4th HCV Therapy Advances Meeting

Paris, December 12-13, 2014

Pivotal "New England Journal of Medicine" papers 2014 Phase 3 Trial data

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MEDIZINISCHE KLINIK 1

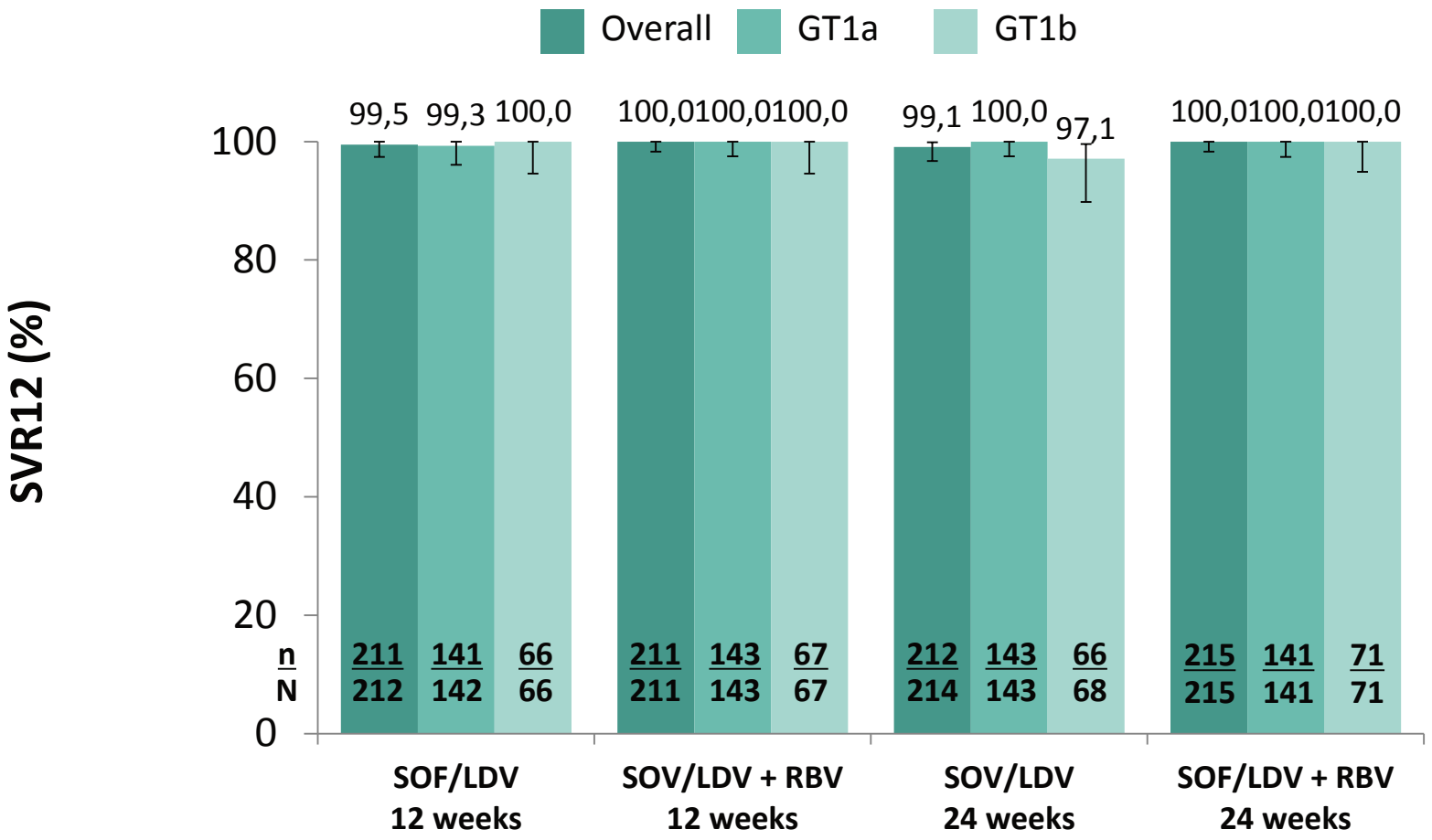
Disclosures

- Consultancies: Abbvie, BMS, (Boehringer Ingelheim), Gilead, (Idenix), Janssen, Merck, Novartis, (Roche), Santaris, (Vertex)
- Honoraria for lectures: Abbvie, BMS, (Boehringer Ingelheim), Gilead, Janssen, Merck, (Roche)

Phase III Trials of IFN-free Regimens: Genotype 1

- **Sofosbuvir + Ledipasvir ± RBV**
- **Ion-1**: TN ± cirrhosis; 12 vs. 24 wks
- **Ion-2**: TE (incl. PI-failure), ± cirrhosis; 12 vs. 24 wks
- **Ion-3**: TN w/o cirrhosis; 8 vs. 12 wks
- **Paritaprevir/r + Ombitasvir + Dasabuvir ± RBV**
- **Sapphire-I**: TN w/o cirrhosis; 12 wks
- **Sapphire-II**: TE w/o cirrhosis; 12 wks
- **Turquoise-II**: TN and TE ± cirrhosis; 12 vs. 24 wks
- **Pearl-II, -III, IV**: ± RBV

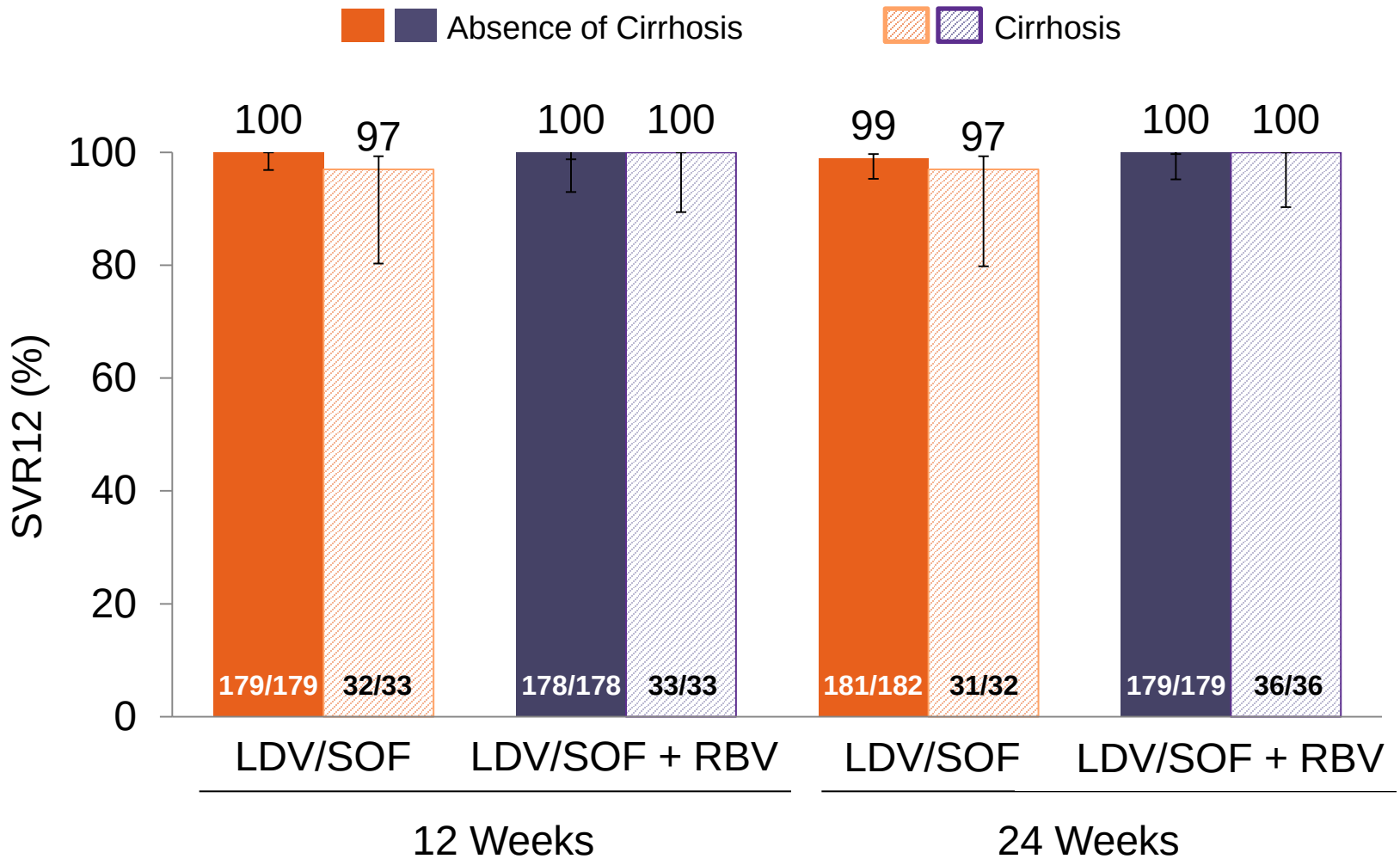
ION-1: SOF/LDV ± RBV in GT1 tx-naive patients



SOF = 400 mg/day; LDV = 90 mg/day;
RBV = 1000 or 1200 mg/day.
Subgroup results do not include patients who withdrew consent or who were lost to follow-up.
Error bars: 95% CI.

Afdhal N, *et al.* N Engl J Med. 2014;370:1889-98

ION-1: SVR12 by Presence of Cirrhosis



Error bars represent 95% confidence intervals

Afdhal N, *et al.* N Engl J Med. 2014;370:1889-98

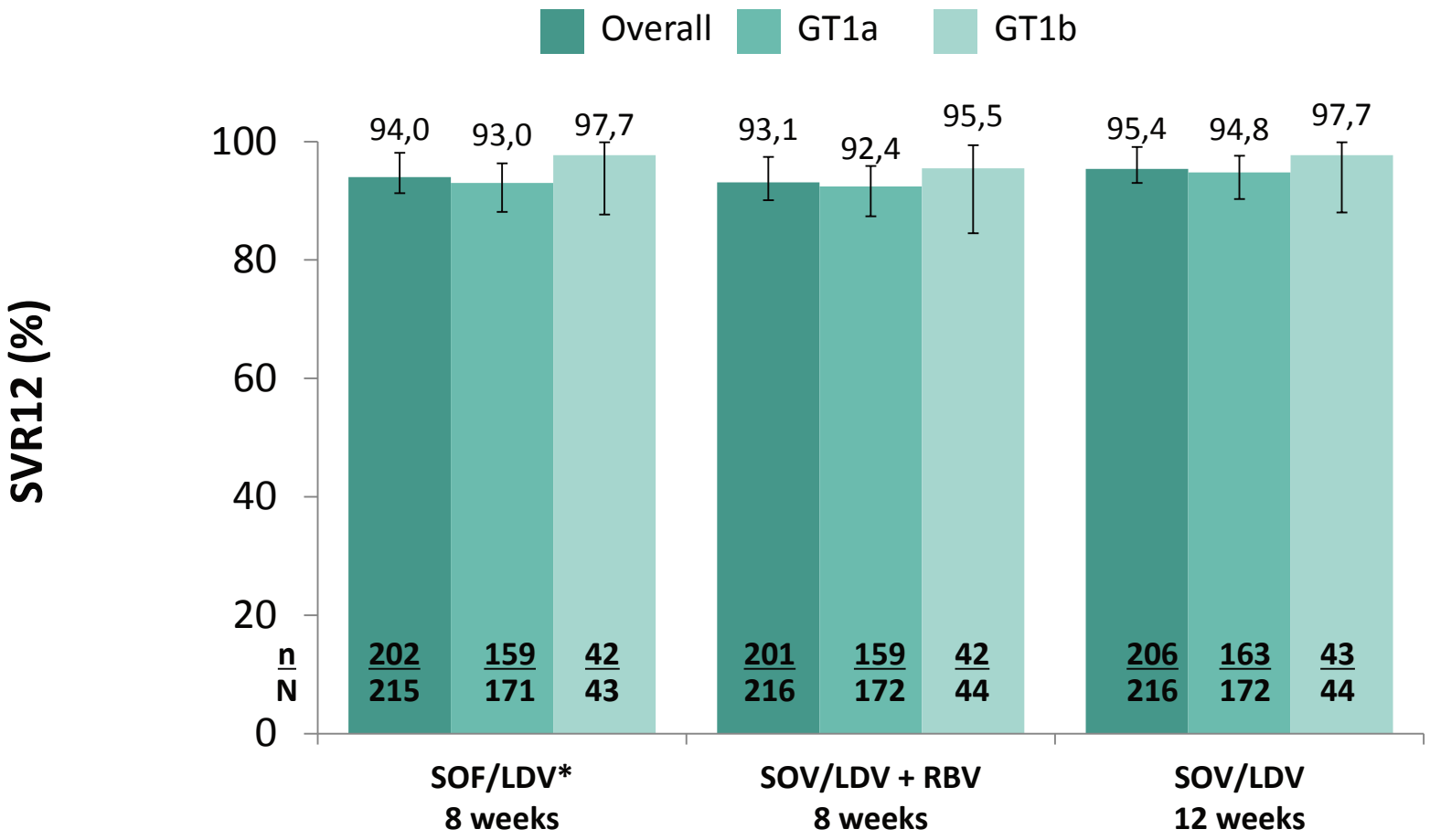
ION-1: Reasons for Not Achieving SVR

Patients, n (%)	12 Weeks		24 Weeks	
	LDV/SOF n=214	LDV/SOF+RBV n=217	LDV/SOF n=217	LDV/SOF+RBV n=217
SVR12	211 (99)	211 (97)	212 (98)	215 (99)
Breakthrough	0	0	1 (<1)	0
Relapse	1 (<1)	0	1 (<1)	0
Lost to Follow-Up	2 (<1)	4 (2)	2 (<1)	2 (<1)
Withdrew Consent	0	2 (<1)	1 (<1)	0

- Single on-treatment breakthrough was due to non-adherence
- Two of 865 subjects (0.23%) had post-treatment relapse
  - Both had NS5A-resistant variants at baseline and at relapse
- 16% of all subjects had NS5A RAVs at baseline, with 96% achieving SVR

Afdhal N, *et al.* N Engl J Med. 2014;370:1889-98

ION-3: SOF/LDV ± RBV in GT1 tx-naive patients



SOF = 400 mg/day; LDV = 90 mg/day;
RBV = 1000 or 1200 mg/day.
* One patient achieved SVR12, but was not subgenotyped.
Error bars: 95% CI.

Kowdley KV, *et al.* N Engl J Med. 2014;370:1879-88

ION-3: Reasons for Not Achieving SVR

Patients, n (%)	8 Weeks		12 Weeks
	LDV/SOF n=215	LDV/SOF + RBV n=216	LDV/SOF n=216
SVR12	202 (94)	201 (93)	206 (95)
Breakthrough	0	0	0
Relapse	11 (5)	9 (4)	3 (1)
Lost to Follow-Up	1 (<1)	5 (2)	7 (3)
Withdrew Consent	1 (<1)	1 (<1)	0

- All virologic failures were due to relapse (n=23)
  - 9 subjects had baseline RAVs, 8 subjects with no RAVs, 6 subjects with new RAVs
- 18% of subjects had baseline NS5A RAVs, and 90% achieved SVR12

Kowdley KV, *et al.* N Engl J Med. 2014;370:1879-88

ION-3: LDV/SOF ± RBV Safety Summary

Patients, n (%)	LDV/SOF 8 Weeks n=215	LDV/SOF + RBV 8 Weeks n=216	LDV/SOF 12 Weeks n=216
AEs	145 (67)	165 (76)	149 (69)
Grade 3–4 AEs	2 (<1)	8 (4)	7 (3)
Death	0	0	0
Grade 3–4 laboratory abnormality	7 (3)	18 (8)	16 (7)
Hemoglobin <10 g/dL	0	11 (5)	1 (<1)
Hemoglobin <8.5 g/dL	0	0	0

SAEs occurred in 4 (2%) of LDV/SOF 8 weeks, 1 (<1%) of LDV/SOF+RBV 8 weeks, and 5 (2%) of LDV/SOF 12 weeks
Treatment D/C due to AEs occurred in 0 of LDV/SOF 8 weeks, 1 (<1%) of LDV/SOF+RBV 8 weeks, and 2 (1%) of LDV/SOF 12 weeks

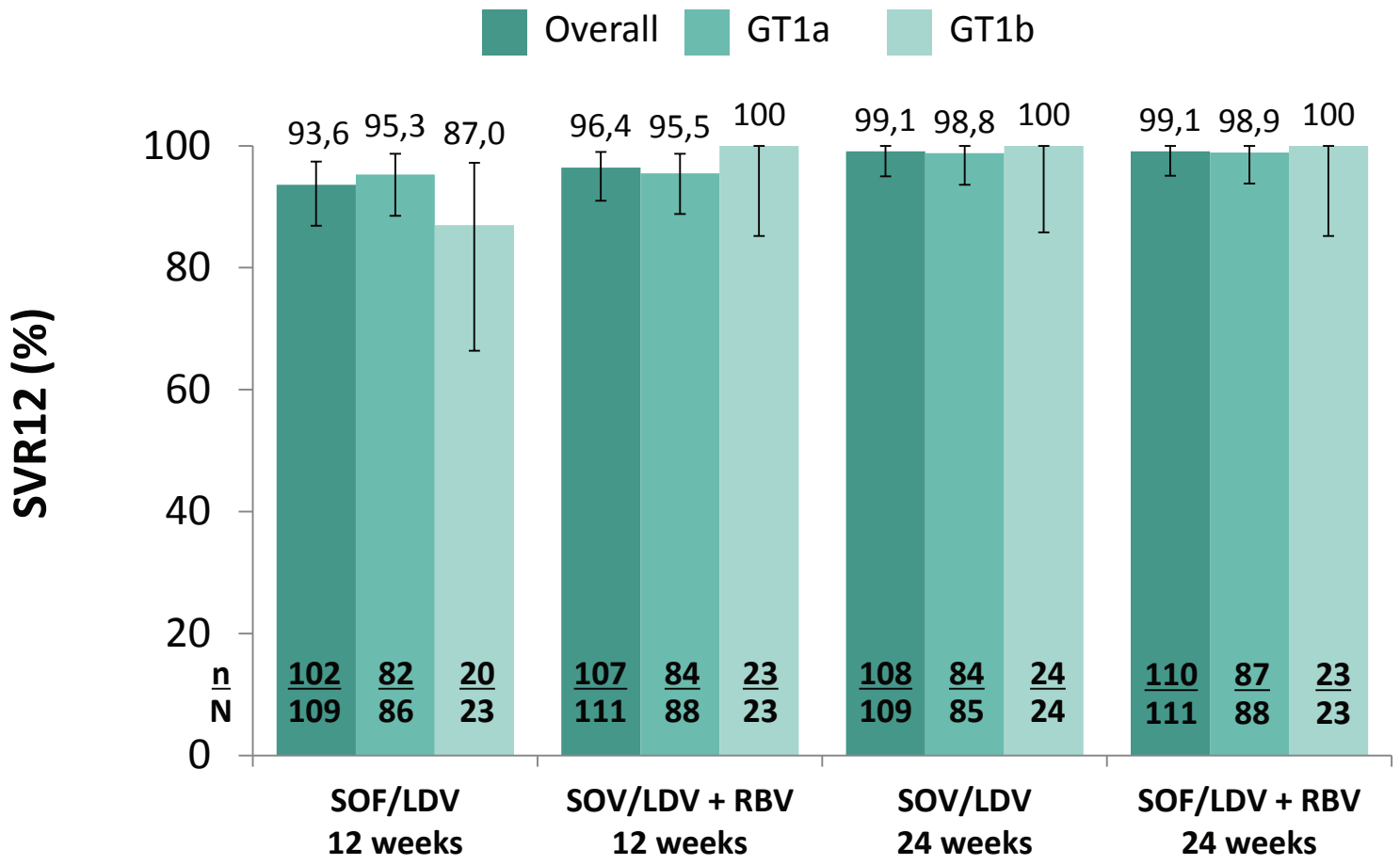
Kowdley KV, *et al.* N Engl J Med. 2014;370:1879-88

ION-3: Adverse Events (≥ 5% in Any Arm)

Preferred term, n (%)	LDV/SOF 8 wk n=215	LDV/SOF + RBV 8 wk n=216	LDV/SOF 12 wk n=216
Overall	145 (67)	165 (76)	149 (69)
Fatigue	45 (21)	75 (35)	49 (23)
Headache	30 (14)	54 (25)	33 (15)
Nausea	15 (7)	38 (18)	24 (11)
Insomnia	11 (5)	26 (12)	15 (7)
Irritability	3 (1)	29 (13)	9 (4)
Diarrhea	15 (7)	13 (6)	9 (4)
Arthralgia	9 (4)	11 (5)	16 (7)
Constipation	9 (4)	13 (6)	8 (4)
Dizziness	6 (3)	13 (6)	9 (4)
Rash	3 (1)	19 (9)	5 (2)
Pruritus	2 (<1)	16 (7)	5 (2)
Cough	3 (1)	12 (6)	7 (3)
Anemia	2 (<1)	17 (8)	2 (<1)
Muscle Spasms	3 (1)	11 (5)	6 (3)
Dyspnea	0	11 (5)	1 (<1)

Kowdley KV, *et al.* N Engl J Med. 2014;370:1879-88

ION-2: SOF/LDV ± RBV in GT1 tx-experienced pts



SOF = 400 mg/day; LDV = 90 mg/day;
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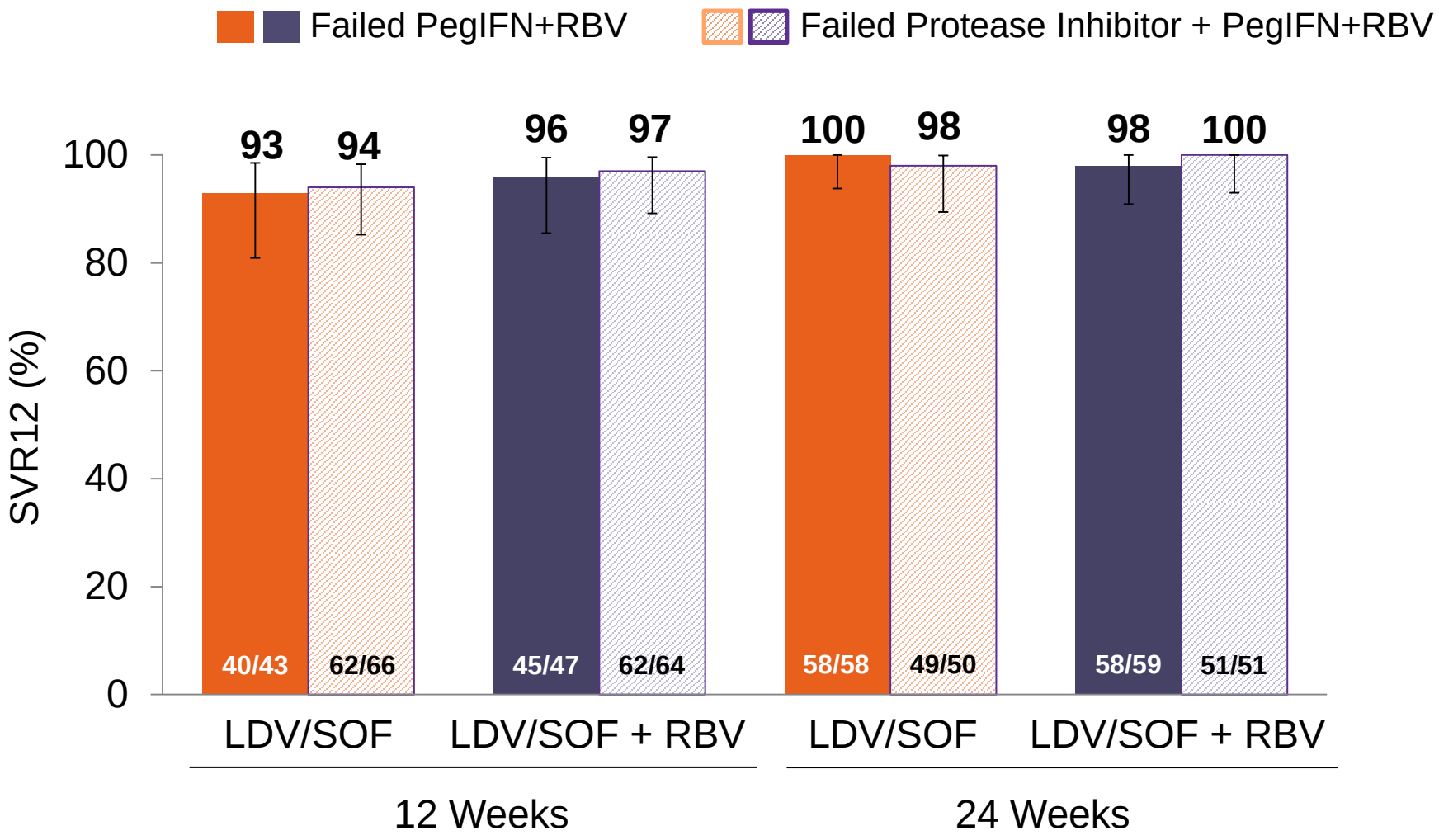
* One patient achieved SVR12, but was not subgenotyped.
Error bars: 95% CI.

Afdhal N, *et al.* N Engl J Med. 2014;370:1483-93

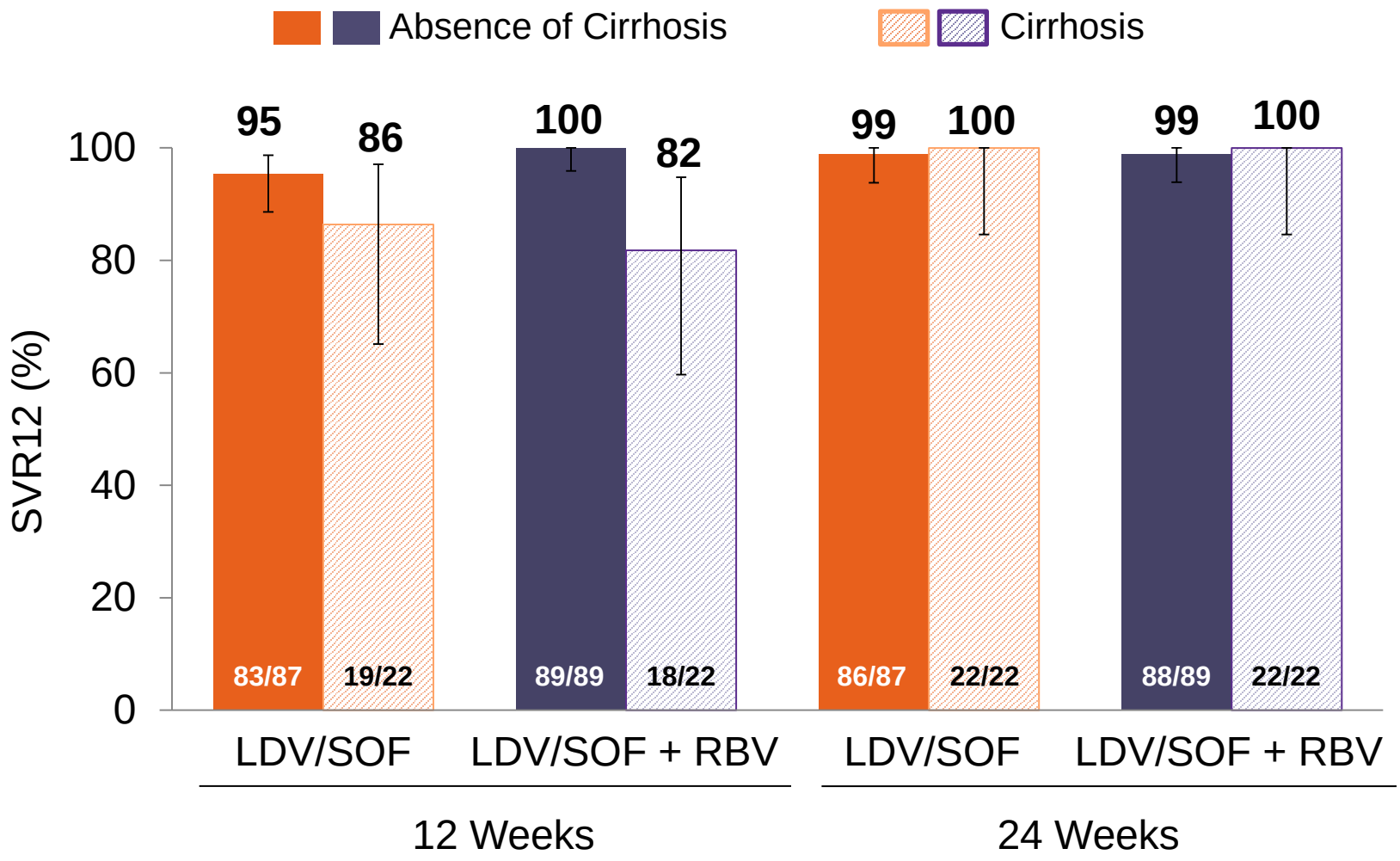
ION-2: SVR12 in PegIFN+RBV vs. PI+PegIFN+RBV Failures



Error bars represent 95% confidence intervals

Afdhal N, *et al.* N Engl J Med. 2014;370:1483-93

ION-2: SVR12 - Absence of Cirrhosis vs. Cirrhosis



Error bars represent 95% confidence intervals

Afdhal N, *et al.* N Engl J Med. 2014;370:1483-93

ION-2: Reasons for Not Achieving SVR

Patients, n (%)	12 Weeks		24 Weeks	
	LDV/SOF n=109	LDV/SOF+RBV n=111	LDV/SOF n=109	LDV/SOF+RBV n=111
SVR12	102 (94)	107 (96)	108 (99)	110 (99)
Breakthrough	0	0	0	1 (<1)
Relapse	7 (6)	4 (4)	0	0
Lost to Follow-Up	0	0	0	0
Withdrew Consent	0	0	1* (<1)	0

- Single on-treatment breakthrough was due to documented non-adherence
- 11 subjects had virologic failure were due to relapse
  - 6 subjects had baseline RAVs, 5 subjects with no RAVs
- 14% of subjects had NS5A RAVs at baseline, with 89% achieving SVR

* One patient withdrew consent after the post-treatment Week 4 visit, at which HCV RNA < 25 IU/mL

Afdhal N, *et al.* N Engl J Med. 2014;370:1483-93

Ledipasvir / Sofosbuvir FDC label (GT 1)

Patient population	US Label	EU Label	Practical recommendation (Germany)
Treatment-naive w/o cirrhosis	12 wks 8 wks (> 6 MIU/mL HCV RNA)	12 wks 8 wks may be considered in TN pts	8 wks (low VL) 12 wks (> 6 MIU/mL HCV RNA)
Treatment-naive with cirrhosis	12 wks	24 wks*	12 wks + RBV
Treatment-experienced w/o cirrhosis	12 wks	12 wks 24 wks should be considered for TE pts with uncertain subsequent tx options	12 wks
Treatment-experienced with cirrhosis	24 wks	24 wks*	12 wks + RBV
Decompensated cirrhosis	---	24 weeks + RBV	24 wks ± RBV

*12 weeks may be considered for pts deemed at low risk for clinical progression and who have subsequent tx options

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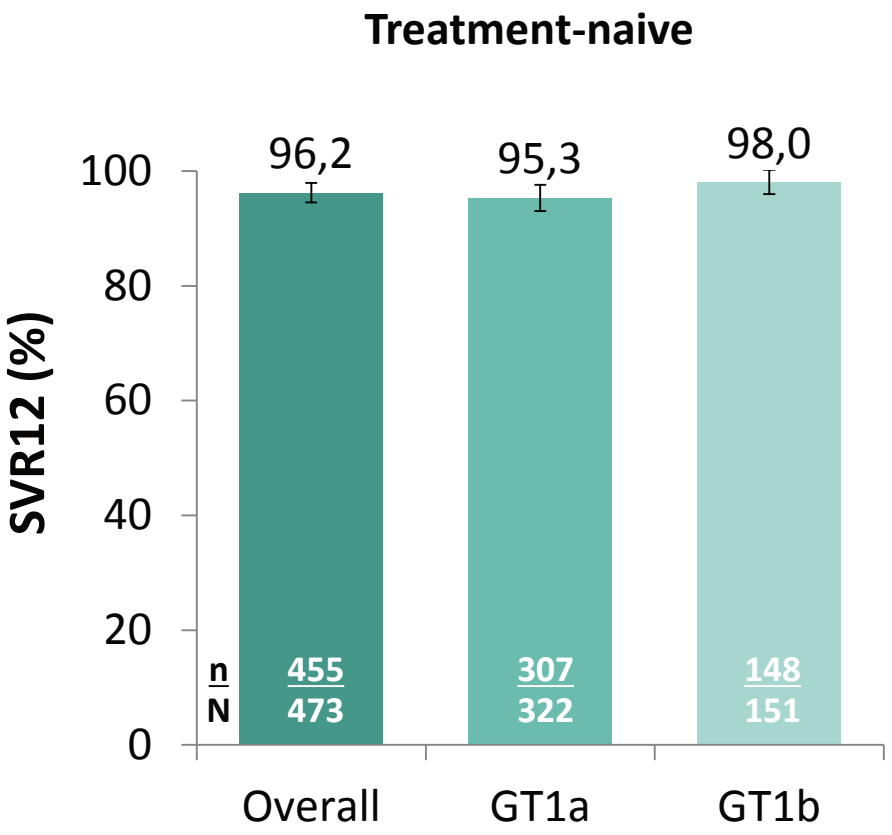
- **Ion-2**: TE (incl. PI-failure), ± cirrhosis; 12 vs. 24 wks
- **Ion-3**: TN w/o cirrhosis; 8 vs. 12 wks

- **Paritaprevir/r + Ombitasvir + Dasabuvir ± RBV**
- **Sapphire-I**: TN w/o cirrhosis; 12 wks
- **Sapphire-II**: TE w/o cirrhosis; 12 wks
- **Turquoise-II**: TN and TE ± cirrhosis; 12 vs. 24 wks
- **Pearl-II, -III, IV**: ± RBV

SAPPHIRE-I: HCV GT1 treatment-naive patients



3D + RBV x 12 wks

3D:
co-formulated Paritaprevir/ritonavir/ombitasvir, 150 mg/100 mg/25 mg qd; dasabuvir, 250 mg bid

RBV: 1000-1200 mg/d

Error bars: 95% CI.

Feld JJ, *et al.* N Engl J Med. 2014;370:1594-603

SAPPHIRE-I: Breakthrough and Relapse Rates

Event, n/N (%)	3D + RBV (N=473)
SVR12	455/473 (96.2)
Virologic failure	
Breakthrough	1/473 (0.2)
Relapse	7/463 (1.5)
Prematurely discontinued study drug*	7/473 (1.5)
Lost to follow-up after completion of treatment	3/473 (0.6)

*Patients (n=7) who prematurely discontinued without breakthrough; 2 due to adverse events, 5 withdrew consent/ lost to follow-up.

Feld JJ, *et al.* N Engl J Med. 2014;370:1594-603

SAPPHIRE-I: AEs Occurring in >10% of Patients

Event, n (%)	3D + RBV (N=473)	Placebo (N=158)	P Value
Any AE	414 (87.5)	116 (73.4)	<0.05
Fatigue	164 (34.7)	45 (28.5)	NS
Headache	156 (33.0)	42 (26.6)	NS
Nausea	112 (23.7)	21 (13.3)	<0.05
Pruritus	80 (16.9)	6 (3.8)	<0.05
Insomnia	66 (14.0)	12 (7.6)	<0.05
Diarrhea	65 (13.7)	11 (7.0)	<0.05
Asthenia	57 (12.1)	6 (3.8)	<0.05
Rash	51 (10.8)	9 (5.7)	NS

Adverse events (AEs) were generally mild.

Feld JJ, *et al.* N Engl J Med. 2014;370:1594-603

SAPPHIRE-I: Laboratory Abnormalities

Event, n (%)	3D + RBV (N=469)
ALT >5X ULN	4 (0.9)
AST >5X ULN	3 (0.6)
Alkaline phosphatase >5X ULN	0
Total bilirubin >3X ULN	13 (2.8)
Hemoglobin	
<10-8.0 g/dL	27 (5.8)
<8.0-6.5 g/dL	0
<6.5 g/dL	0

No cases consistent with Hy's law

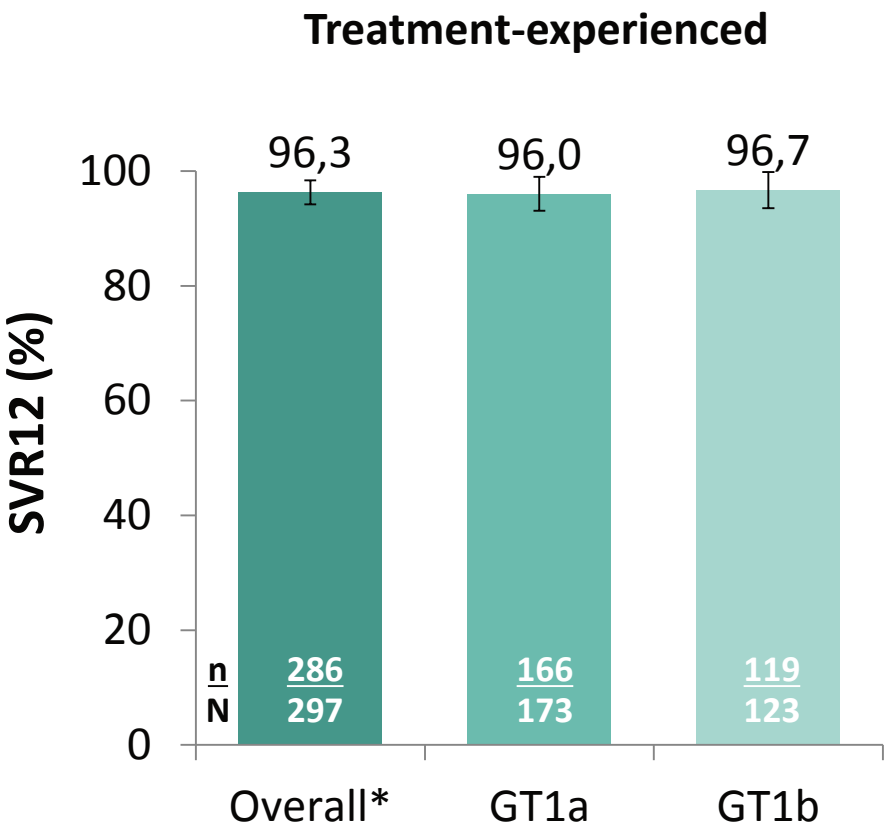
Elevations in total bilirubin were mainly transient and predominantly indirect bilirubin

1 patient received EPO; no patient was transfused

Ribavirin dose was modified due to AE(s) in 26 (5.5%) 3D + RBV recipients

Feld JJ, *et al.* N Engl J Med. 2014;370:1594-603

SAPPHIRE-II: HCV GT1 tx-experienced patients



3D + RBV x 12 wks

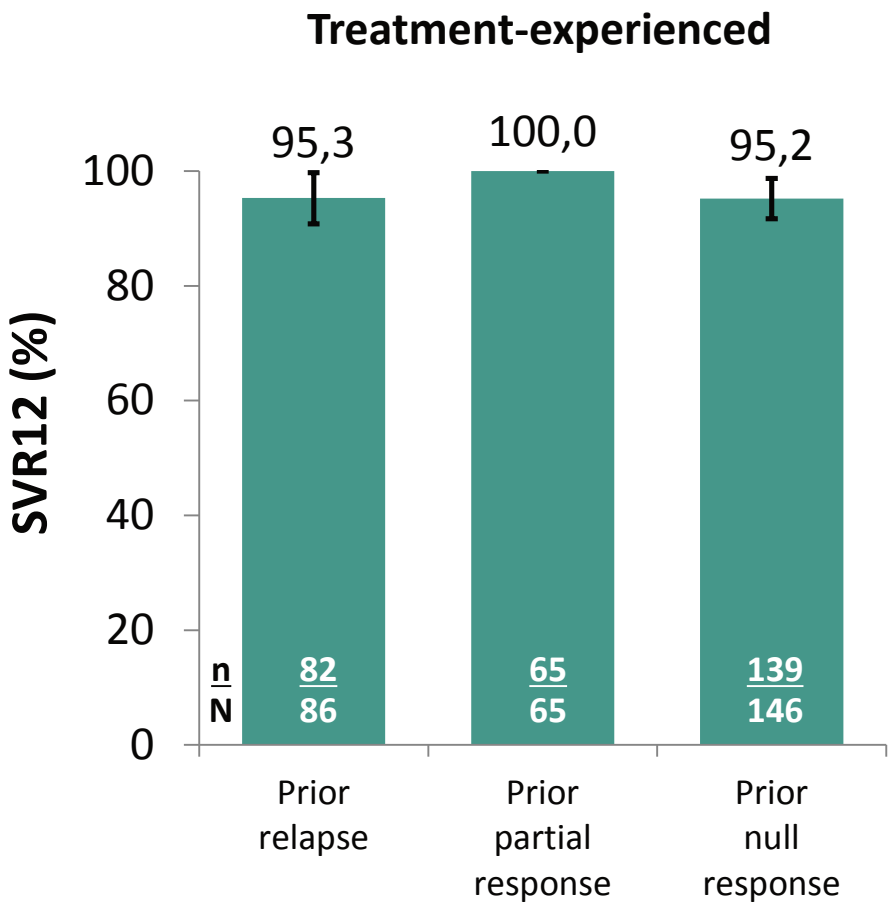
3D:
co-formulated Paritaprevir/ritonavir/ombitasvir, 150 mg/100 mg/25 mg qd; dasabuvir, 250 mg bid

RBV: 1000-1200 mg/d

* One patient achieved SVR12, but was unable to be subgenotyped.
Error bars: 95% CI.

Zeuzem S, *et al.* N Engl J Med. 2014;370:1604-141

SAPPHIRE-II: HCV GT1 tx-experienced patients



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RBV: 1000-1200 mg/d

Error bars: 95% CI.

Zeuzem S, *et al.* N Engl J Med. 2014;370:1604-141

SAPPHIRE-II: SVR12 and Reasons for Non-Response

	All Patients (N=297)	Prior Relapsers (N=86)	Prior Partial Responders (N=65)	Prior Null Responders (N=146)
SVR12, n/N (%)	286/297 (96.3)	82/86 (95.3)	65/65 (100)	139/146 (95.2)
Virologic failure, n				
Breakthrough	0	0	0	0
Relapse	7	1	0	6
Prematurely discontinued study drug,* n	4	3	0	1

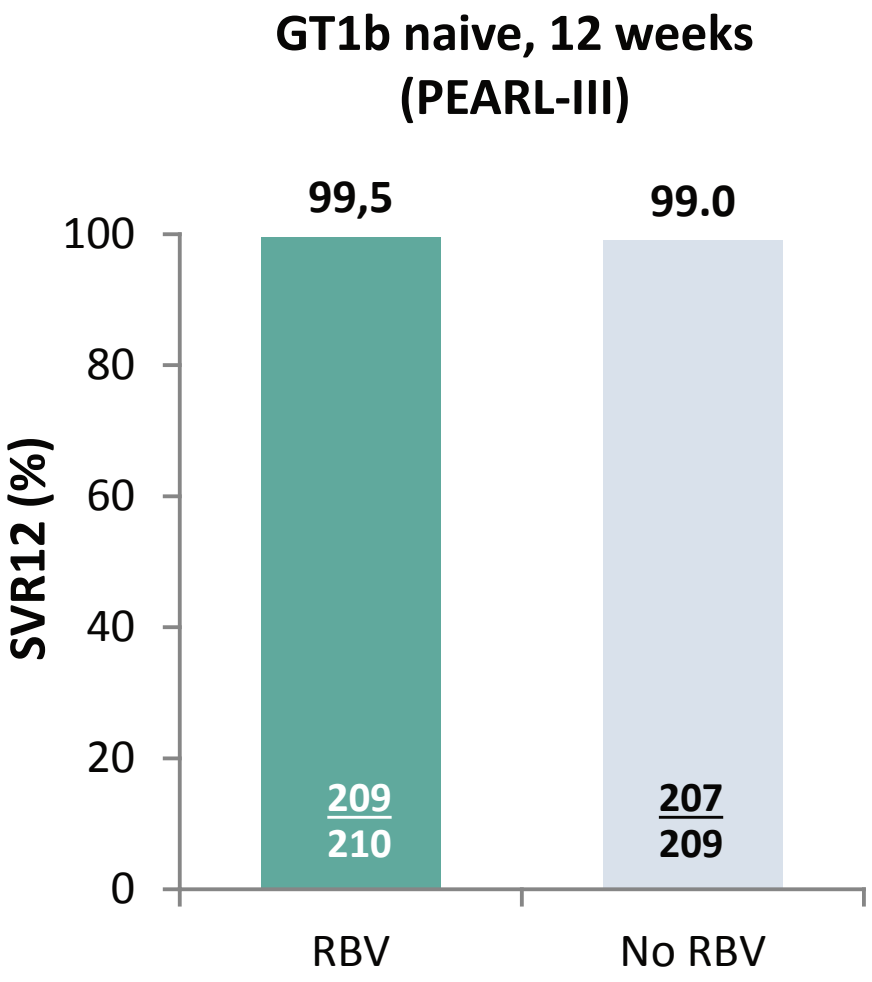
No patient had breakthrough and 2.4% of patients had a relapse

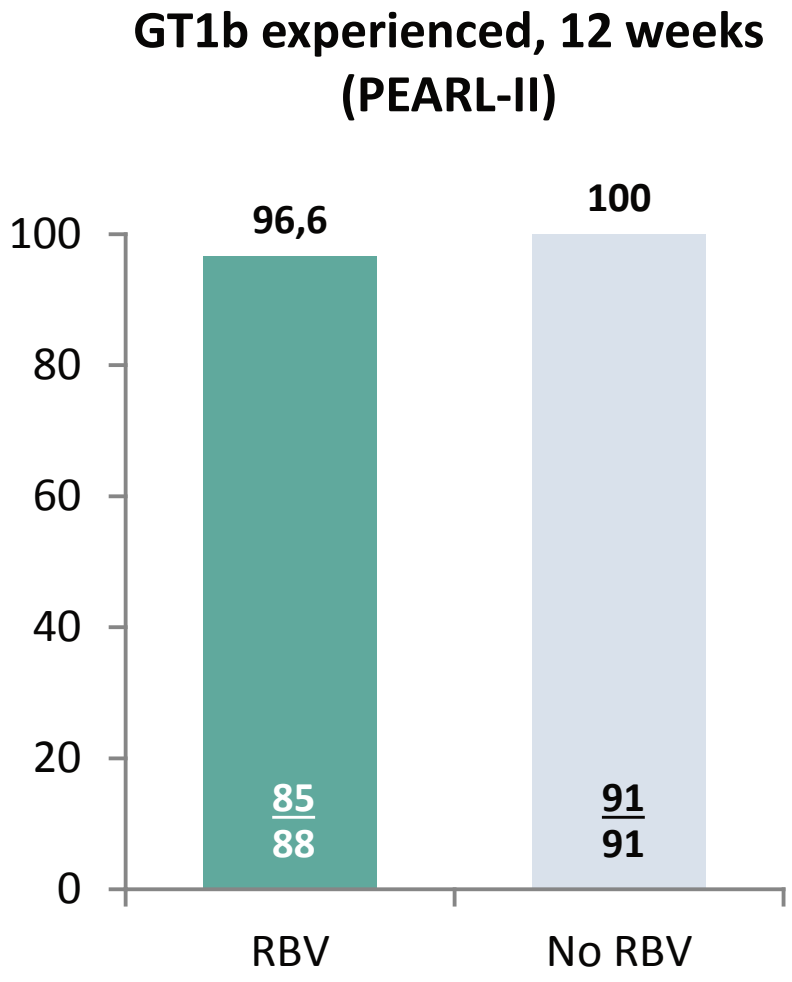
All relapses occurred 2-8 weeks post-treatment

*Patients (n=4) who prematurely discontinued without breakthrough; 3 due to adverse events, 1 withdrew consent during week 11

Zeuzem S, *et al.* N Engl J Med. 2014;370:1604-141

PEARL-II and -III: Paritaprevir/r + Ombitasvir + Dasabuvir ± RBV

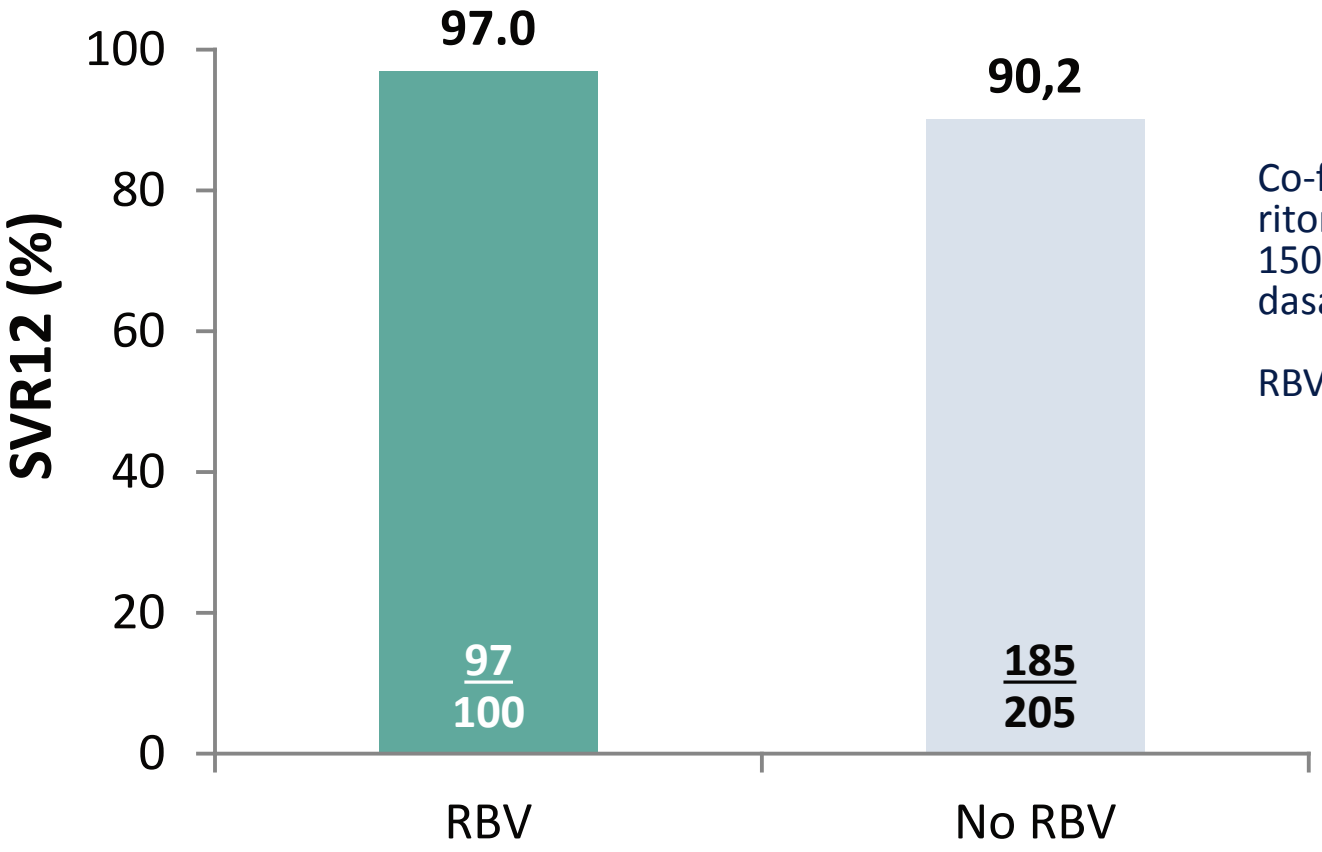




Co-formulated paritaprevir/ritonavir/ombitasvir, 150 mg/100 mg/25 mg qd; dasabuvir, 250 mg bid
RBV: 1000-1200 mg/d

Ferenci P, *et al.* N Engl J Med. 2014;370:1983-92
Andreone P, *et al*. Gastroenterology. 2014;147:359-365

PEARL-IV: Paritaprevir/r + Ombitasvir + Dasabuvir ± RBV for 12 weeks in GT1a treatment-naive patients

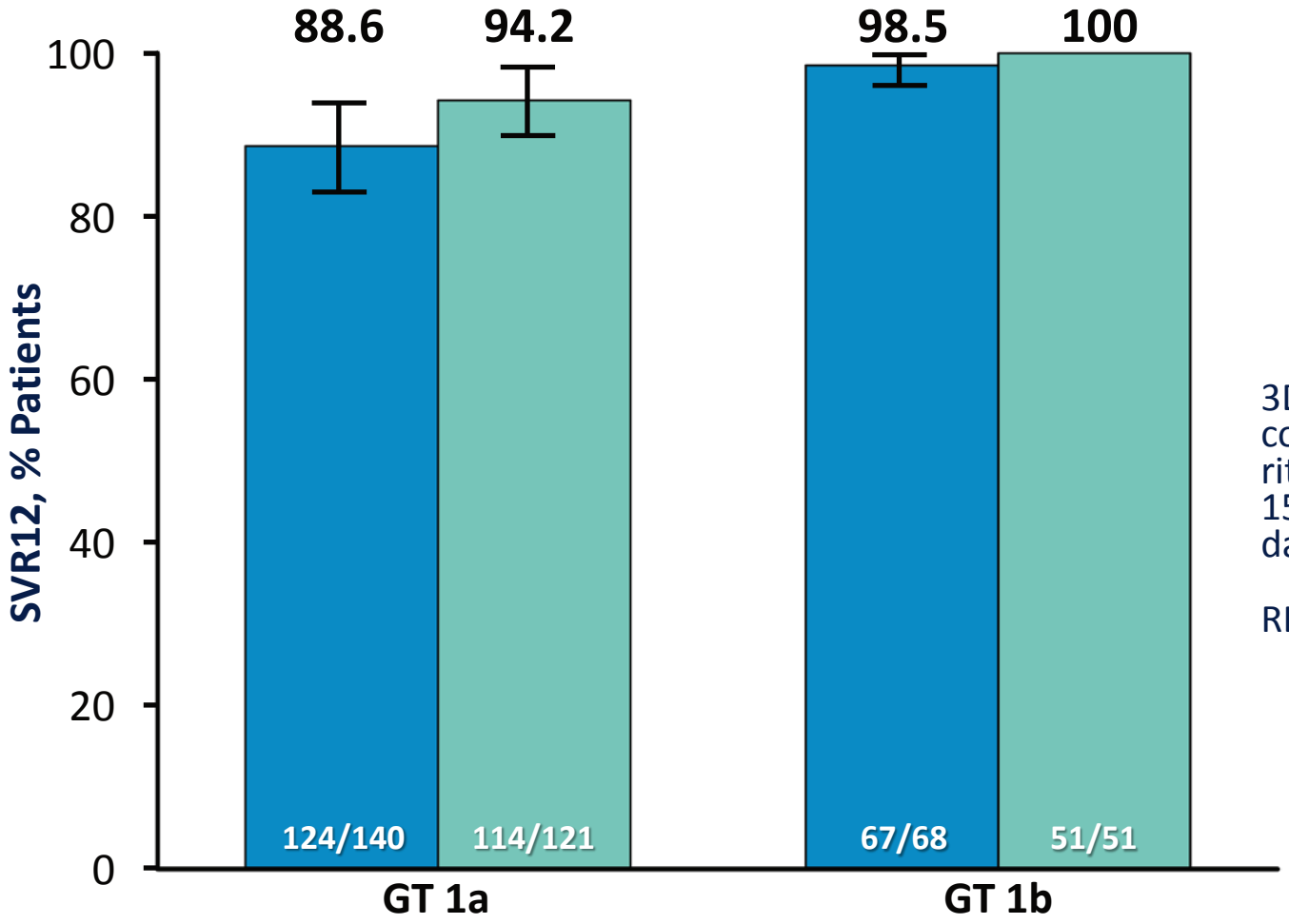


Co-formulated paritaprevir/ ritonavir/ombitasvir, 150 mg/100 mg/25 mg qd; dasabuvir, 250 mg bid

RBV: 1000-1200 mg/d

Ferenci P, *et al*. N Engl J Med. 2014;370:1983-92

TURQUOISE-II: SVR12 rates in HCV GT1 treatment-naive and experienced cirrhotic patients

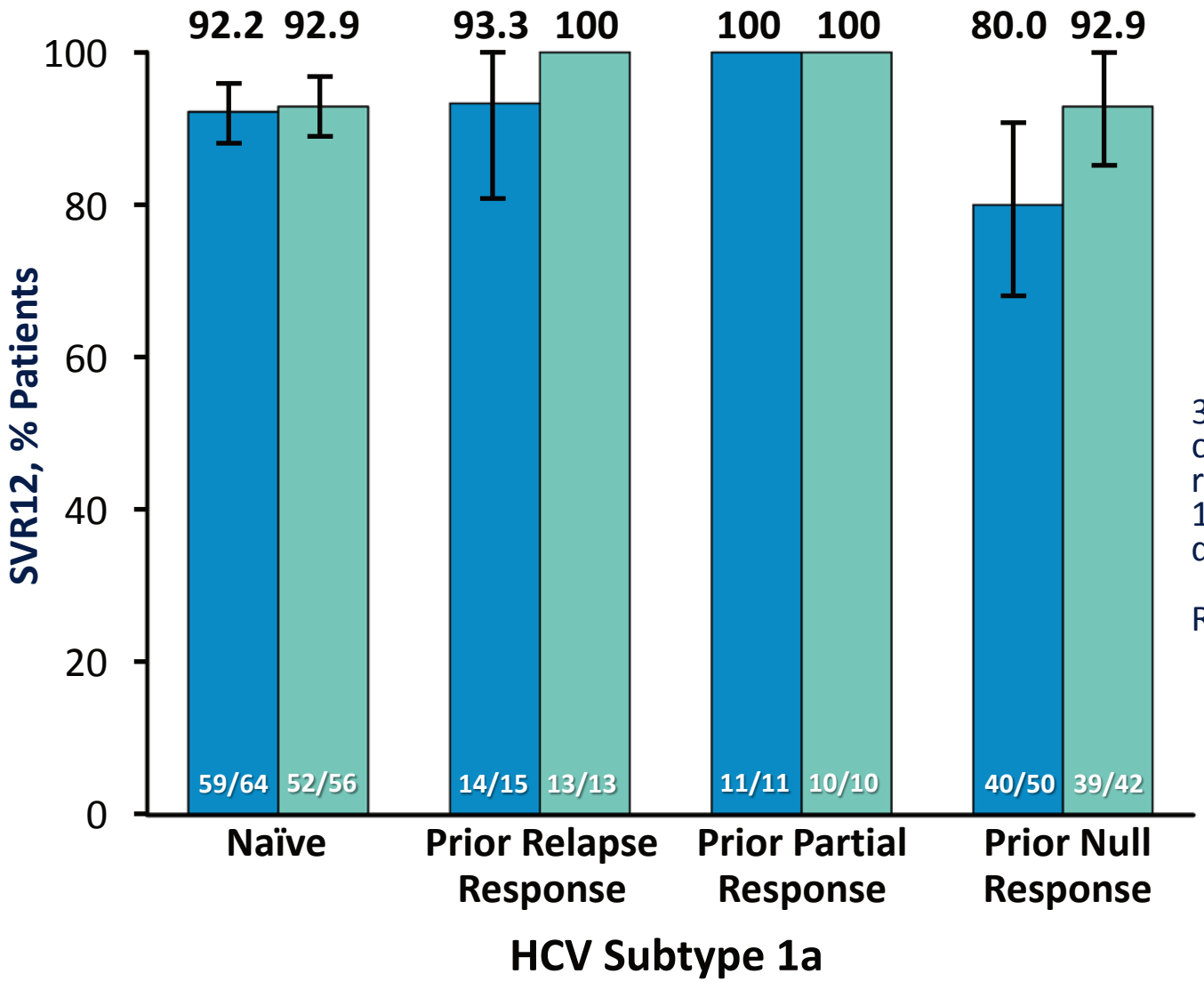


3D:
co-formulated paritaprevir/ritonavir/ombitasvir, 150 mg/100 mg/25 mg qd; dasabuvir, 250 mg bid

RBV: 1000-1200 mg/d

Poordad F, *et al.* N Engl J Med. 2014;370:1973-82

TURQUOISE-II: SVR12 Rates by Prior Treatment Response in HCV Subtype 1a

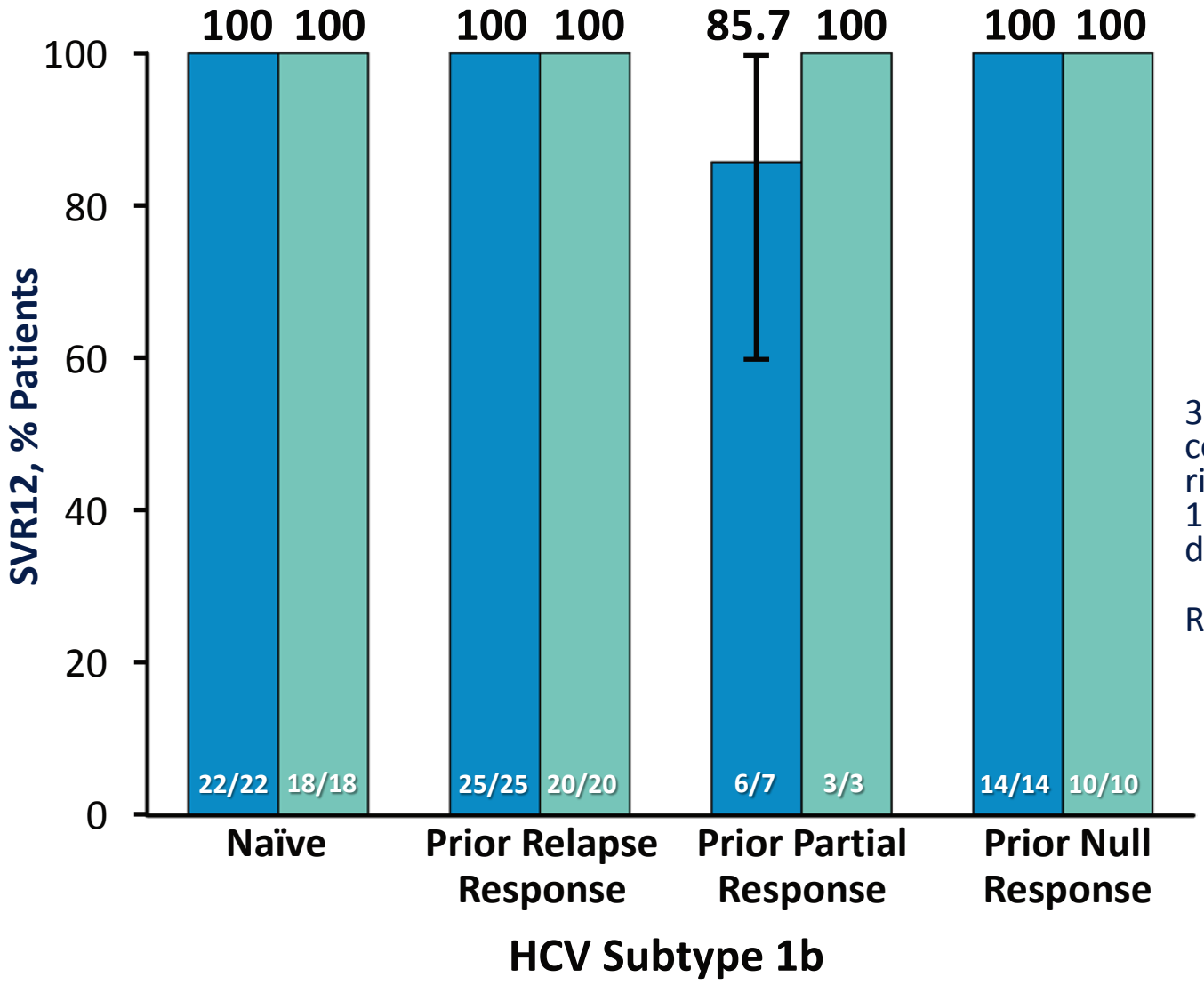


3D:
co-formulated paritaprevir/ritonavir/ombitasvir, 150 mg/100 mg/25 mg qd; dasabuvir, 250 mg bid

RBV: 1000-1200 mg/d

Poordad F, *et al.* N Engl J Med. 2014;370:1973-82

TURQUOISE-II: SVR12 Rates by Prior Treatment Response in HCV Subtype 1b

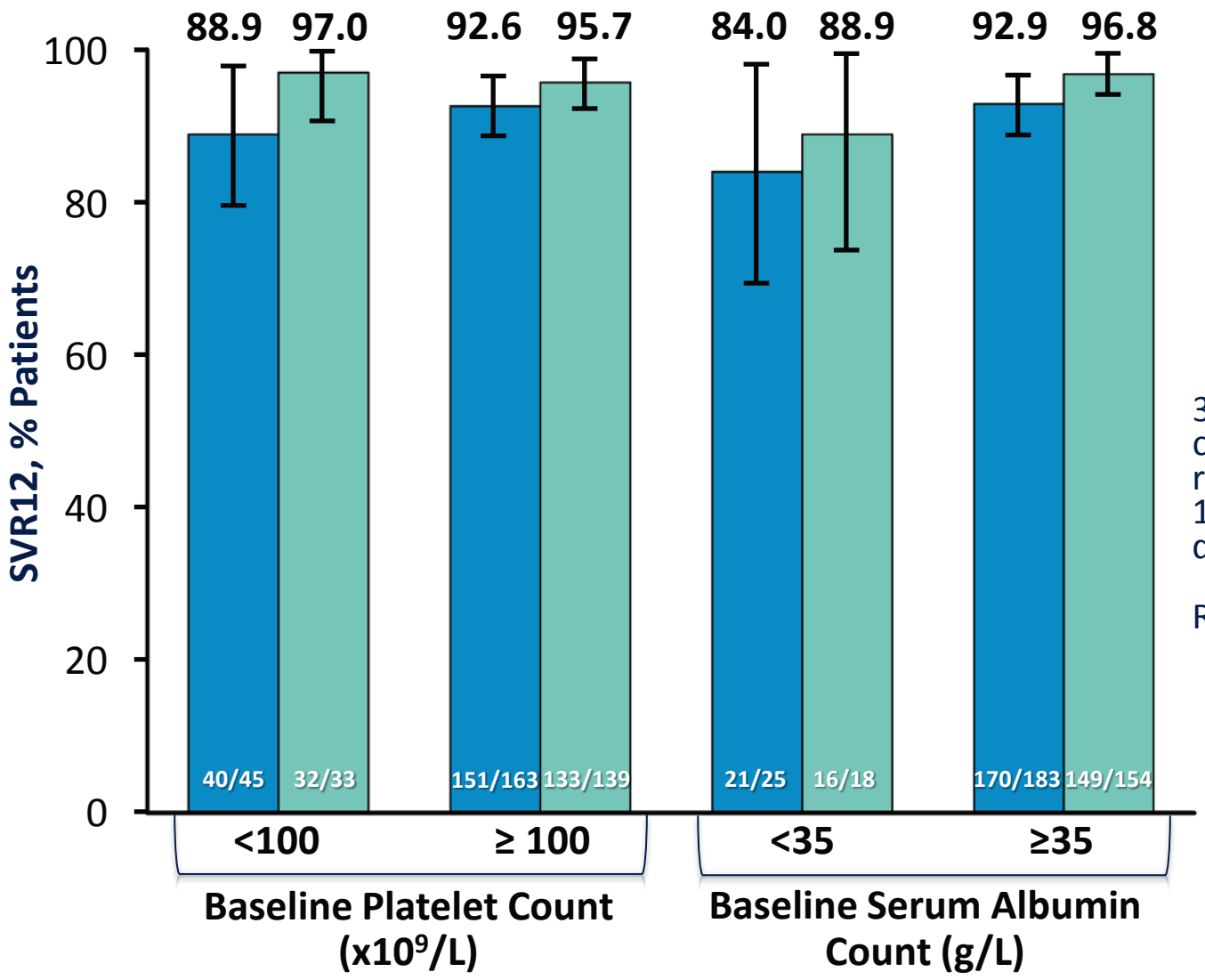


3D:
co-formulated paritaprevir/ritonavir/ombitasvir, 150 mg/100 mg/25 mg qd; dasabuvir, 250 mg bid

RBV: 1000-1200 mg/d

Poordad F, *et al.* N Engl J Med. 2014;370:1973-82

TURQUOISE-II: SVR12 Rates by Surrogates of Portal Hypertension and Hepatic Function



3D:
co-formulated paritaprevir/ritonavir/ombitasvir, 150 mg/100 mg/25 mg qd; dasabuvir, 250 mg bid

RBV: 1000-1200 mg/d

Poordad F, *et al.* N Engl J Med. 2014;370:1973-82

TURQUOISE-II: Patients Not Achieving SVR12

Event, n/N (%)	12-Week Arm	24-Week Arm
Patients not achieving SVR12	17/208 (8.2)	7/172 (4.1)
Premature discontinuation	4/208 (1.9)	3/172 (1.7)
Adverse event, n	4	1
Withdrew consent/other, n	0	2
Virologic failure		
Breakthrough	1/208 (0.5)	3/172 (1.7)
Relapse through PTW12	12/203 (5.9)*	1/164 (0.6)**

*7/12 were GT1a null responders. **Significant difference.

Virologic failure occurred in 17/380 patients (4.5%)

15 of these patients had at least 1 resistance-associated variant at the time of virologic failure

- D168V (NS3) and Q30R (NS5A) seen most frequently in GT1a-infected patients

The significance and persistence of these variants are under investigation

Poordad F, *et al.* N Engl J Med. 2014;370:1973-82

TURQUOISE-II: Chemical and Hematologic Abnormalities

	12-Week Arm (N=208)	24-Week Arm (N=172)
ALT >5x ULN (%)	2.9	0
Total bilirubin >3x ULN (%)	13.5	5.2
Hemoglobin (%)		
<10 g/dL	7.2	11.0
<8.0 g/dL	1.4	0.6

ALT elevation

- Asymptomatic, transient, and improved or resolved with ongoing study drug dosing

Bilirubin elevation

- Transient, predominantly indirect, no discontinuations due to hyperbilirubinemia

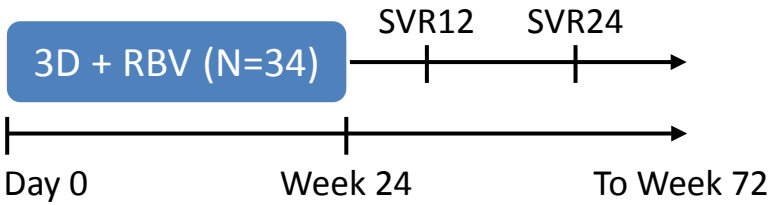
Hemoglobin decrease

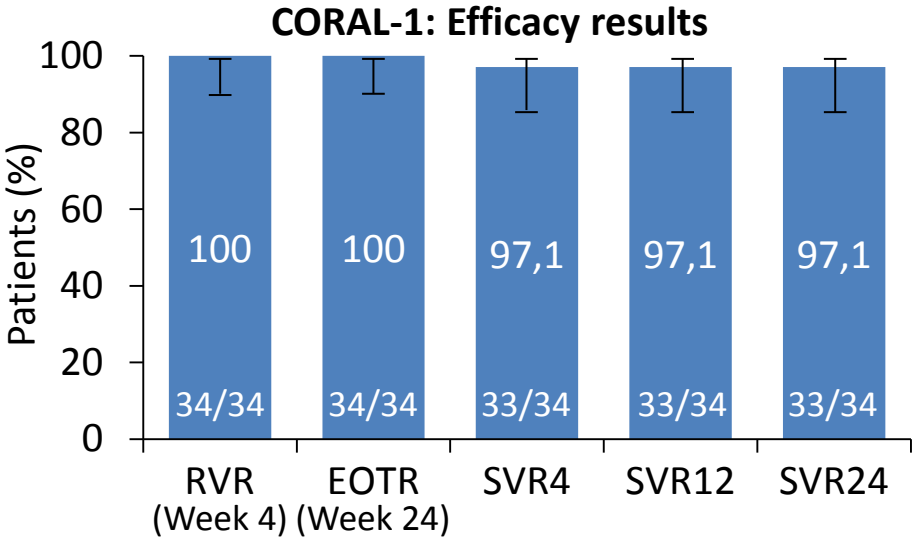
- Managed with reduction of ribavirin dose in 34 patients (8.9%)

ULN: upper limit of normal.

Poordad F, *et al.* N Engl J Med. 2014;370:1973-82

SVR rates in liver transplant recipients with recurrent HCV G1 infection receiving ABT-450/r/ombitasvir + dasabuvir + RBV





- Due to interactions between calcineurin inhibitors (CNIs) and study regimen, modified dosing was advised
  - Tacrolimus: 0.5 mg QW or 0.2 mg every 3 days; cyclosporine: 1/5 the daily pre-study dose QD
- No acute or chronic rejection
- 1 d/c due to AEs; 2x SAEs
- 5 patients (14.7%) received EPO

Baseline demographics	3D + RBV (N=34)
Median time since transplantation	39.5 months
Male (%)	79.4
Mean age (years)	59.6
Fibrosis stage F0/F1/F2 (%)	17.6/38.2/44.1
IL28B non-CC	76.5
HCV subtype G1a/G1b (%)	85.3/14.7
Mean HCV RNA (log_{10} IU/mL)	6.6
Immunosuppression TAC/CSA (%)	85.3/14.7
Mean CrCl (mL/min)	90.5
Mean ALT (U/L)	78.9
Mean AST (U/L)	63.9
Mean GGT (U/L)	170.3

- No lab abnormalities, except 2 x elevated bilirubin at a single time point
- No virologic breakthrough
- One pt had virologic relapse (post-treatment day 3)

- High RVR and SVR rates in F0–2 patients
- Well-tolerated
- CNI dosing was manageable using PK guidance established in prior DDI study in volunteers
- Antiviral therapy may benefit patients before acceleration of fibrosis

Kwo et al., NEJM 2014

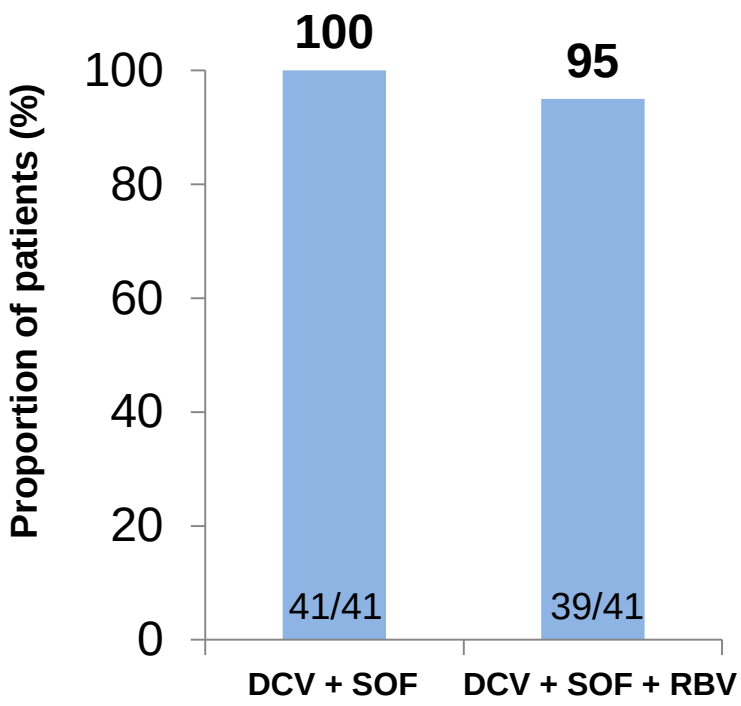
Putative Label of Paritaprevir/r + Ombitasvir + Dasabuvir ± Ribavirin

Patient population	Recommended schedule
Treatment-naive w/o cirrhosis	HCV-1a for 12 weeks with RBV HCV-1b for 12 weeks w/o RBV
Treatment-naive with cirrhosis	12 weeks with RBV
Treatment-experienced w/o cirrhosis	HCV-1a for 12 weeks with RBV HCV-1b for 12 weeks w/o RBV (?)
Treatment-experienced with cirrhosis	12 weeks with RBV 24 weeks in HCV-1a prior NR

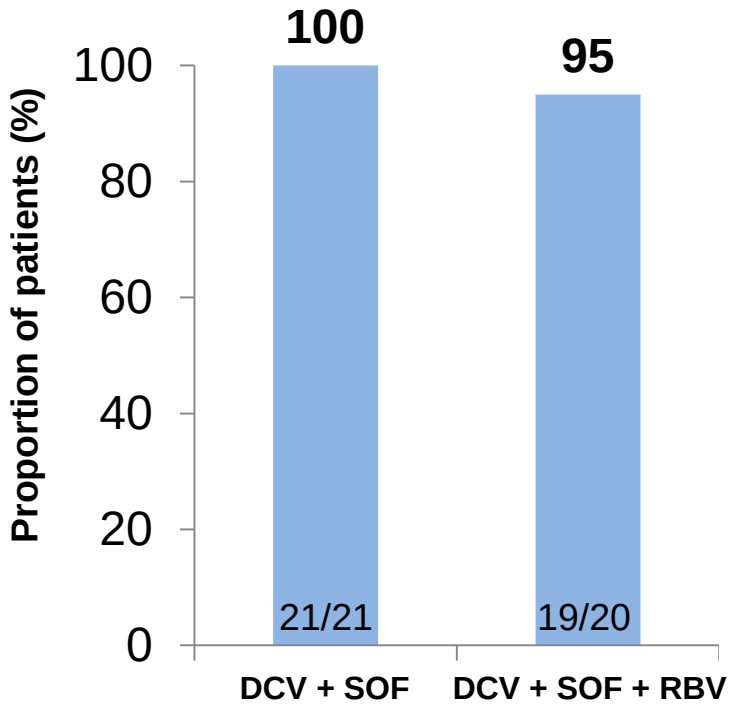
Other Studies in Patients Infected with HCV-1

SVR12 rates for daclatasvir (DCV) + SOF ± RBV in GT 1

GT 1 (82% GT 1a), Rx-naïve
N=82: DCV + SOF ± RBV for 12 weeks*



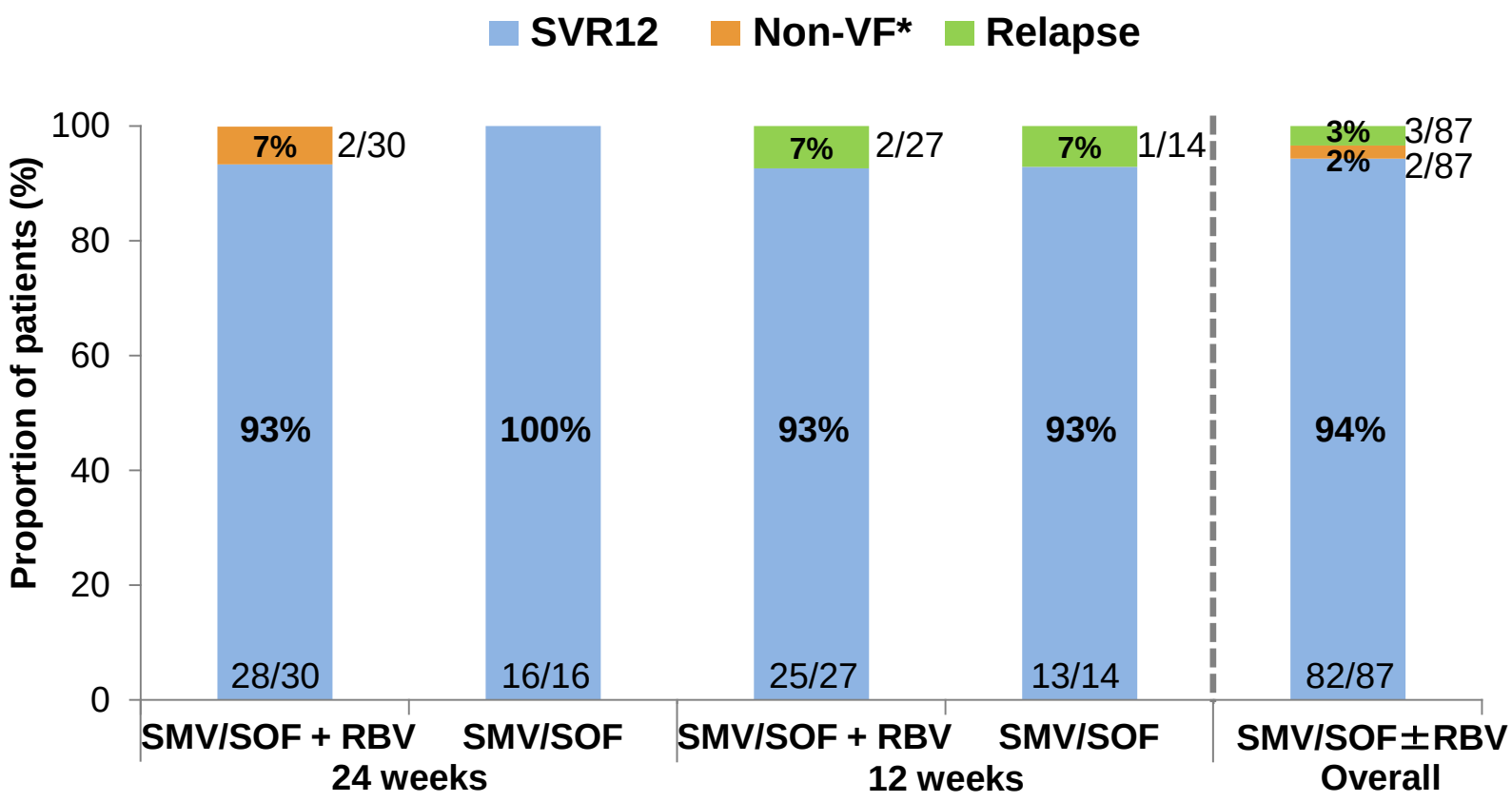
GT1 (80% GT 1a), prior PI non-responder
N=41: DCV + SOF ± RBV for 24 weeks*



*DCV 60 mg once daily, SOF 400 mg once daily ± RBV 1000/1200 mg/day

Sulkowski MS, et al. N Engl J Med 2014;370:211–21

COSMOS Cohort 2: SVR12 – primary endpoint (ITT population)

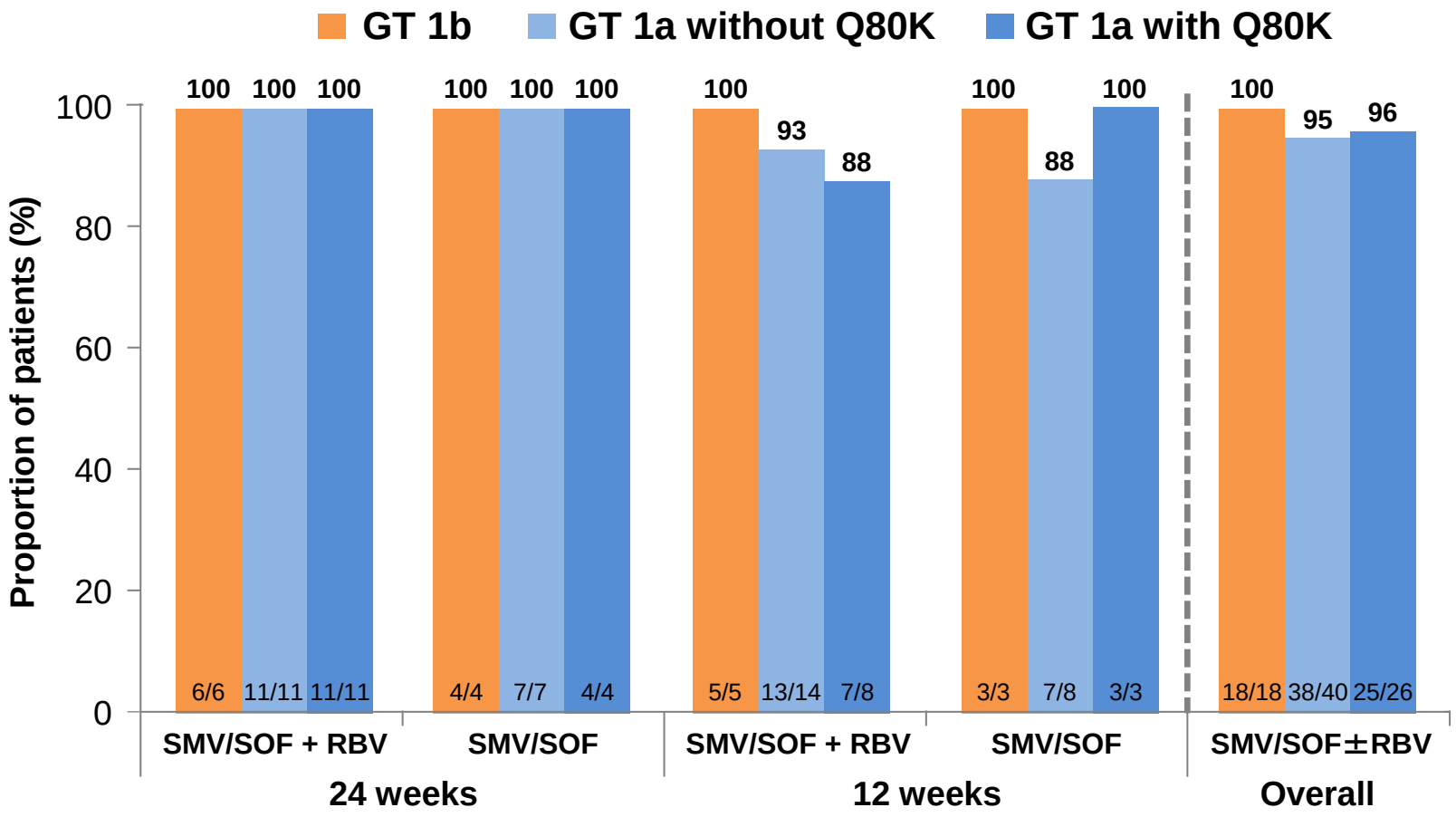


*Patients who did not achieve SVR12 for reasons other than virological failure

Lawitz E, et al. Lancet 2014

ITT: intent-to-treat;
SMV: simeprevir; VF: virological failure

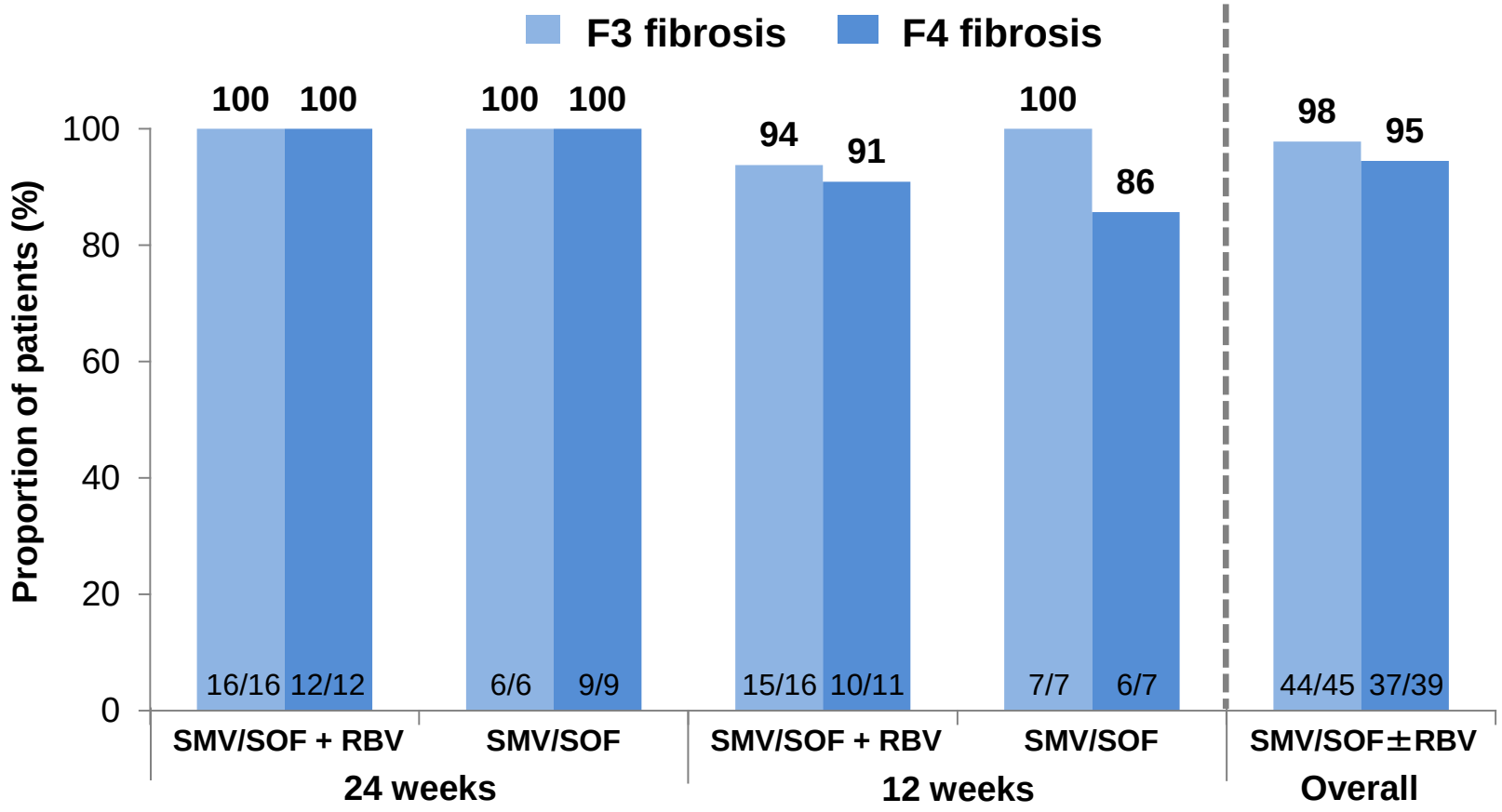
COSMOS Cohort 2: SVR12 by GT 1 subtype and baseline NS3 Q80K polymorphism*



*Excluding patients who discontinued for non-virological reasons

Lawitz E, et al. Lancet 2014

COSMOS Cohort 2: SVR12 by METAVIR score*



*Excluding patients who discontinued for non-virological reasons

Lawitz E, et al., Lancet 2014

HALLMARK-DUAL: SVR12 With Daclatasvir + Asunaprevir in GT1b HCV

SVR12, % (n/N)	Daclatasvir (60 mg qd) + Asunaprevir (100 mg bid) x 24 weeks
Treatment naive	90 (182/203)
Null responders	82 (98/119)
Partial responders	81 (68/84)
All IFN ineligible/intolerant	82 (192/235)
Advanced fibrosis/cirrhosis with thrombocytopenia	73 (56/77)

- Breakthrough: 9 (4%) treatment naive, 26 (13%) nonresponders, 20 (9%) IFN ineligible/intolerant
- Relapse: 5 (3%) treatment naive, 7 (4%) nonresponders, 12 (6%) IFN ineligible/intolerant
- 28 of 73 patients with NS5A-L31 and/or Y93 variants at baseline achieved SVR12

Manns M, *et al*. Lancet 2014; Jul 26 epub ahead of print

HALLMARK-DUAL: Adverse Events

- Serious AEs* occurred in 6% treatment-naive pts, 5% nonresponders and 7% IFN ineligible-intolerant pts
- AE leading to discontinuation† in 3%, 1% and 1%, respectively
- Grade 3/4 hemoglobin < 90 g/L in 0, 0.5% and 0, respectively
- Grade 3/4 ALT > 5 x ULN in 3%, 2% and 2%, respectively
- Grade 3/4 AST > 5 x ULN in 3%, 1% and 1%, respectively
- Grade 3/4 total bilirubin > 2.5 x ULN in 0.5%, 0 and 1%, respectively

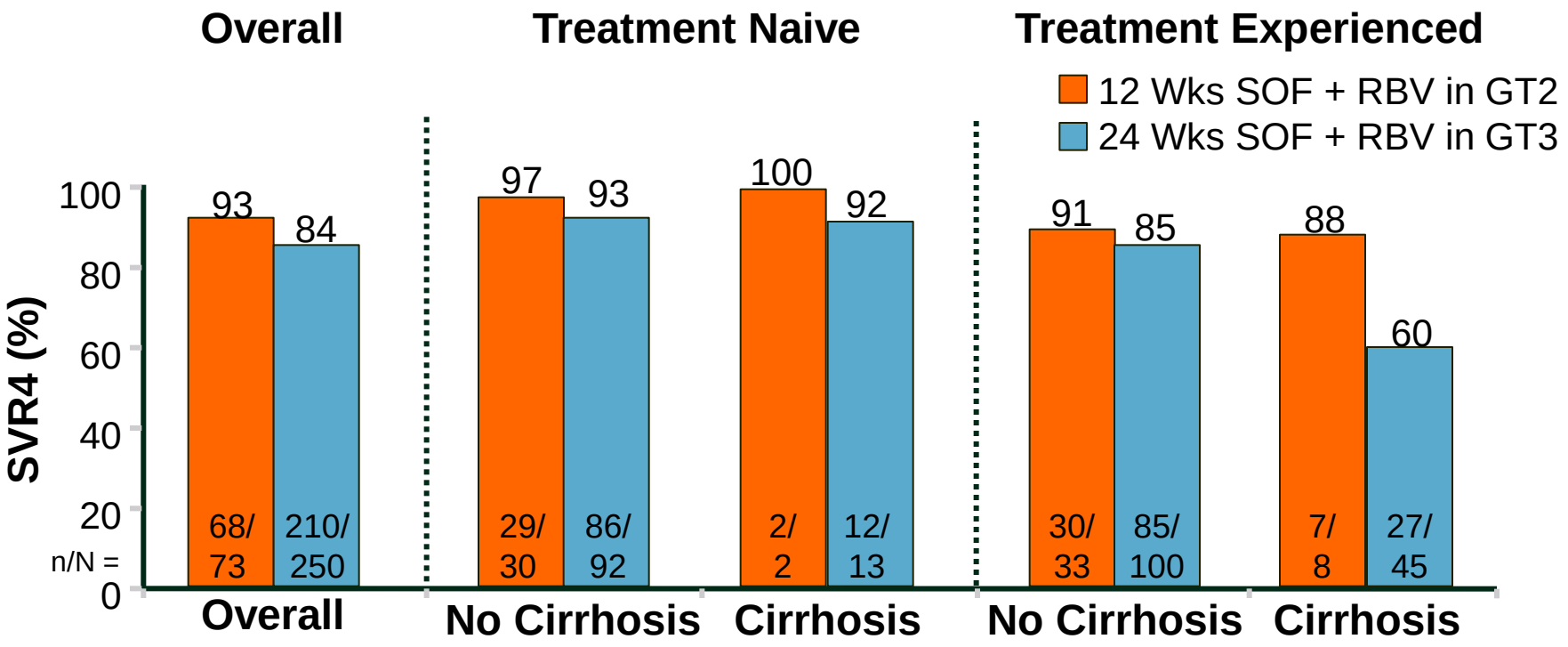
*1 patient with confirmed Gilbert's syndrome met laboratory but not clinical criteria for potential drug-induced liver injury. Patient had grade 3 increased hepatic enzymes and grade 4 ALT abnormality. Patient completed treatment and achieved SVR12.

†Most commonly ALT/AST elevations that resolved off treatment (7 patients, 6 of 7 achieved SVR12).

Manns M, *et al*. Lancet 2014; Jul 26 epub ahead of print

Other Studies in Patients Infected with HCV-2 or 3

VALENCE Efficacy : SVR12



Zeuzem S, et al., NEJM 2014

Conclusions

- Two IFN-free regimen will be / are approved for HCV genotype 1 infected patients in IV/2014 – I/2015
- Response to previous (IFN-based) therapy will be less relevant
- Cirrhosis (more granular differentiated) and potentially baseline HCV RNA are expected to remain as baseline predictors for SVR
- Main differentiation between regimens
  - SVR and safety in patients with advanced disease
  - Drug-drug interactions
- Treatment options for cirrhotic patients, patients with renal impairment and those infected with HCV-3 need further refinement