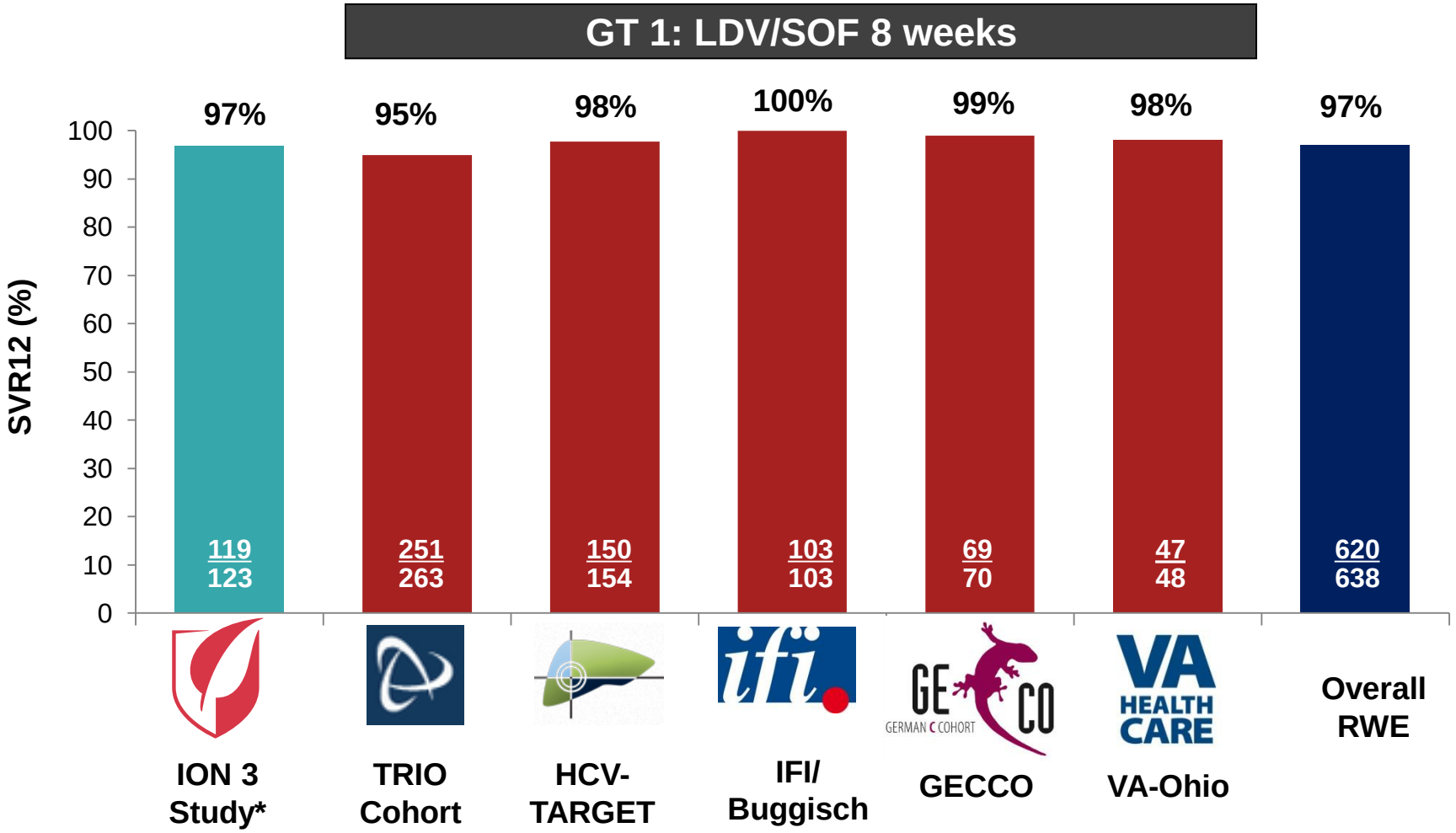
TRIO Cohort



Overall discontinuation rate was <1% (7/895)

Curry, AASLD, 2015, 1046

SVR12 in ION-3 Compared to Real-World Cohorts



*Post hoc analysis

Kowdley KV, et al. N Engl J Med 2014;370:1879-88; Curry M, et al AASLD 2015;
Terrault N, et al AASLD 2015; Buggisch P, et al. AASLD 2015; Christensen, et al. AASLD 2015; Marshall et al. AASLD 2015

Conclusions

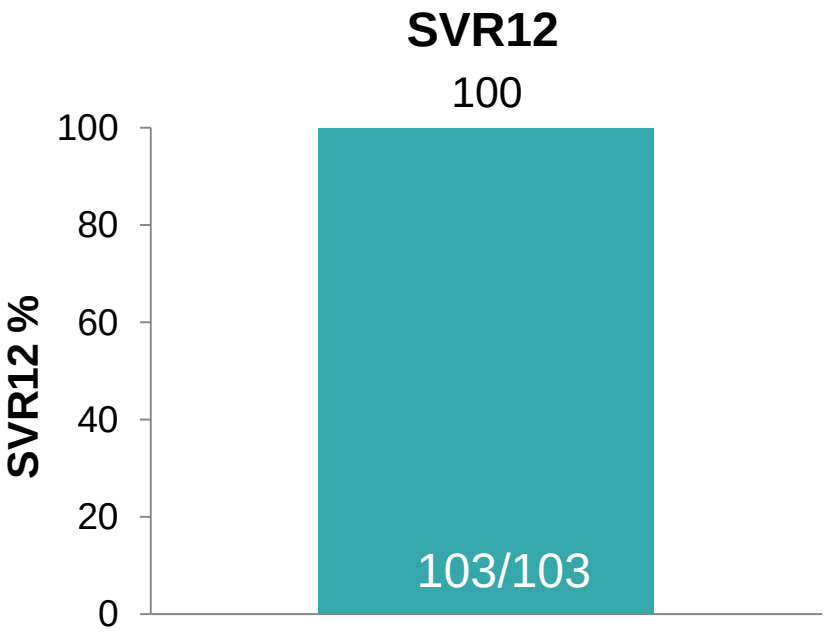
- 8 weeks of LDV/SOF resulted in SVR rates of 97% in multiple, large, real-world cohorts
  - comparable to the SVR seen in the ION-3 post hoc analysis
  - real-world patients were more heterogeneous as many do not fit the standard criteria of TN, NC and VL < 6million
- These data confirm the use of the 8 week LDV/SOF regimen, and the validity of the post-hoc analysis that led to the dosing recommendation
- Data from these cohorts suggest that the 8 week regimen is highly efficacious and underutilized in both community and academic centers

Back Up

German Real-World LDV/SOF for 8 Weeks

Single center German study of 103 primarily naïve, non-cirrhotic patients with baseline HCV RNA < 6 million IU/mL treated with LDV/SOF for 8 weeks

	N=103
Median (range) age, years	50 (22–77)
Male gender, n (%)	43 (42)
Caucasian, n (%)	103 (100)
Genotype, n (%)	
GT 1a	49 (46)
GT 1b	52 (51)
GT 4	2 (2)
Metavir stage, n (%)	
F0	56 (54)
F1	25 (24)
F2	17 (17)
F3	5 (5)
Median baseline HCV RNA, IU/mL*	870,964
Treatment-naïve, n (%)†	100 (97)
HIV/HCV coinfection, n (%)	3 (3)
At least one comorbidity, n (%)	94 (91)



LDV/SOF for 8 weeks resulted in high rates of SVR12 and was well tolerated

- 2.3% (n=2) had Grade 3 or 4 AEs
- No AE led to treatment discontinuation or death

*Roche COBAS® AmpliPrep/COBAS® TaqMan®, cut-off < 12 IU/mL † including 3 PegIFN+RBV Relapsers
Fibrosis was measured by FibroScan® with cut-off values for METAVIR stage F3 or less of ≤12.3kPa.

Buggisch, AASLD, 2015, 1205.

LDV/SOF for 8 Weeks in HCV-Monoinfected and HIV/HCV-Coinfected Patients: Interim Analysis

Real-world data from Germany on 148 GT 1 and 4 HCV patients receiving LDV/SOF for 8 weeks

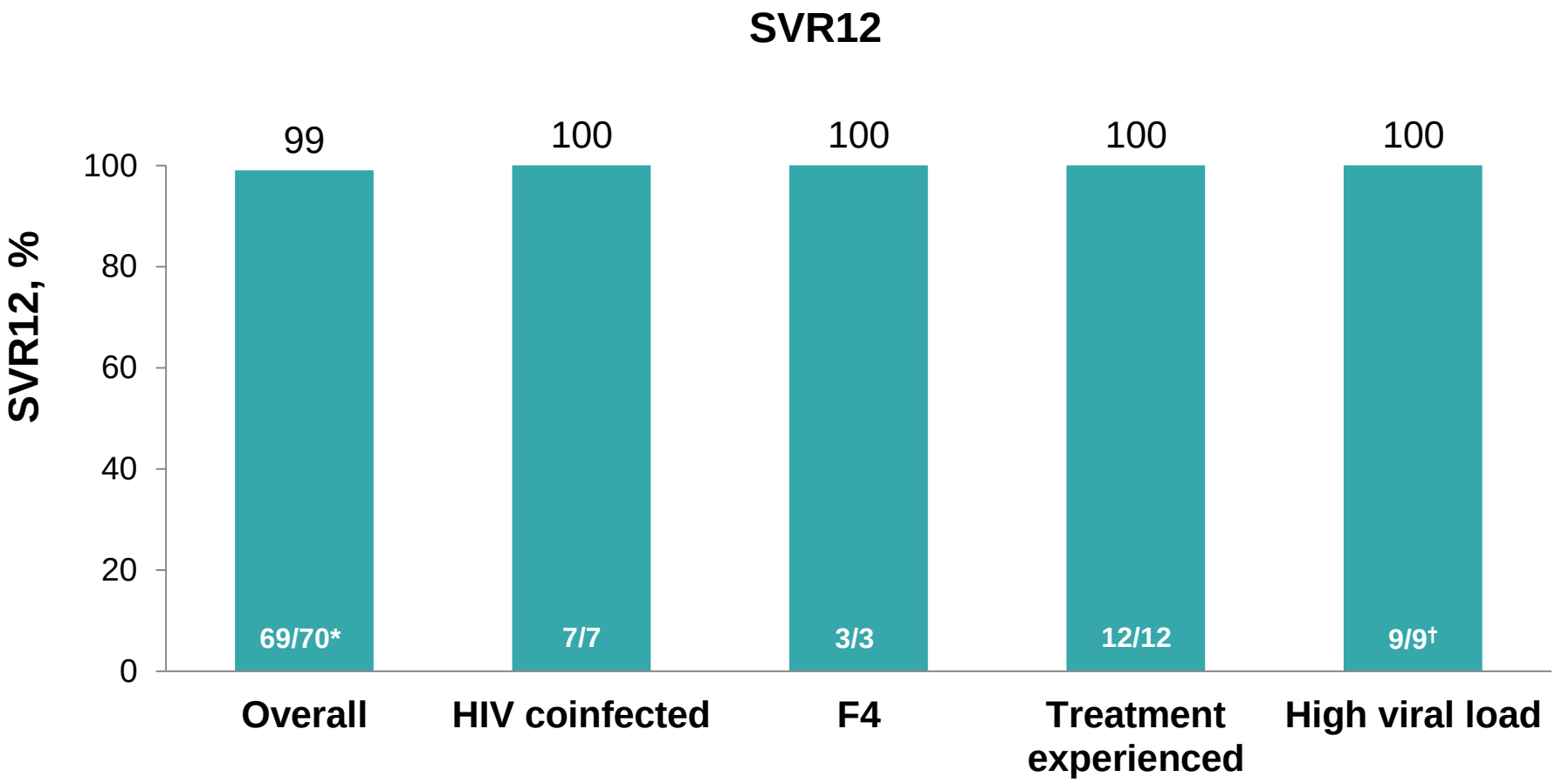
Baseline Demographics

Patients	n=148
Male, n (%)	72 (49)
Median age, years (IQR)	52 (44–58)
GT 1, n (%)	144 (97)
GT 4, n (%)	3 (2)
HIV/HCV coinfection, n (%)	28 (19)
Prior HCV treatment, n (%)	26 (18)
FibroScan >12.5 kPa or APRI >2, n (%)	5 (3)
Median HCV viral load, IU/mL (IQR)	8.1×10^5 (2.5×10^5 – 1.7×10^6)
High viral load*	13 (8.8)

* High viral load defined as > 6 million IU/mL by Roche assay, or > 2 million IU/mL by Abbott assay

Christensen, AASLD, 2015, 1081

LDV/SOF for 8 Weeks in HCV-Monoinfected and HIV/HCV-Coinfected Patients: Interim Analysis



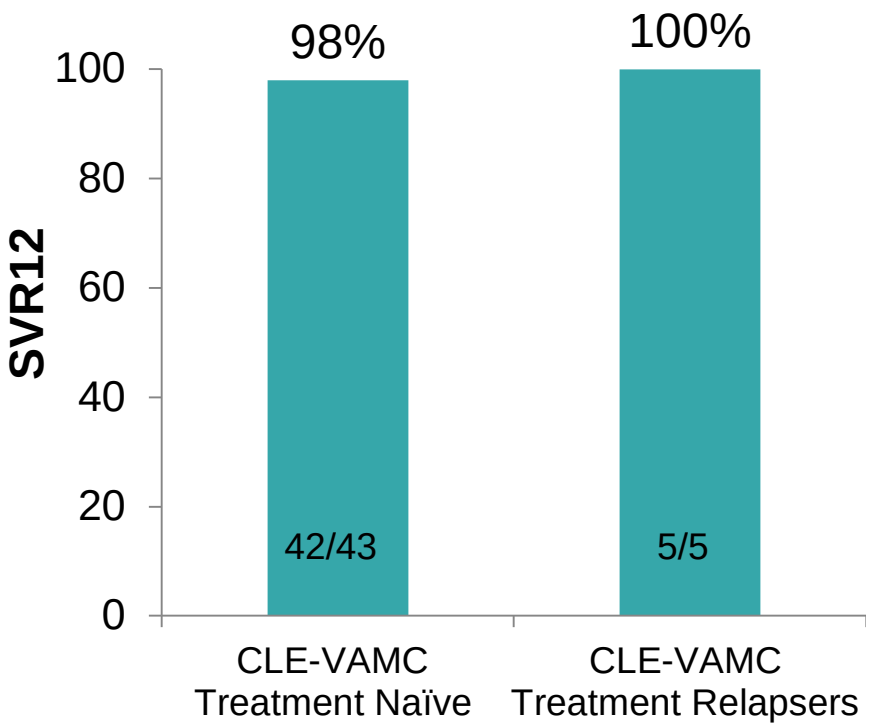
*1 patient relapsed
†High viral load defined as >6M IU/mL (Roche) or >2M IU/mL (Abbott) at baseline

Christensen, AASLD, 2015, 1081

Real Life Outcomes with LDV/SOF for 8 Weeks in Veterans without Cirrhosis Confirmed by Transient Elastography (TE)

Study of 60 GT 1 Treatment-Naïve or PegIFN+RBV Relapser Cleveland Veterans (CLE-VAMC) with TE scores < 12.5 kPa and HCV RNA < 6M IU/mL

Characteristics	N=60
Age	Mean:61 (range 32-75)
Male Sex	56 (93%)
Race	
Black	33 (54%)
White	17 (29%)
Other/Not answered	10 (17%)
Ethnicity	
Non Hispanic	59 (99%)
Genotype	
GT1a	36 (59%)
GT1b	21 (36%)
GT1 or GT1a/b	3 (5%)
Treatment History	
Naive	53 (88%)
Previous IFN/RBV Relapsers	7 (12%)
TE Scores	
TE <9.5 kPa	45 (75%)
TE 9.5-12.5 kPa	15 (25%)



- SVR4: 59/60 (98%); SVR24: 24/25 (96%)

- Using TE score < 12.5 kPa to qualify patients for LDV/SOF for 8 weeks resulted in similar or higher SVR rates than seen in ION-3
- ~$160,000-288,000 in saved resources by using TE instead of APRI or FIB-4

Marshall V, et al. AASLD 2015, Poster 1154.