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HCV: Highlights From EASL 2013

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HCV: Highlights From EASL 2013

- Current treatments
- Upcoming treatments
- Future regimens

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Abstract 60

SVR12 Rates and Safety of Triple Therapy Including Telaprevir or Boceprevir in 221 Cirrhotic Non Responders Treated in The French Early Access Program (ANRS CO20-CUPIC)

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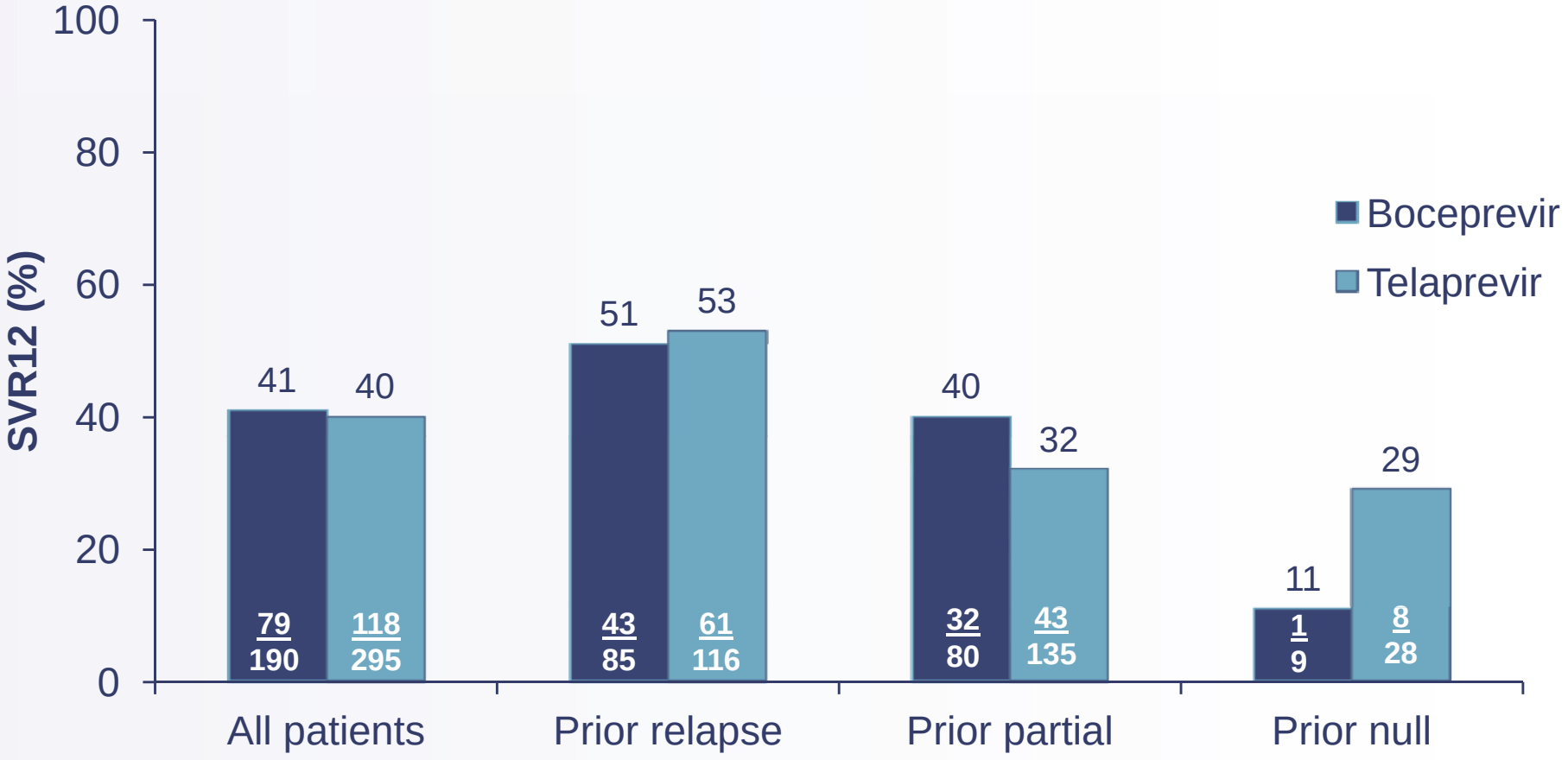
CUPIC: French early access program

- EASL 2012 report: increased SAEs and deaths
- Design: cohort study
  - Selection of boceprevir or telaprevir made by the clinician
- Patients
  - Genotype 1
  - Patients with compensated cirrhosis
    - Approximately 1/3 would not have qualified for phase 3 trials
  - Prior relapse and partial response
- Regimens
  - Standard protocols for boceprevir (lead-in) and telaprevir
  - 48 weeks for all patients

H. Fontaine et al, Abstract 60. EASL, April 2013

CUPIC SVR12 Results



H. Fontaine et al, Abstract 60. EASL, April 2013

CUPIC: French early access program

- Predictors of response
  - Prior relapse > prior partial/null response
  - Genotype 1b > 1a

H. Fontaine et al, Abstract 60. EASL, April 2013

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Abstract 60

CUPIC: Safety Findings

Patients, n (% patients with at least one event)	Telaprevir n=295	Boceprevir n=190
Serious adverse events (SAEs)	535 in 160 patients (54.2%)	321 in 97 patients (51.0%)
Premature discontinuation / Due to SAEs	139 (47.1%) / 63 (21.3%)	80 (42.1%) / 27 (14.2%)
Death	7 (2.4%)	3 (1.6%)
Infection (Grade 3/4)	27 (9.1%)	8 (4.2%)
Hepatic decompensation (Grade 3/4)	15 (5.1%)	9 (4.7%)
Anemia (Grade 3/4 : Hb < 8 g/dL)	38 (12.9%)	19 (10%)
Rash (Grade 3/SCAR)	16 (5.4%) / 2 (0.6%)	2 (1.0%) / 0
EPO use / Blood transfusion	168 (57%) / 53 (18%)	119 (62.6%) / 26 (13.7%)
GCSF use	8 (2.7%)	13 (6.8%)
TPO use	6 (2%)	3 (1.6%)

SCAR: severe cutaneous adverse reaction

Fontaine H, et al. 48th EASL; Amsterdam, Netherlands; April 24-28, 2013. Abstract 60

CUPIC: French early access program

- Large “real life” cohort of patients with cirrhosis
- SVR_{12} rate comparable to subgroup of patients with severe fibrosis or cirrhosis of phase III studies
- Increased risk of serious adverse events, particularly severe infections and anemia

H. Fontaine et al, Abstract 60. EASL, April 2013

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Abstract 65

Safety of Triple Therapy With Telaprevir or Boceprevir in Hepatitis C Patients With Advanced Liver Disease - Predictive Factors For Sepsis

K. Rutter[1]*, *A. Ferlitsch*[1], *A. Maieron*[2], *A.F. Stättermayer*[1], *I. Graziadei*[3], *M. Dulic*[4], *M. Gschwantler*[4], *R. Stauber*[5], *H. Hofer*[1], *M. Peck-Radosavljevic*[1], *W. Vogel*[3], *M. Trauner*[1], *P. Ferenci*[1]

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Predictive factors for sepsis

- 110 genotype 1 patients
- Boceprevir or telaprevir regimen x 48 weeks
- Serious adverse events: 22 (20%)
  - Severe infections: 11
- Predictors of severe infection
  - Platelet count < 100,000/L: 13.4% vs. 8.7%, P< 0.05
  - Serum albumin < 3.5g/dL: 55.6% vs. 5.4%, P< 0.05
  - Hepatovenous pressure gradient (HVPG) measurement
    - available in 27 patients with cirrhosis
    - HVPG ≥ 10 mm Hg: 6/18 infections
    - HPVG < 10 mm Hg: 0/9 infections

K. Rutter et al, Abstract 65. EASL, April 2013

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Abstract 818

High SVR Rates (SVR4) For 12-week Total Telaprevir Combination Therapy In IL28b CC Treatment-Naïves And Prior Relapsers With G1 Chronic Hepatitis C: CONCISE Interim Analysis

D.R. Nelson[1]*, *F. Poordad*[2], *J.J. Feld*[3], *M.W. Fried*[4], *I.M. Jacobson*[5], *P.J. Pockros*[6], *M.S. Sulkowski*[7], *S. Zeuzem*[8], *L. Bengtsson*[9], *S. George*[9], *M.I. Friedman*[9], *on behalf of the CONCISE Study Team*

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CONCISE

- Patients
  - IL28B CC (favorable genotype)
  - Treatment-naïve or prior relapse
  - No cirrhosis
- Treatment
  - Peginterferon alfa-2a 180 mcg subcu weekly
  - Ribavirin 1000/1200 mg daily
  - Telaprevir 1125 mg bid
- Regimen
  - Patients with RVR were randomized 2:1 at week 12
    - T12/PR12
    - T12/PR24

D.R. Nelson et al, Abstract 818. EASL, April 2013

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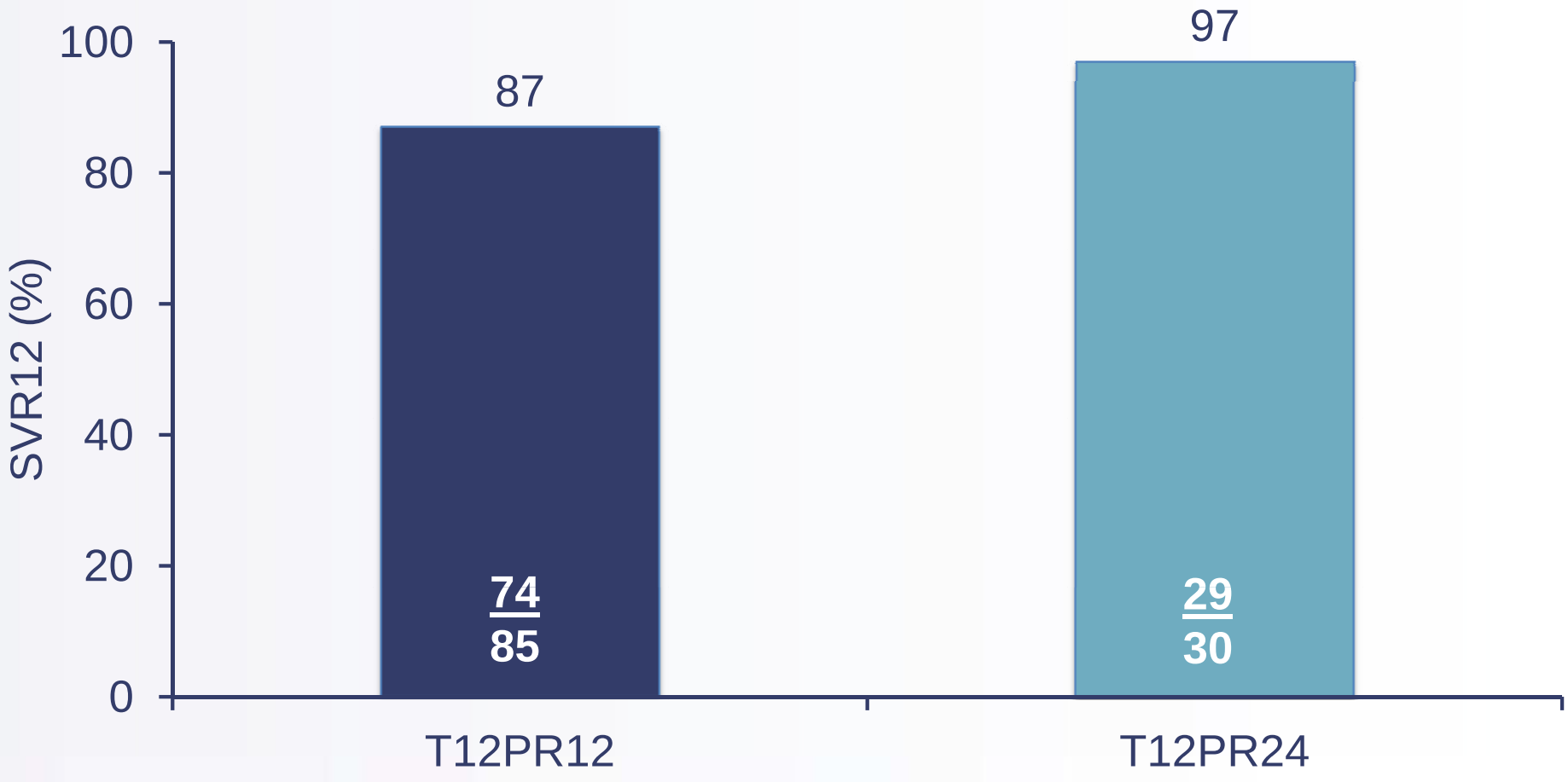
Abstract 818

CONCISE Interim SVR12



D.R. Nelson et al, Abstract 818. EASL, April 2013

CONCISE

- Conclusion
  - High SVR rates from the CONCISE study interim analysis suggest the potential for the defined IL28B CC patients with RVR to shorten duration of telaprevir plus peginterferon/ribavirin to 12 weeks

D.R. Nelson et al, Abstract 818. EASL, April 2013

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Abstract 5

Phase 3 Randomized Controlled Trial Of All-Oral Treatment With Sofosbuvir+Ribavirin For 12 Weeks Compared To 24 Weeks Of PEG+Ribavirin In Treatment-Naïve GT2/3 HCV-Infected Patients (FISSION)

E. Gane[1]*, *E. Lawitz*[2], *M. Rodriguez-Torres*[3], *S. Gordon*[4], *H. Dvory-Sobol*[5], *S. Arterburn*[5], *J. McNally*[5], *D.M. Brainard*[5], *W.T. Symonds*[5], *J.G. McHutchison*[5], *A. Sheikh*[6], *A. Mangia*[7]

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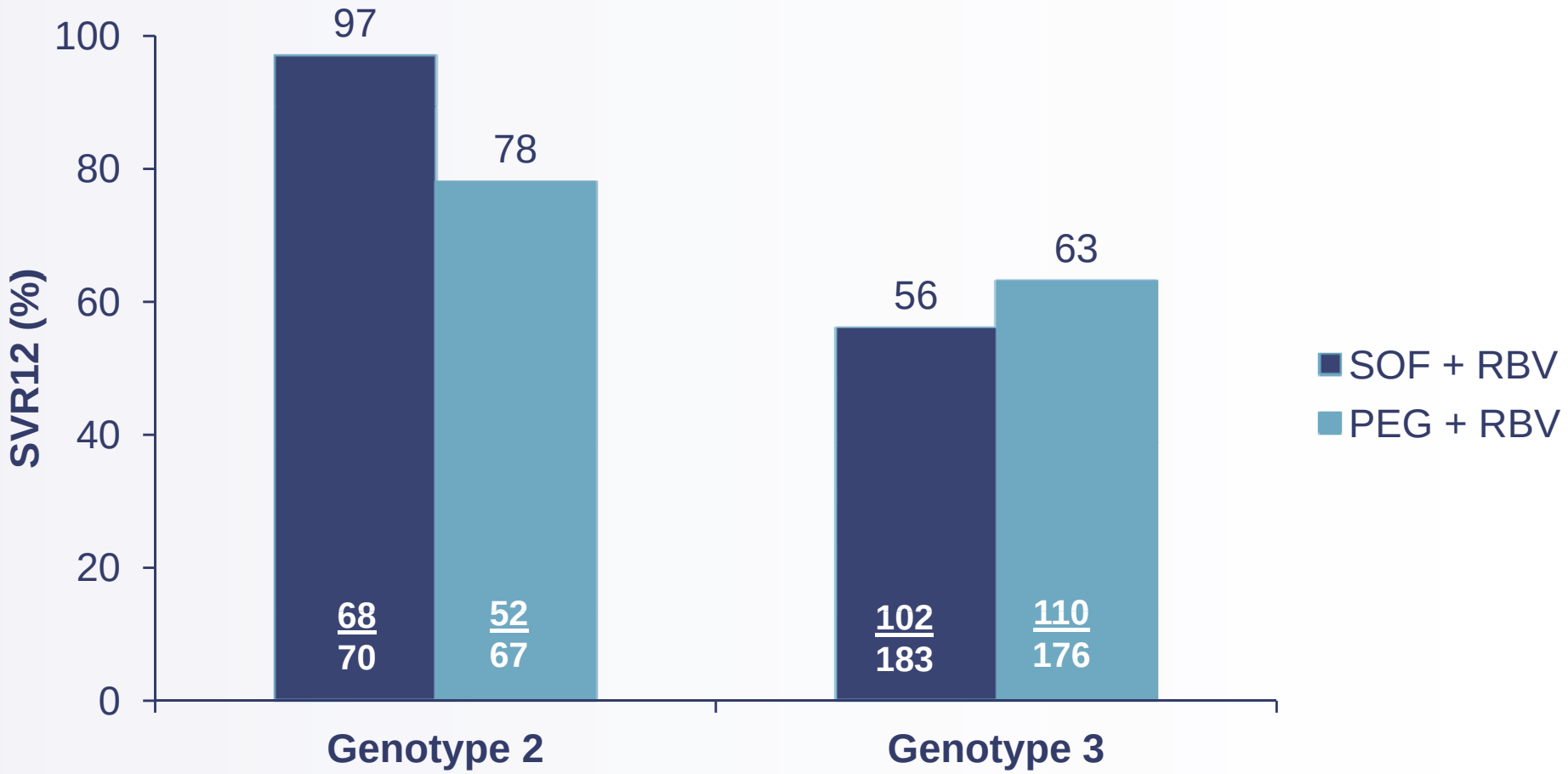
FISSION

- Phase 3 study
- Sofosbuvir (GS-7977): nucleoside polymerase inhibitor
  - Favorable administration profile
    - Once daily, no food effect
    - No drug-drug interactions
- Patients
  - Genotype 2/3 treatment naive
  - 20% cirrhosis
- Regimen
  - Sofosbuvir 400 mg qd + ribavirin 1000/1200 mg for 12 weeks
  - Peginterferon alfa-2a 180 mcg + ribavirin 800 mg for 24 weeks

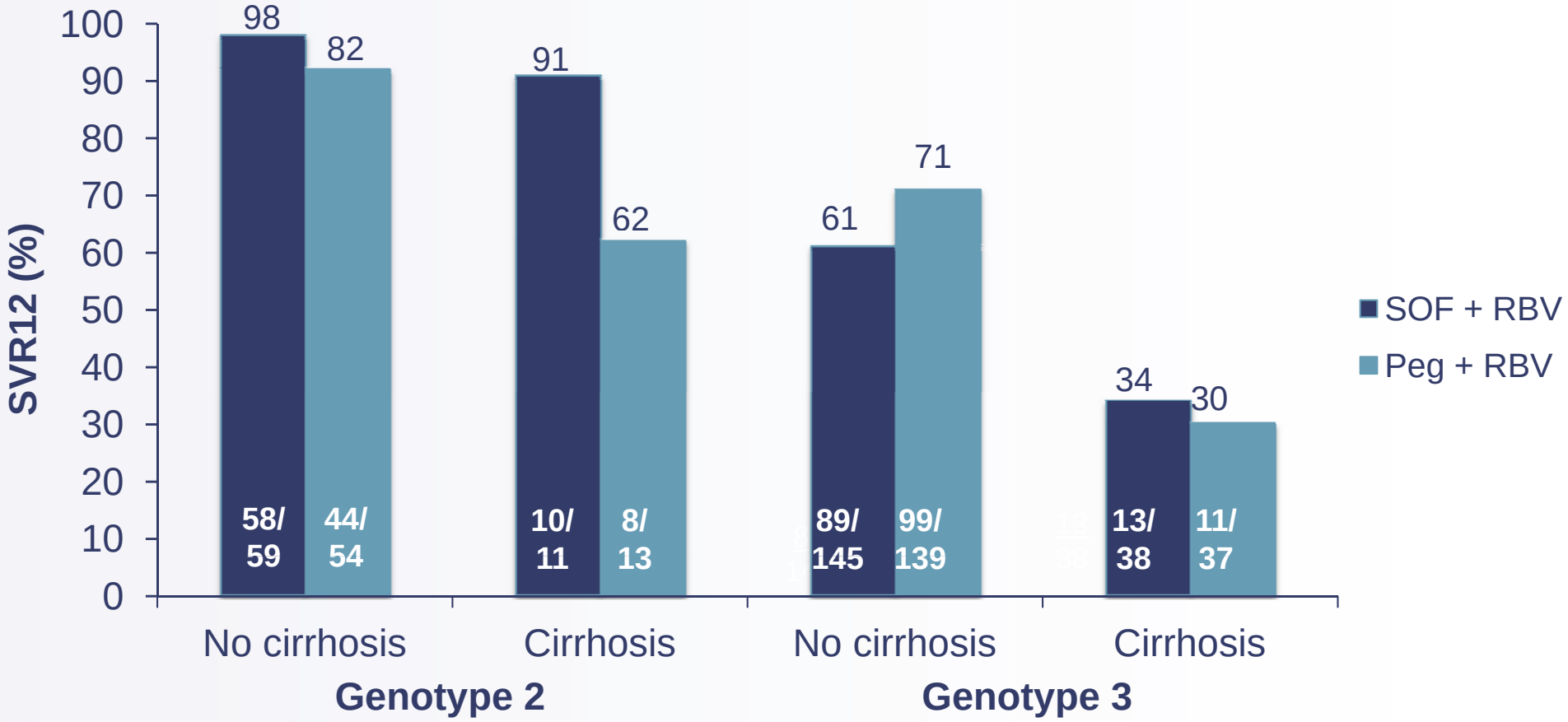
E. Gane et al, Abstract 5. EASL, April 2013; Lawitz et al., N Engl J Med 2013. DOI: 10.1056/NEJMoa1214853

FISSION: SVR12 by genotype



E. Gane et al, Abstract 5. EASL, April 2013; Lawitz et al., N Engl J Med 2013. DOI: 10.1056/NEJMoa1214853

FISSION: SVR12 by genotype and cirrhosis/no cirrhosis



E. Gane et al, Abstract 5. EASL, April 2013; Lawitz et al., N Engl J Med 2013. DOI: 10.1056/NEJMoa1214853

FISSION

- Sequencing
  - 79 SOF + RBV patients who did not achieve SVR12
  - No resistance associated variants (S282T)
- Safety summary

	SOF + RBV	PEG + RBV
Grade 3-4 Adverse events	7%	19%
Serious adverse events	3%	1%
D/C due to adverse events	1%	11%
Hemoglobin <10 gm/dL	9%	15%
Neutrophils <750/mm^3	0%	15%
Platelets <50,000/mm^3	0%	7%

E. Gane et al, Abstract 5. EASL, April 2013; Lawitz et al., N Engl J Med 2013. DOI: 10.1056/NEJMoa1214853

FISSION

- Conclusions
  - SOF + RBV (12 weeks) led to excellent results (SVR12 > 90%) in genotype 2 patients with and without cirrhosis
  - SOF + RBV (12 weeks) led to similar results as PEG + RBV (24 weeks) for genotype 3 patients
    - Lowest rates observed in patients with cirrhosis
    - Strategies to improve genotype 3 results are needed
  - SOF + RBV well tolerated with fewer adverse events than PEG + RBV

E. Gane et al, Abstract 5. EASL, April 2013; Lawitz et al., N Engl J Med 2013. DOI: 10.1056/NEJMoa1214853

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Abstract 1411

Sofosbuvir + Peginterferon + Ribavirin For 12 Weeks Achieves 90% SVR12 In Genotype 1, 4, 5, Or 6 HCV Infected Patients: The NEUTRINO Study

E. Lawitz[1]*, *D. Wyles*[2], *M. Davis*[3], *M. Rodriguez-Torres*[4], *K.R. Reddy*[5], *K.V. Kowdley*[6], *E. Svarovskaia*[7], *D. Jiang*[7], *J. McNally*[7], *D.M. Brainard*[7], *W.T. Symonds*[7], *J.G. McHutchison*[7], *L. Nyberg*[8], *Z. Younossi*[9]

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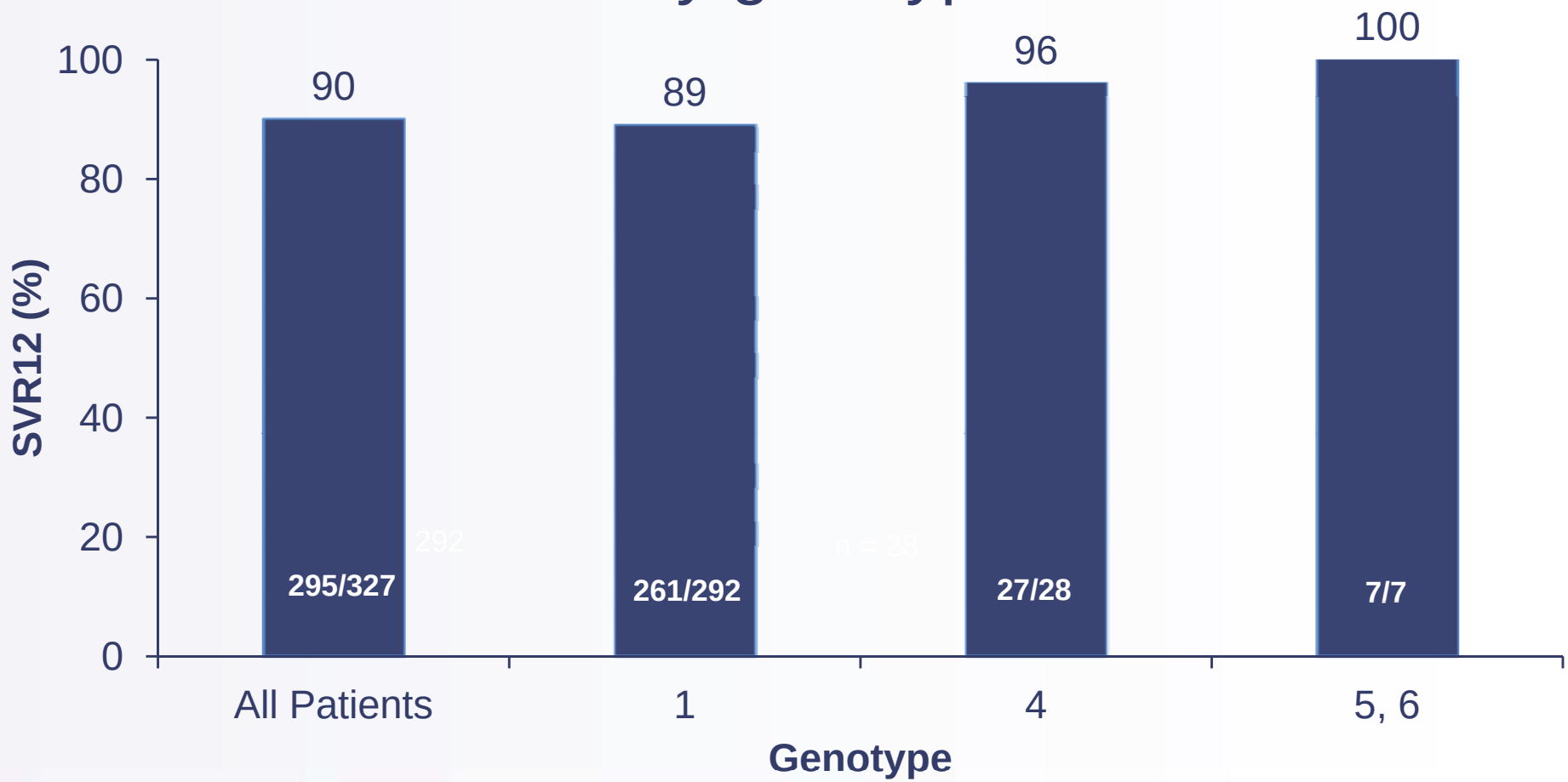
NEUTRINO

- Sofosbuvir (GS-7977)
- Patients
  - Genotypes 1, 4, 5, 6 treatment naive
  - 17% compensated cirrhosis
  - 17% black
  - 29% IL28B genotype CC
- Regimen for all patients
  - Sofosbuvir 400 mg qd
  - Ribavirin 1000/1200 mg
  - Peginterferon alfa-2a 180 mcg weekly
- Duration: 12 weeks

E. Lawitz et al, Abstract 1411. EASL, April 2013; Lawitz et al., N Engl J Med 2013. DOI: 10.1056/NEJMoa1214853

NEUTRINO: SVR12 by genotype



E. Lawitz et al, Abstract 1411. EASL, April 2013; Lawitz et al., N Engl J Med 2013. DOI: 10.1056/NEJMoa1214853

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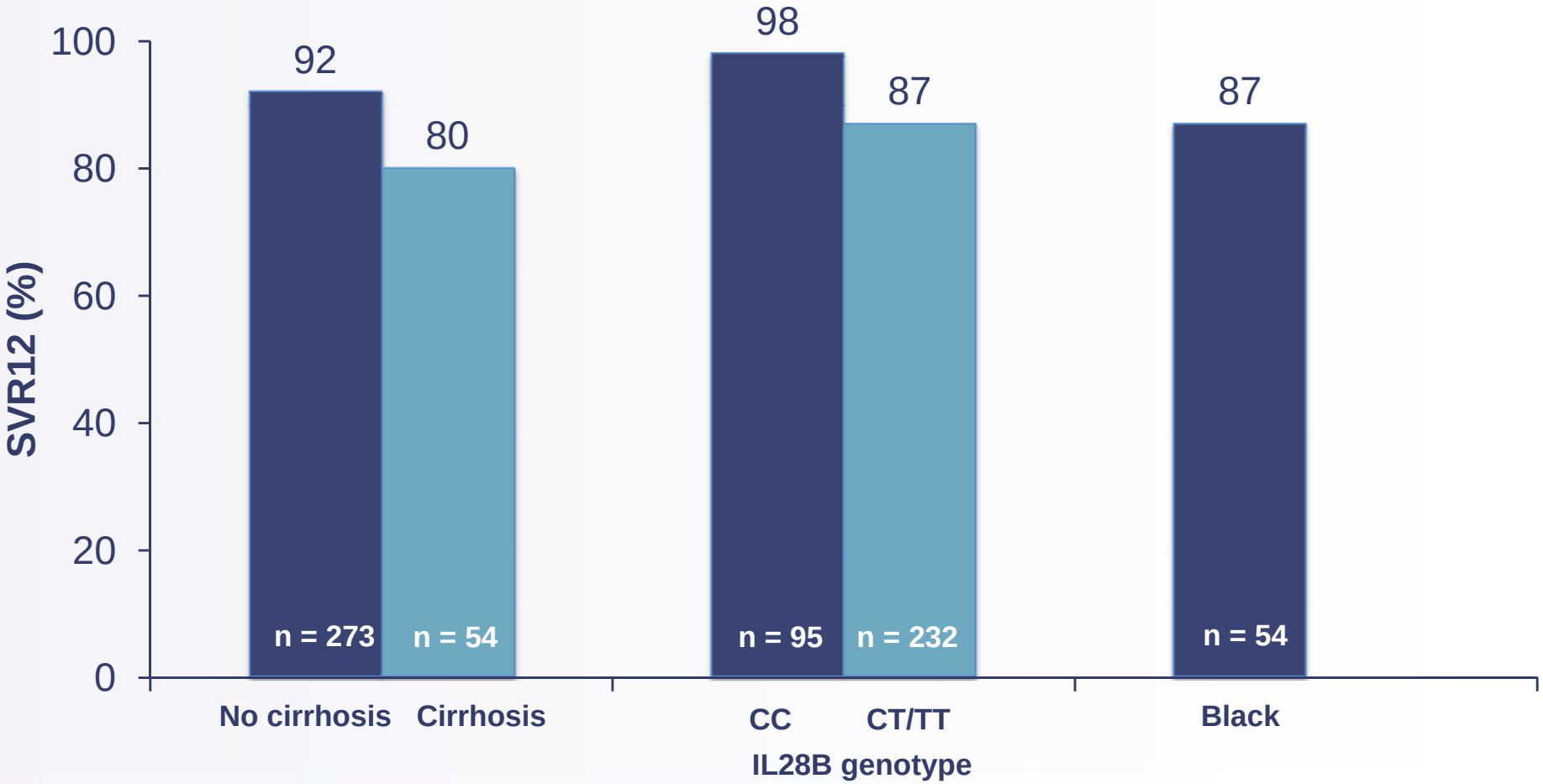
Abstract 1411

NEUTRINO: SVR12 rates by subgroups



E. Lawitz et al, Abstract 1411. EASL, April 2013; Lawitz et al., N Engl J Med 2013. DOI: 10.1056/NEJMoa1214853

Conclusions

- 12 weeks of treatment with SOF + PEG-IFN + RBV achieved 90% SVR12 in treatment naïve patients with HCV genotype 1, 4, 5, or 6
- 99% of patients had HCV RNA < LLOQ by treatment week 4 and relapse accounted for all virologic failures
- This regimen was well tolerated

E. Lawitz et al, Abstract 1411. EASL, April 2013; Lawitz et al., N Engl J Med 2013. DOI: 10.1056/NEJMoa1214853

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Abstract 1425

Simeprevir (TMC435) with peginterferon/ribavirin for chronic HCV genotype-1 infection in treatment naïve patients: results from QUEST-1, a phase III trial

I. Jacobson[1]*, *G.J. Dore*[2], *G.R. Foster*[3], *M.W. Fried*[4], *M. Radu*[5], *V.V. Rafalskiy*[6], *L. Moroz*[7], *A. Craxì*[8], *M. Peeters*[9], *O. Lenz*[9], *S. Ouwerkerk-Mahadevan*[10], *R. Kalmeijer*[11], *M. Beumont-Mauviel*[9]

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QUEST-1

- Simeprevir: potent, once-daily, oral HCV NS3/4A protease inhibitor
- Phase III, randomized, double-blind, placebo-controlled trial
- Patients
  - Treatment naïve genotype 1 infection
- Regimen
  - PEG + RBV + simeprevir 150 mg qd
  - PEG + RBV + placebo
- Algorithm
  - Simeprevir for first 12 weeks
  - Response guided therapy
    - RVR: PEG/RBV x 24 weeks
    - No RVR: PEG/RBV x 48 weeks

I. Jacobson et al, Abstract 1425. EASL, April 2013

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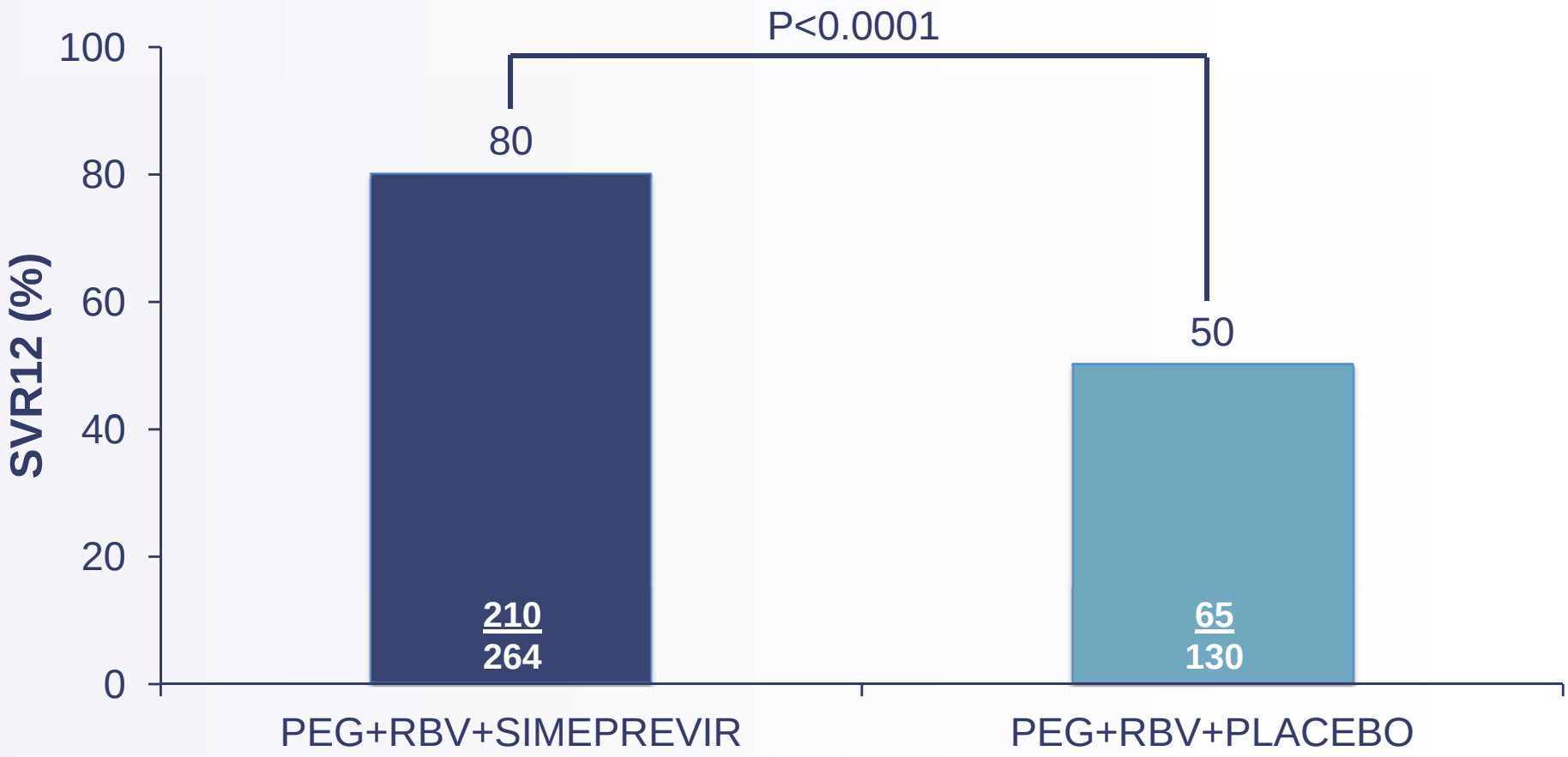
Abstract 1425

QUEST-1: SVR12 rates



I. Jacobson et al, Abstract 1425. EASL, April 2013

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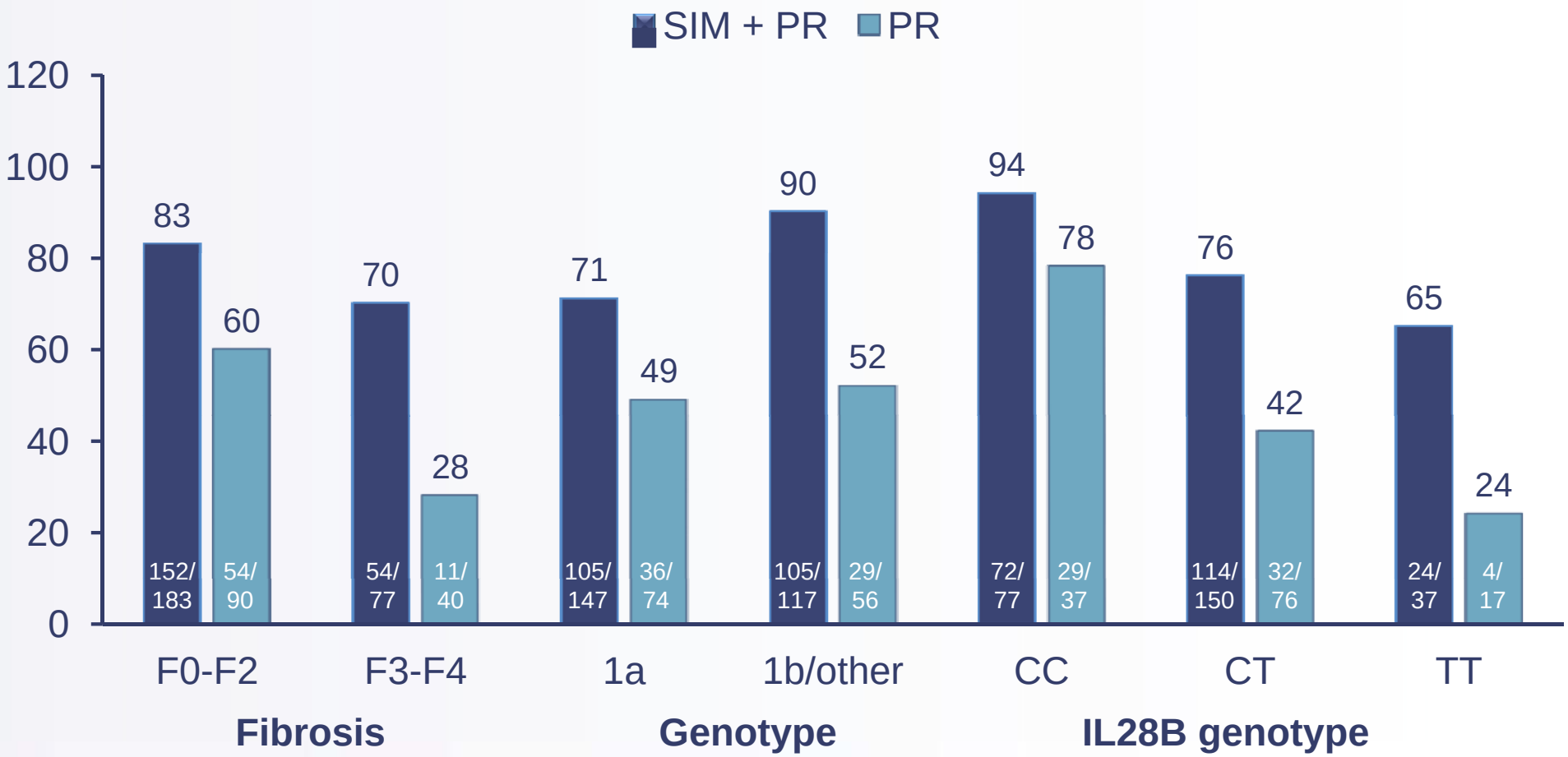
Abstract 1425

QUEST-1: SVR12 rates in subgroups



I. Jacobson et al, Abstract 1425. EASL, April 2013

QUEST-1 Conclusions

- Simeprevir 150 mg + PEG/RBV was highly effective against HCV genotype 1 treatment naïve patients with SVR12 (80%)
- Most patients (85%) receiving simeprevir were able to shorten therapy to 24 weeks
- Simeprevir 150 mg + PEG/RBV was generally well tolerated
  - Rates of anemia and rash were similar in the simeprevir and placebo groups

I. Jacobson et al, Abstract 1425. EASL, April 2013

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Abstract 1416

Faldaprevir Plus Pegylated Interferon Alfa-2a and Ribavirin In Chronic HCV Genotype-1 Treatment-Naïve Patients: Final Results From STARTVerso1, A Randomised, Double-blind, Placebo-controlled Phase III Trial

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STARTVerso1

- Faldaprevir (FDV) is a once-daily NS3/4A protease inhibitor
- Phase III, randomized, double-blind, placebo-controlled trial
- Patients
  - Treatment naïve genotype 1 infection
  - 78% Caucasian, 20% Asian
  - 39% IL28B CC
  - 66% genotype 1b
- Regimen
  - PEG + RBV for 24 weeks plus
    - Placebo for 24 weeks
    - Faldaprevir 120 mg qd
    - Faldaprevir 240 mg qd
  - Patients with early treatment success (ETS, HCV RNA < 25IU/mL at Week 4 and undetectable at Week 8) in Arms 2 and 3 stopped all treatment at Week 24
  - Patients without ETS and those in Arm 1 received PegIFN/RBV for 48 weeks.

P. Ferenci et al, Abstract 1416. EASL, April 2013

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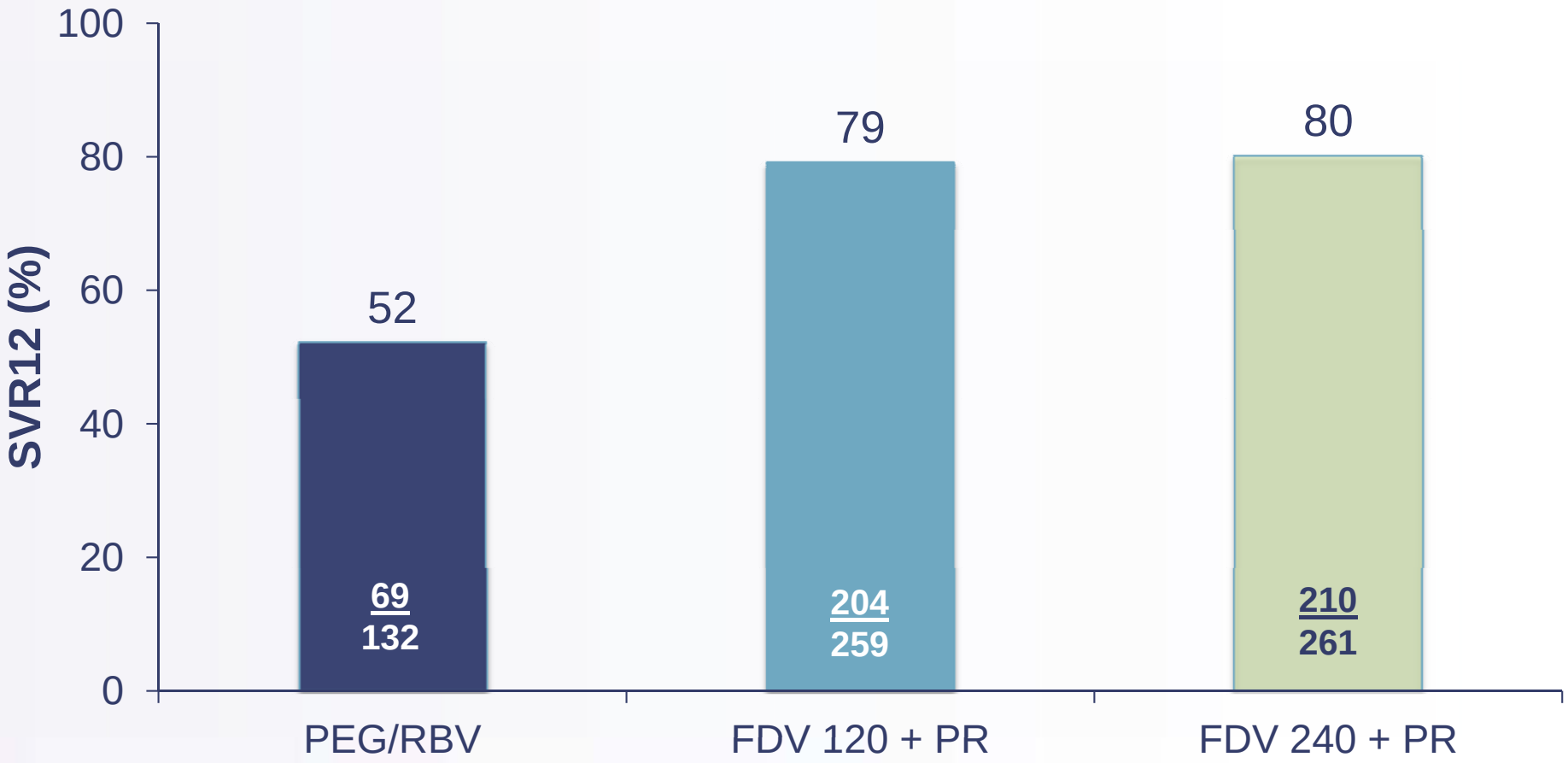
Abstract 1416

STARTVerso1 SVR12 rates



P. Ferenci et al, Abstract 1416. EASL, April 2013

STARTVerso1 Conclusions

- FDV plus PegIFN/RBV significantly increased SVR12 rates in HCV GT-1 patients in Europe and Japan compared with PegIFN/RBV
- In total, 88% of patients treated with FDV were eligible to stop all treatment at Week 24
- FDV plus PegIFN/RBV was well tolerated

P. Ferenci et al, Abstract 1416. EASL, April 2013

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Abstract 3

Safety and Efficacy of Interferon-free Regimens of ABT-450/R, ABT-267, ABT-333 +/- Ribavirin In Patients With Chronic HCV GT1 Infection: Results From The AVIATOR Study

K.V. Kowdley[1]*, *E. Lawitz*[2], *F. Poordad*[2], *D.E. Cohen*[3], *D. Nelson*[4], *S. Zeuzem*[5], *G.T. Everson*[6], *P. Kwo*[7], *G.R. Foster*[8], *M. Sulkowski*[9], *W. Xie*[3], *L. Larsen*[3], *A. Khatri*[3], *T. Podsadecki*[3], *B. Bernstein*[31]

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AVIATOR

- Phase 2, randomized, open-label, multicenter study
- Patients
  - Genotype 1 (66% genotype 1a)
  - Treatment-naïve and prior null response
  - Non-cirrhotic
- Medications
  - ABT-450/r (HCV protease inhibitor boosted with ritonavir 100 mg)
  - ABT-267 (NS5A inhibitor)
  - ABT-333 (non-nucleoside NS5B inhibitor)
  - Ribavirin
- Duration
  - 8, 12 and 24 weeks

K.V. Kowdley et al, Abstract 3. EASL, April 2013

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Abstract 3

Treatment naive

N	Regimen/duration	SVR12 (%)	SVR24** (%)	VBT/ Relapse
80	ABT450 ABT267 ABT333 RBV	89	88	0/10
41	ABT450 ABT333 RBV	85	83	1/4
79	ABT450 ABT267 RBV	91	89	1/8
79	ABT450 ABT267 ABT333	90	87	1/5
79	ABT450 ABT267 ABT333 RBV	99	96	0/1
80	ABT450 ABT267 ABT333 RBV	93	90	0/2

Week 8 12 24

Null response

N	Regimen/duration	SVR12 (%)	SVR24 (%)	VBT/ Relapse
45	ABT450 ABT267 RBV	89	89	0/5
45	ABT450 ABT267 ABT333 RBV	93	93	3/0
43	ABT450 ABT267 ABT333 RBV	98	95	1/0

** 8 patients who achieved SVR12 did not return > 24 weeks and were counted as virological failures for SVR24
3 patients relapsed between SVR12 and SVR24

K.V. Kowdley et al, Abstract 3. EASL, April 2013

AVIATOR Conclusions

- Comparable SVR12 and 24 seen with 12 and 24 weeks of treatment
  - Selection of a 12-week duration of therapy in these populations
- SVR rates >90% were achieved in naïve and prior null responder patients with a 3-DAA+RBV regimen
  - No clinically meaningful differences were observed by sex, HCV subtype, IL28B genotype, baseline HCV-RNA or severity of fibrosis.

K.V. Kowdley et al, Abstract 3. EASL, April 2013

International Coalition of Hepatology Education Providers

Abstract 1417

Sustained Virologic Response With Daclatasvir Plus Sofosbuvir ± Ribavirin (RBV) In Chronic HCV Genotype (Gt) 1-infected Patients Who Previously Failed Telaprevir (TVR) or Boceprevir (BOC)

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Background

- Patients who experience virologic failure on telaprevir or boceprevir-based regimens currently have no treatment options
- Daclatasvir (DCV): NS5A inhibitor
- Sofosbuvir (SOF): nucleotide NS5B polymerase inhibitor
- DCV plus SOF with or without RBV achieved SVR4 in 98% of 126 HCV GT 1-infected treatment-naive patients (Sulkowski et al. AASLD 2012)

Aim:

- To evaluate the efficacy and safety of DCV plus SOF with or without RBV for 24 weeks in HCV GT 1-infected patients who failed prior treatment with TVR or BOC + pegIFN-alfa/RBV

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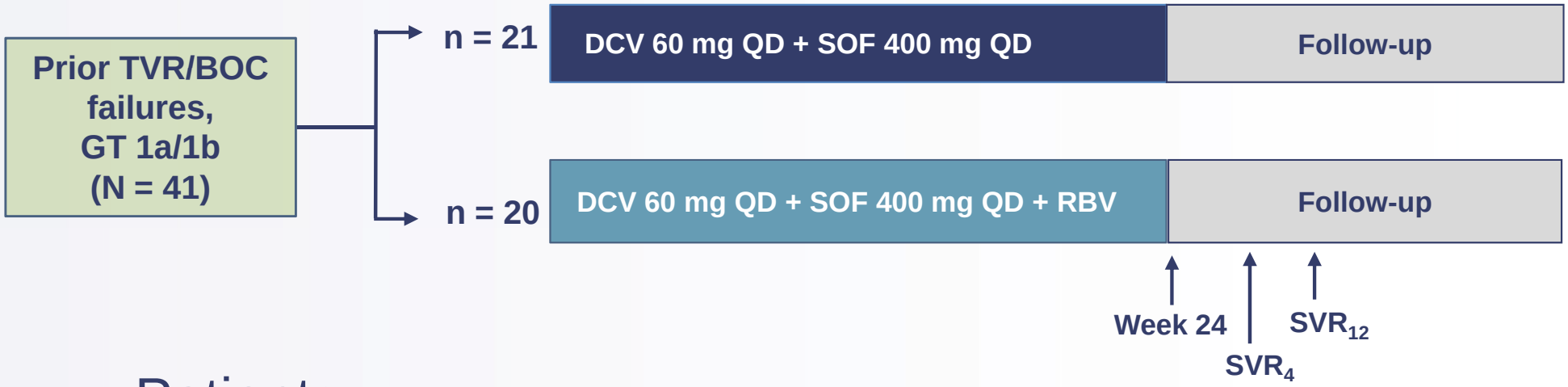
Study design



– Patients
  - Genotype 1, non-cirrhotic
  - Prior nonresponse, relapse, or breakthrough during treatment with PEG/RBV + TVR or BOC
  - Patients who discontinued TVR or BOC due to an adverse event were excluded

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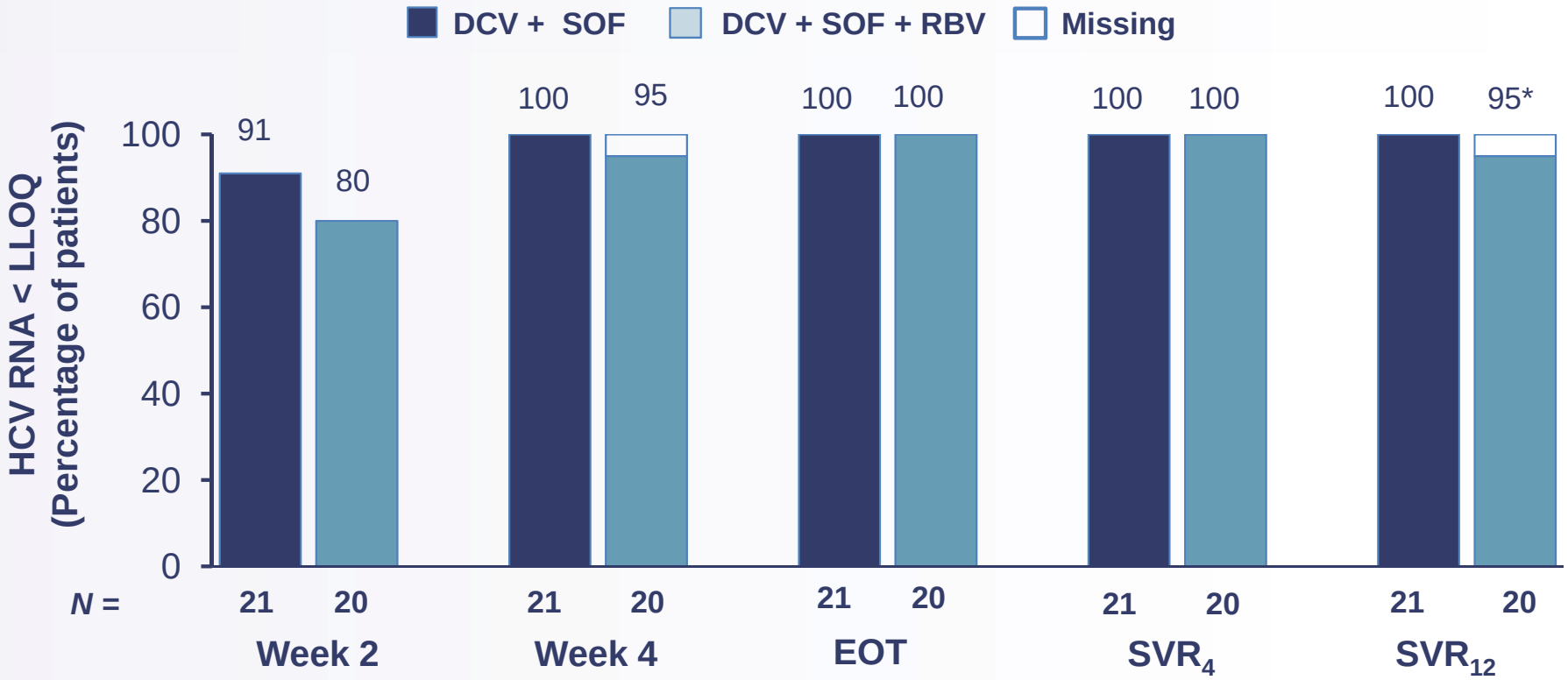
Virologic Response: DCV + SOF in TVR or BOC/ PR failures (mITT)



*1 patient missing at post-treatment (PT) Week 12: HCV RNA was undetectable at PT Week 4 and at PT Week 24
21/41 patients have reached PT Week 24; all have achieved SVR24

Sulkowski M, et al. 48th EASL; Amsterdam, Netherlands; April 24-28, 2013. Abstract 1417.

Conclusion

- The all-oral, once-daily combination of DCV + SOF with or without RBV achieved SVR in all HCV GT 1-infected patients (n=41) who failed prior treatment with TVR or BOC + pegIFN-alfa/RBV
- DCV + SOF with or without RBV was well tolerated
  - No grade 3 or 4 hepatic or hematologic abnormalities

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HCV: Highlights From EASL 2013

- Current treatments
- Upcoming treatments
- Future regimens