A Phase 3 Double-Blind Placebo-Controlled Evaluation of Sofosbuvir/Velpatasvir Fixed-Dose Combination for 12 Weeks in Genotype 1, 2, 4, 5, 6 HCV-Infected Patients: Results of the ASTRAL-1 Study

Anne Luetkemeyer[1], Jordan J. Feld[2], Kosh Agarwal[3], Christophe Hezode[4],Tarik Asselah[5], Peter J. Ruane[6] Norbert Gruener[7], Armand Abergel[8], Alessandra Mangia[9], Ching-Lung Lai[10], Henry Lik Yuen Chan[11], Francesco Mazzotta[12], Christophe Moreno[13], Eric Yoshida[14], Stephen D. Shafran[15], William J. Towner[16], Tram T. Tran[17], Yanni Zhu[18], Evguenia Svarovskaia[18], John McNally[18], Anu Osinusi[18], Thomas A. Hahambis[18], Kyle Hammond[18], Diana M. Brainard[18], John G. McHutchison[18], Ira M. Jacobson[19], Stefan Zeuzem[20]

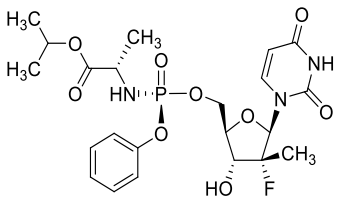
[1]San Francisco General Hospital, San Francisco, CA; [2]Toronto Western Hospital, Ontario, Canada; [3]Kings College Hospital Foundation Trust, London, UK; [4]Université Paris-Est, Créteil, France; [5]University Paris Diderot, Clichy, France; [6]Ruane Medical and Liver Health Institute, Los Angeles, California; [7]Ludwig-Maximilians-University, Munich, Germany; [8]Université d'Auvergne, Clermont-Ferrand, France; [9]Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Italy, [10]University of Hong Kong; [11]The Chinese University of Hong Kong; [12]Maria Annunziata Hospital, Florence, Italy, [13]Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium; [14]University of British Columbia, Vancouver, British Columbia; [15]University of Alberta, Edmonton, Canada; [16]Southern California Permanente Medical Group, Los Angeles, CA; [17]Cedars-Sinai Medical Center, Los Angeles, CA; [18]Gilead Sciences, Inc. Foster City, CA; [19]Mount Sinai Beth Israel Medical Center, NY; [20]JW Goethe University Medical Center, Frankfurt, Germany

Disclosures

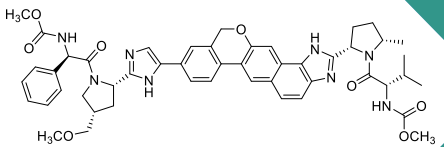
- Dr Luetkemeyer has the following financial disclosures:
  - Research grant support: Abbvie, BMS, Gilead, Merck, and Pfizer.

Background

SOF
Nucleotide polymerase inhibitor



- **Sofosbuvir (SOF)[1,2]**
  - Potent antiviral activity against HCV GT 1–6
  - Once-daily, oral, 400-mg tablet



VEL
NS5A inhibitor

- **Velpatasvir (VEL; GS-5816)[3-5]**
  - Picomolar potency against GT 1–6
  - 2nd-generation inhibitor with improved resistance profile

SOF **VEL**

- **SOF/VEL FDC**
  - Once daily, oral, FDC (400/100 mg)

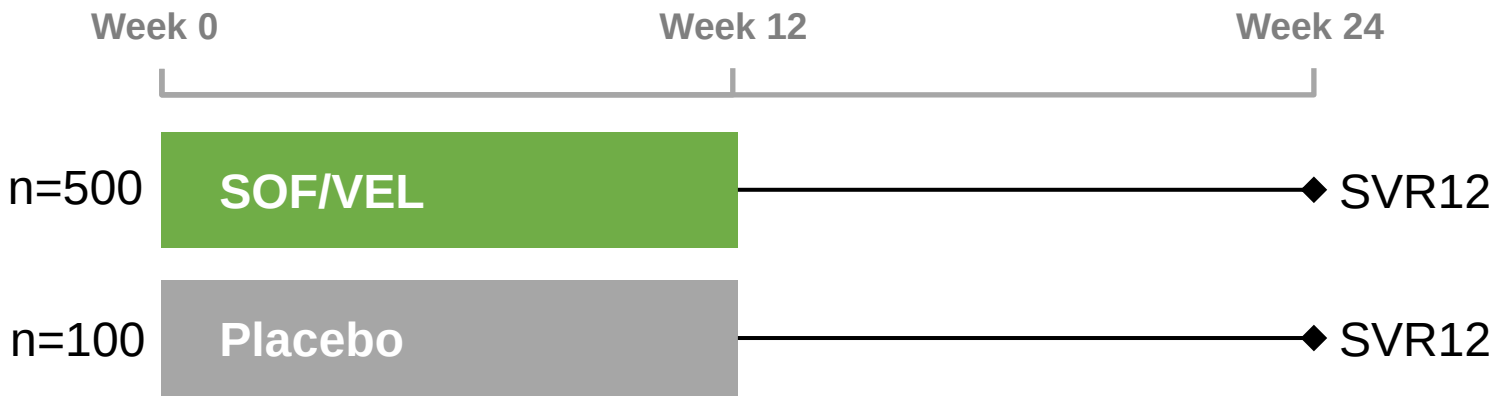
1. Jacobson IM, et al. N Engl J Med 2013;368:1867-77; 2. Lawitz E, et al. N Engl J Med 2013;368:1878-87;
3. Cheng G, et al. EASL 2013, poster 1191; 4. German P, et al. EASL 2013, poster 1195;
5. Lawitz E, et al. J Vir Hep 2015;22:1011-19.

Background and Aim
ASTRAL-1

- Currently available interferon-free treatments for HCV infection are not pangenotypic
- Phase 2 studies demonstrated that SOF + VEL administered as single agents resulted in high SVR12 rates in patients with HCV GT 1–6 infection[1,2]
- SOF and VEL have been co-formulated as an FDC
- This Phase 3 study evaluated SOF/VEL for 12 weeks in patients with HCV GT 1, 2, 4, 5, or 6 infection
  - Patients with GT 3 infection were evaluated in the ASTRAL-3 study

1. Everson G, et al. Ann Intern Med 2015;epub Nov 10; 2. Pianko S, et al. Ann Intern Med 2015;epub Nov 10.

Study Design
ASTRAL-1



- Double blind, placebo controlled
- Broad inclusion criteria
- 5:1 randomization to SOF/VEL or placebo
  - Stratified by HCV genotype and cirrhosis (presence/absence)
  - GT 5 patients not randomized
- Conducted at 81 sites in US, Canada, UK, Germany, France, Italy, Belgium, and Hong Kong

Results: Demographics
ASTRAL-1

	Placebo n=116	SOF/VEL n=624
Mean age, y (range)	53 (25–74)	54 (18–82)
Male, n (%)	68 (59)	374 (60)
White, n (%)	90 (78)	493 (79)
Mean BMI, kg/m^2 (range)	26 (18–40)	27 (17–57)
US enrolled, n (%)	45 (39)	234 (38)
Cirrhosis, n (%)	21 (18)	121 (19)
Treatment experienced*, n (%)	33 (28)	201 (32)
IL28B CC, n (%)	36 (31)	186 (30)
Median HCV RNA, log_{10} IU/mL (range)	6.4 (4.7–7.5)	6.4 (1.1–7.8)

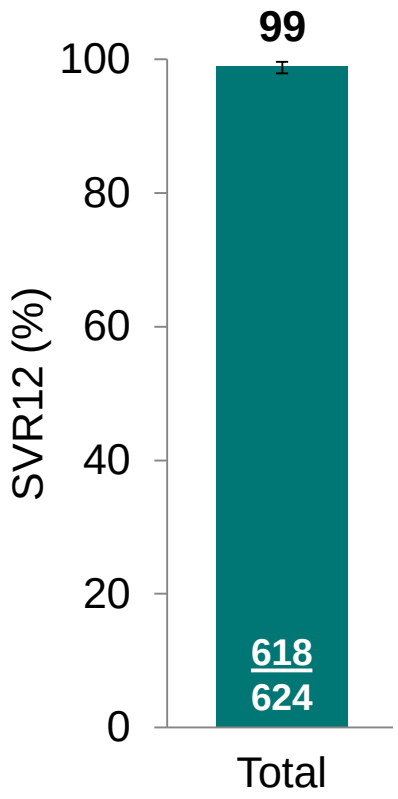
*Includes peg-IFN + RBV failures and PI + peg-IFN + RBV failures.

Results: HCV Genotype Distribution
ASTRAL-1

Patients, n (%)	Placebo n=116	SOF/VEL n=624
GT 1	65 (56)	328 (53)
1a	46 (40)	210 (34)
1b	19 (16)	118 (19)
GT 2	21 (18)	104 (17)
GT 4	22 (19)	116 (19)
GT 5*	0	35 (6)
GT 6	8 (7)	41 (7)

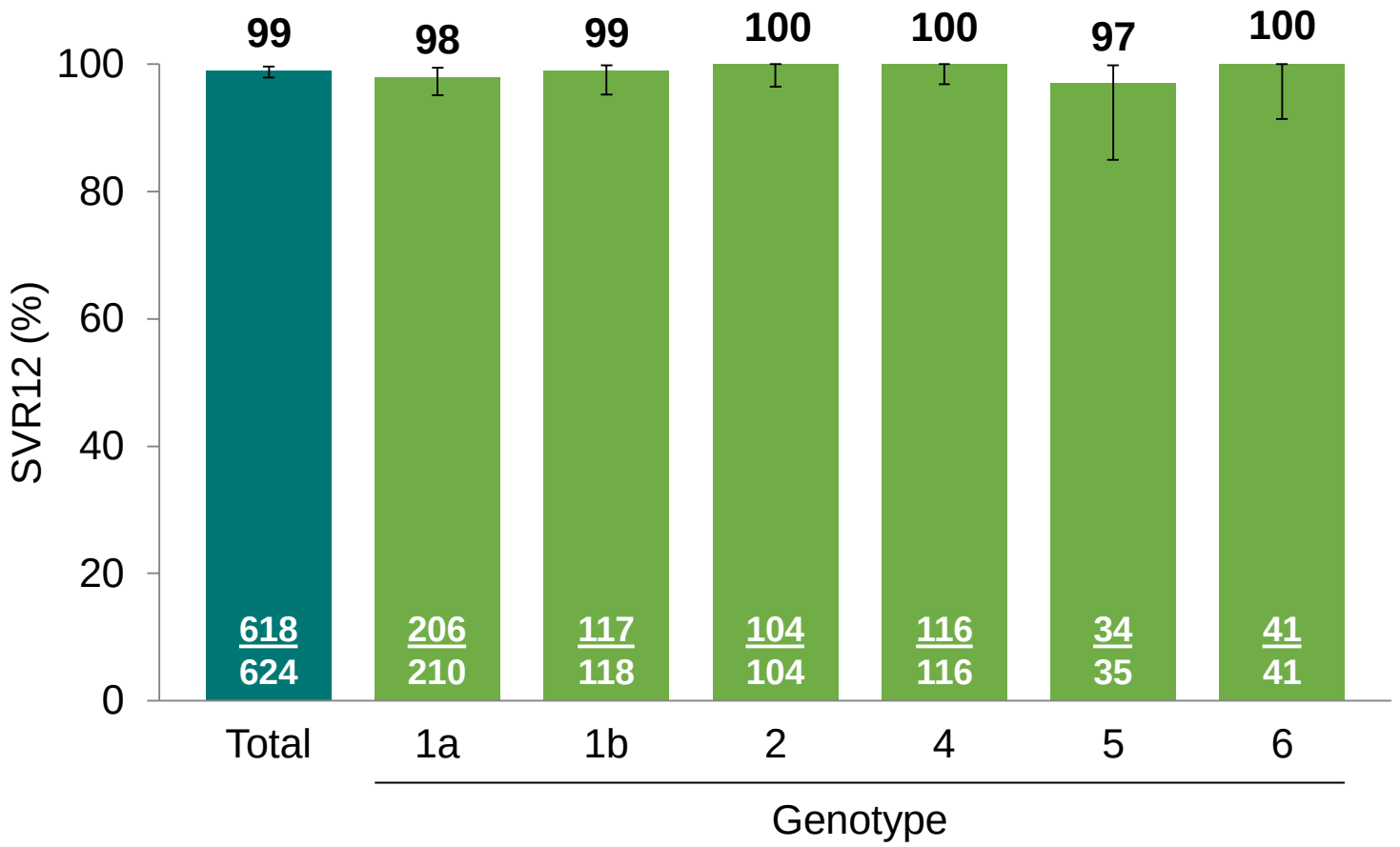
*All enrolled to SOF/VEL group.

Results: SVR12
ASTRAL-1, SOF/VEL



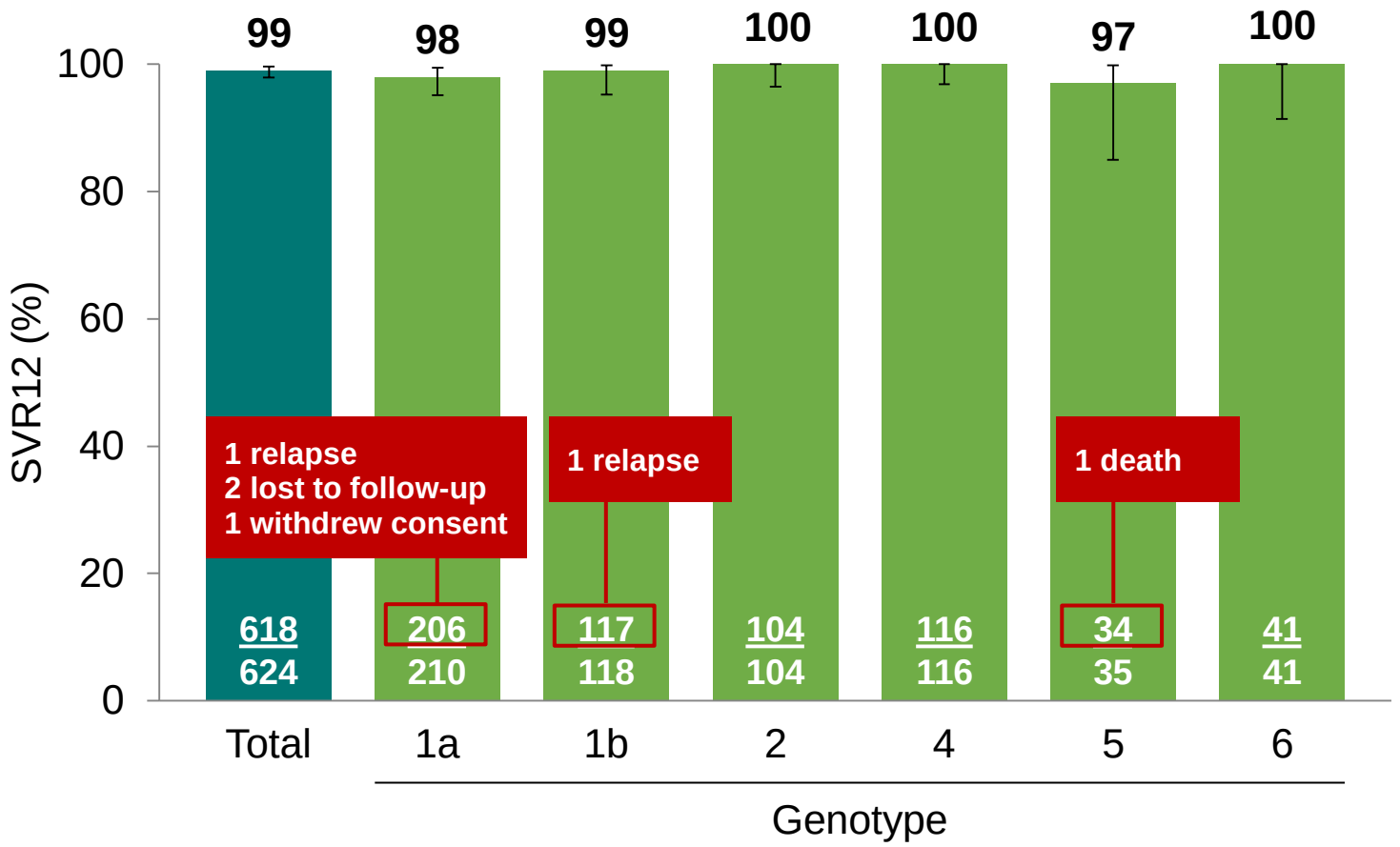
Error bars represent 95% confidence intervals.

Results: SVR12 by Genotype
ASTRAL-1, SOF/VEL



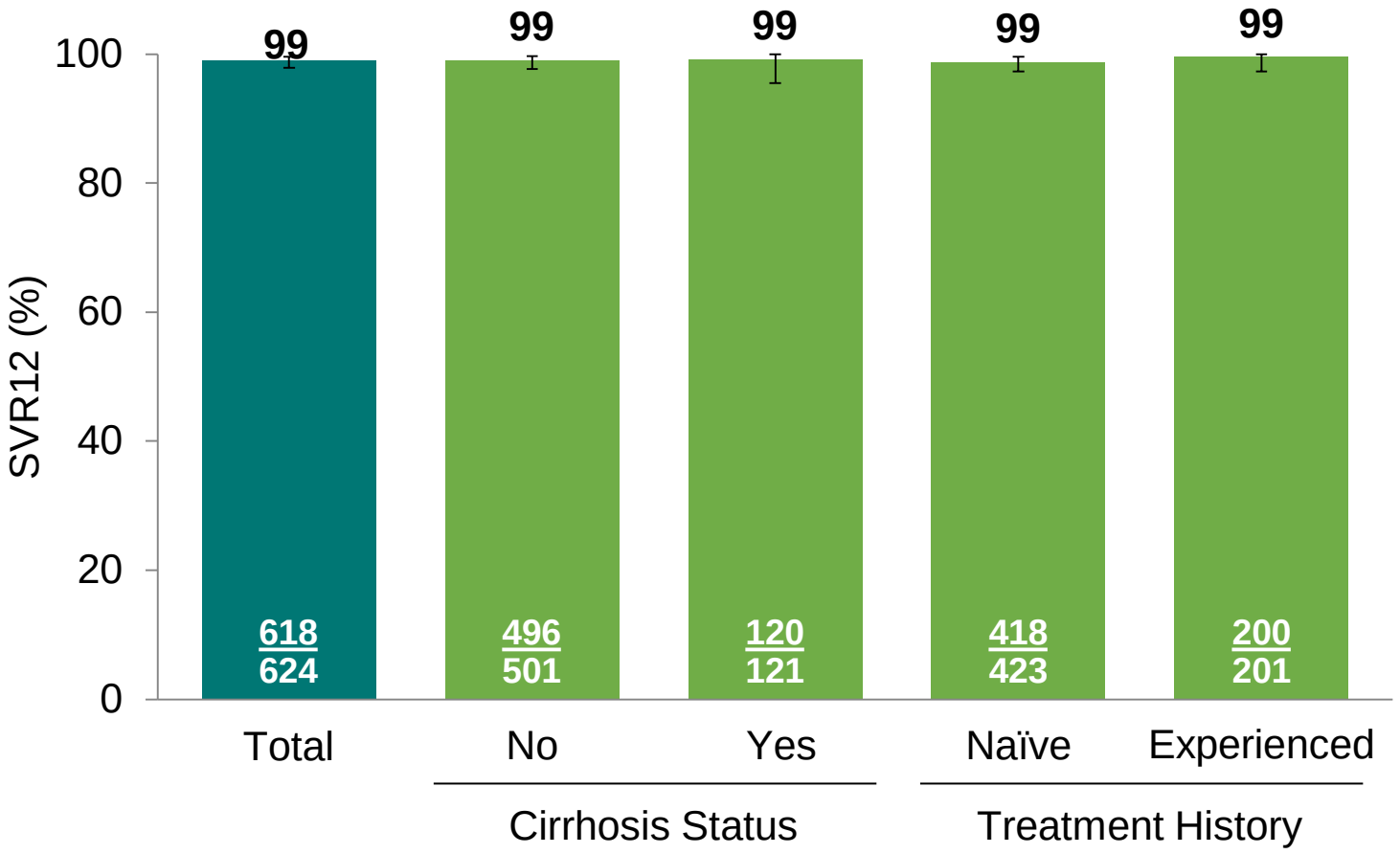
Error bars represent 95% confidence intervals.

Results: SVR12 by Genotype
ASTRAL-1, SOF/VEL



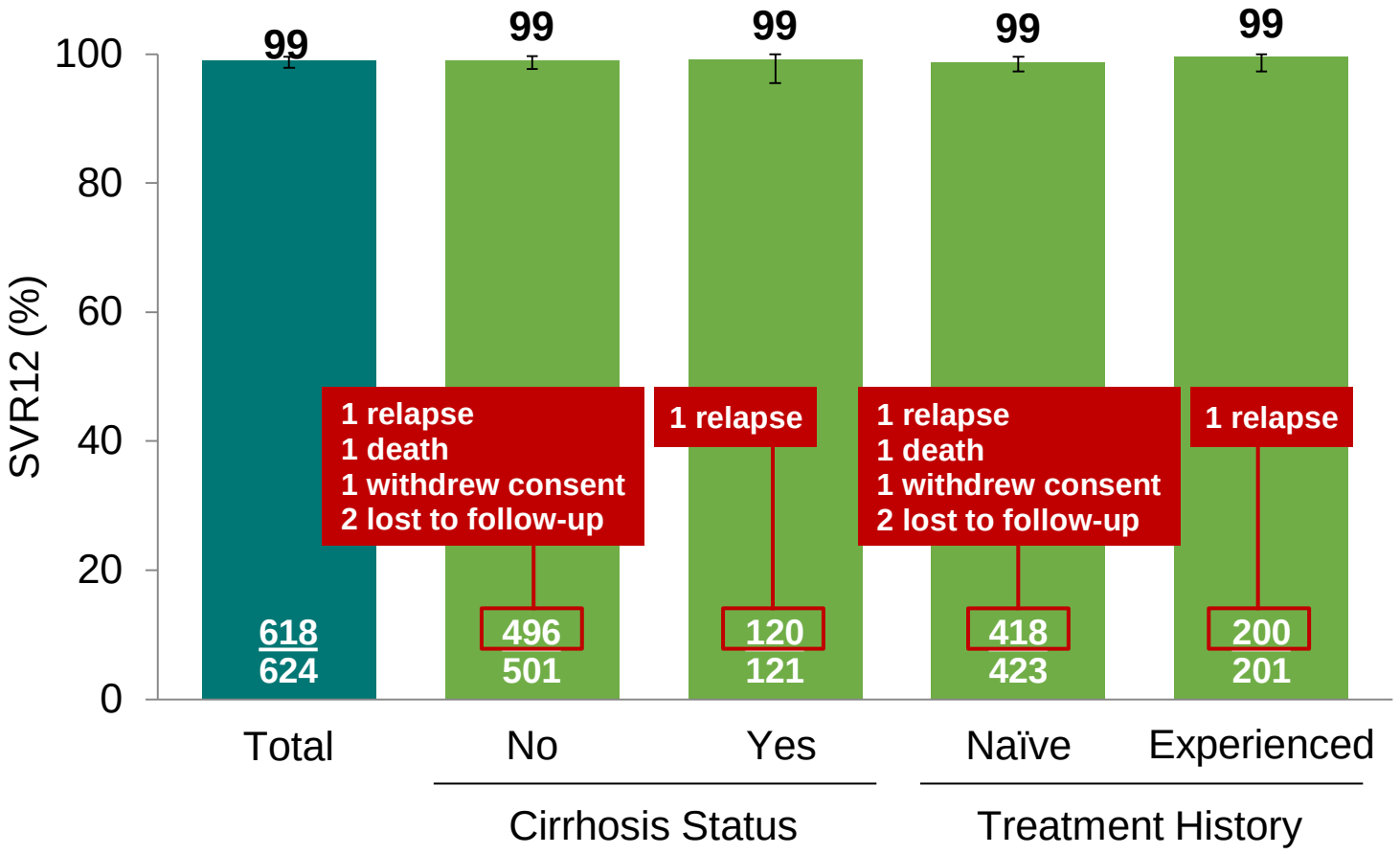
Error bars represent 95% confidence intervals.

Results: SVR12 by Cirrhosis or Prior Treatment
ASTRAL-1, SOF/VEL



Error bars represent 95% confidence intervals.

Results: SVR12 by Cirrhosis or Prior Treatment
ASTRAL-1, SOF/VEL



Error bars represent 95% confidence intervals.

Results: Safety
ASTRAL-1

	Patients, n (%)	Placebo n=116	SOF/VEL n=624
Adverse Events	AE	89 (77)	485 (78)
	Grade 3−4 AE	1 (<1)	18 (3)
	Serious AE	0	15 (2)
	D/C due to AE	2 (2)	1 (<1)
	Death	0	1 (<1)
Laboratory Abnormalities	Grade 3−4	14 (12)	45 (7)
	Hb <10 g/dL	0	2 (<1)
	Hb <8.5 g/dL	0	0

- 55-year-old white male died in sleep 8 days after completing treatment; death assessed as unrelated to study drug by investigator

Conclusions
ASTRAL-1

- Treatment with SOF/VEL for 12 weeks resulted in a 99% SVR12 rate in patients with HCV GT 1, 2, 4, 5, or 6 infection
  - 99% SVR12 rate in patients with cirrhosis
  - 99% SVR12 rate in patients with prior treatment failure
- Presence of baseline NS5A RAVs did not impact SVR12
- Treatment with SOF/VEL for 12 weeks was well tolerated, with a safety profile similar to that of placebo treatment
- SOF/VEL for 12 weeks provides a simple, safe, and highly effective treatment for patients with HCV GT 1, 2, 4, 5, or 6 infection

Acknowledgments

We extend our thanks to the patients and their families and all participating investigators:

USA: Nid Afdhal, Michael Bennett, Norbert Bräu, Stuart Cohen, Michael Curry, Mitchell Davis, Kyle Etzkorn, Gregory Everson, Steven Flamm, Norman Gitlin, Stuart Gordon, Curt Hagedorn, Robert Herring, Federico Hinestrosa, Ira Jacobson, Sonal Kumar, Eric Lawitz, Guiseppe Morelli, Timothy Morgan, Mindie Nguyen, Lisa Nyberg, David Pound, Mordechai Rabinovitz, K. Rajender Reddy, Maribel Rodriguez-Torres, Peter Ruane, Michael Ryan, Eugene Schiff, Thomas Sepe, Obaid Shaikh, Aasim Sheikh, Mitchell Shiffman, Mark Sulkowski, Paul Thuluvath, William Towner, Tram Tran, Kimberly Workowski, Ziad Younes BELGIUM: Christophe George, Christophe Moreno, Stefan Bourgeois CANADA: Brian Conway, Curtis Cooper, Jordan Feld, Stephen Shafran, Mark Swain, Bernard Willems, Eric Yoshida FRANCE: Armando Abergel, Laurent Alric, Tarik Asselah, Marc Bourliere, Victor De Ledinghen, Christophe Hezode, Veronique Loustaud-Ratti, Philippe Mathurin, Stanislas Pol, Didier Samuel, Fabien Zoulim GERMANY: Keikawus Arasteh, Thomas Berg, Guido Gerken, Tobias Goeser, Norbert Gruener, Michael Manns, Stefan Mauss, Joerg Petersen, Stefan Zeuzem HONG KONG: Henry Chan, Ching Lung Lai ITALY: Alessandra Mangia, Francesco Mazzotta UK: Kosh Agarwal, Richard Aspinall, Ashley Brown, Jane Collier, Matthew Cramp, Daniel Forton, Graham Foster, Raymond Fox, William Rosenberg, Stephen Ryder, Andrew Ustianowski

This study was funded by Gilead Sciences, Inc.

Back Up

The NEW ENGLAND JOURNAL of MEDICINE

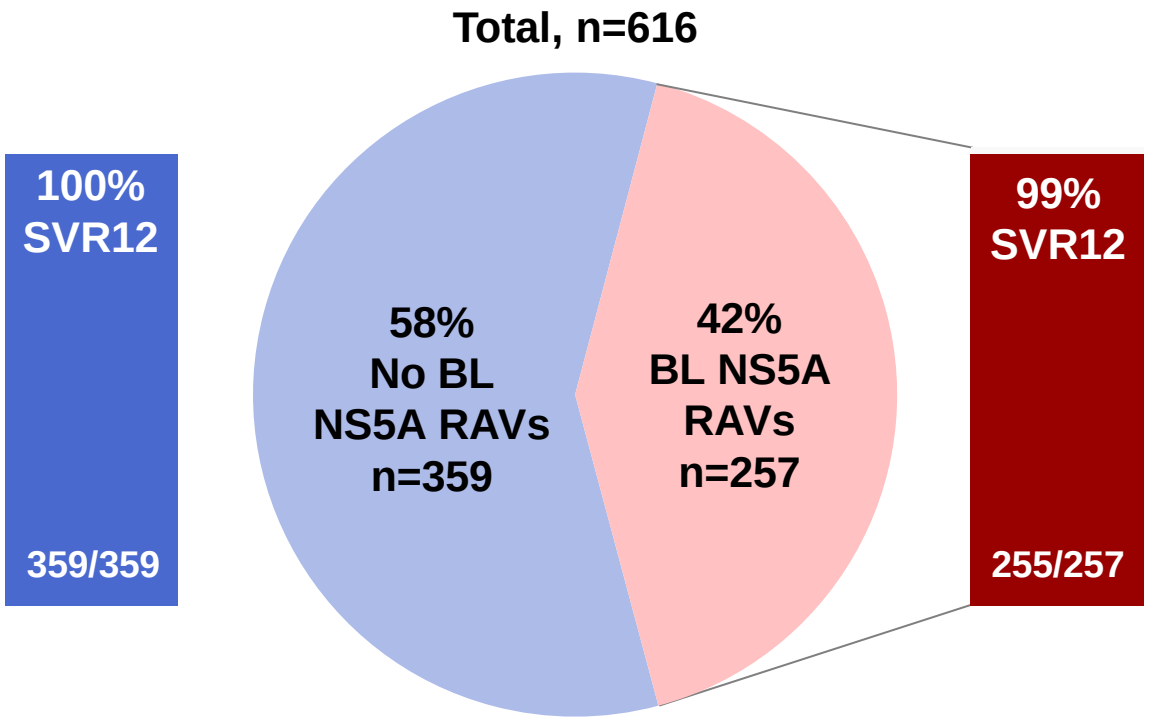
ORIGINAL ARTICLE

Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection

J.J. Feld, I.M. Jacobson, C. Hézode, T. Asselah, P.J. Ruane, N. Gruener, A. Abergel, A. Mangia, C.-L. Lai, H.L.Y. Chan, F. Mazzotta, C. Moreno, E. Yoshida, S.D. Shafran, W.J. Towner, T.T. Tran, J. McNally, A. Osinusi, E. Svarovskaia, Y. Zhu, D.M. Brainard, J.G. McHutchison, K. Agarwal, and S. Zeuzem, for the ASTRAL-1 Investigators*

Available at N Engl J Med. 2015 Dec 31;373(27):2599-607.

Results: Resistance Analysis (1% cut-off)
ASTRAL-1, SOF/VEL



Results: Disposition
ASTRAL-1

Patients, n (%)	Placebo n=116	SOF/VEL n=624
Completed study drug	113 (97)	622 (99)
Discontinued	3 (3)	2 (<1)
AE	2 (2)	1 (<1)
Investigator decision*	1 (<1)	0
Lost to follow-up	0	1 (<1)

*Due to poor venous access.

Results: Adverse Events in ≥10%
ASTRAL-1

Adverse Event, n (%)	Placebo n=116	SOF/VEL n=624
Headache	33 (28)	182 (29)
Fatigue	23 (20)	126 (20)
Nasopharyngitis	12 (10)	79 (13)
Nausea	13 (11)	75 (12)

Study Methods
ASTRAL-1

- HCV genotyping
  - Versant HCV genotype LiPA 2.0
  - TruGene
- HCV RNA
  - COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0 with LLOQ of 15 IU/mL
- HCV deep sequencing
  - Illumina MiSeq platform (1% cut-off)
- Cirrhosis
  - Liver biopsy Metavir stage 4 or Ishak stage 5 or 6, or
  - Fibrotest >0.75 and APRI >2, or
  - Fibroscan >12.5 kPa

Study Endpoints
ASTRAL-1

- Primary endpoint: SVR12
  - HCV RNA <LLOQ at post-treatment Week 12
- Efficacy analysis
  - Superiority to an SVR12 goal of 85%
- Safety
  - AEs and discontinuations
  - Laboratory abnormalities