

The Evolution of HCV Infection Treatment and Future Therapeutic Options

Dr Ashley Brown

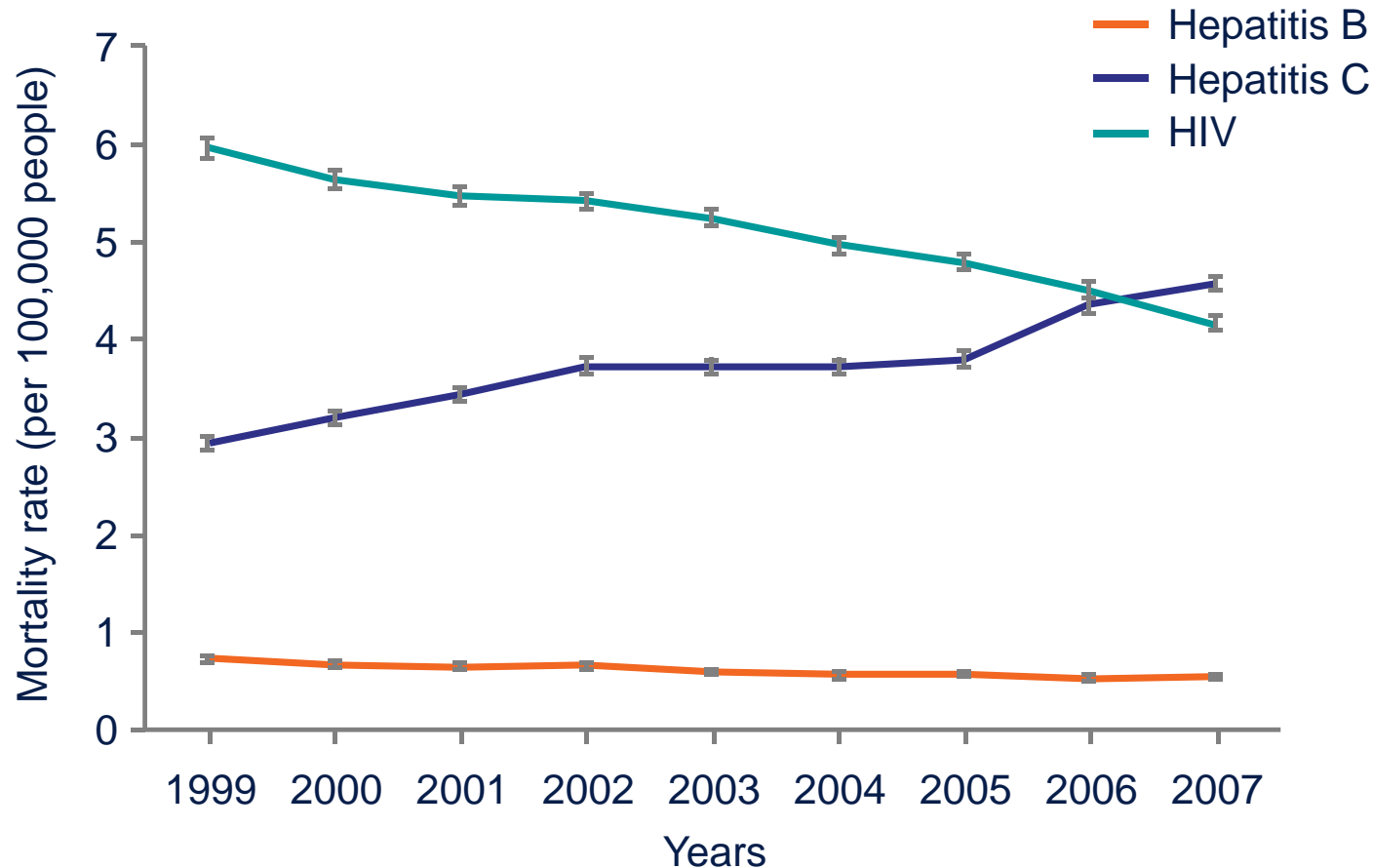
Imperial College Healthcare NHS Trust

Lietuvos Infektologų Draugijos Konferencija, Palanga
6th June 2014



Growing burden of mortality associated with viral hepatitis C in the US (1999–2007)

CDC, Atlanta; 21.8 million records examined for HBV and HCV; comparison HIV

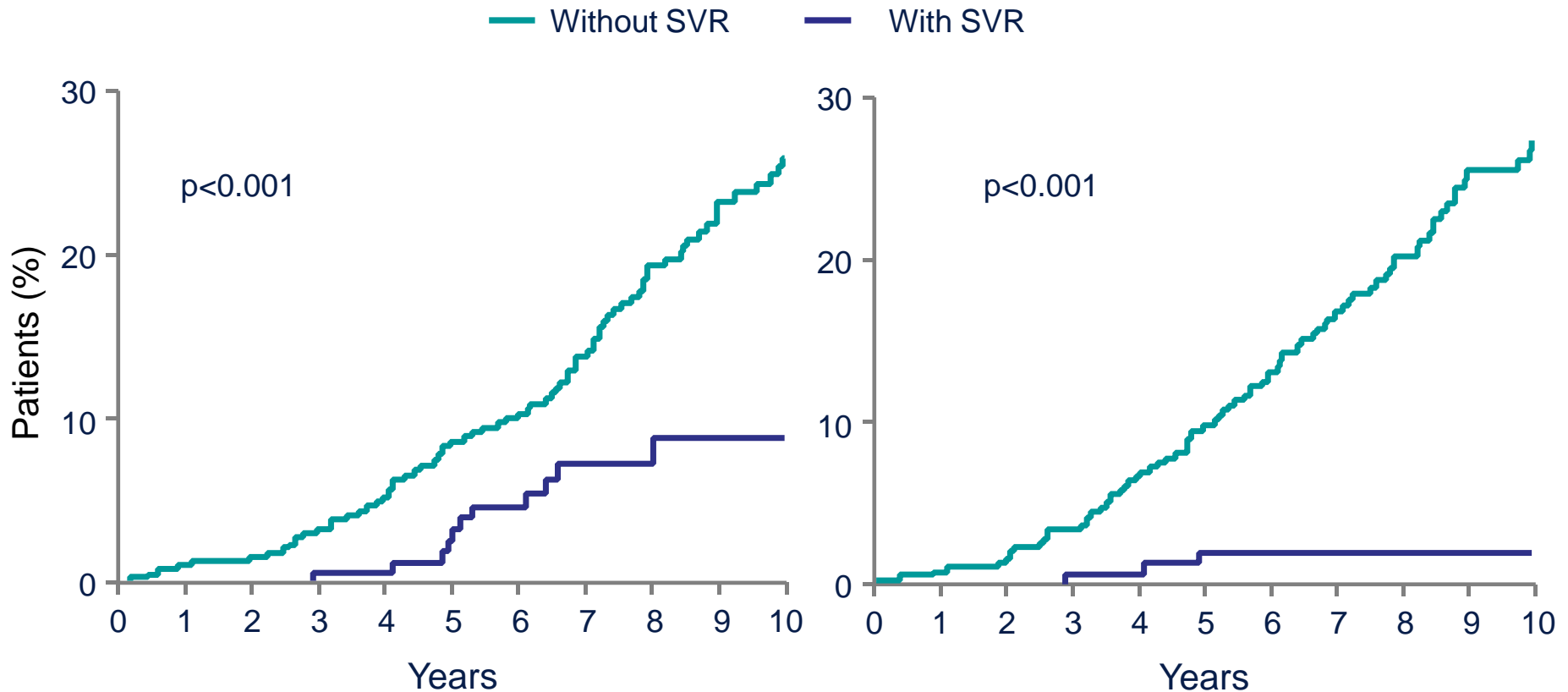


CDC = Centers for Disease Control and Prevention; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus

HCV: virus elimination reduces mortality

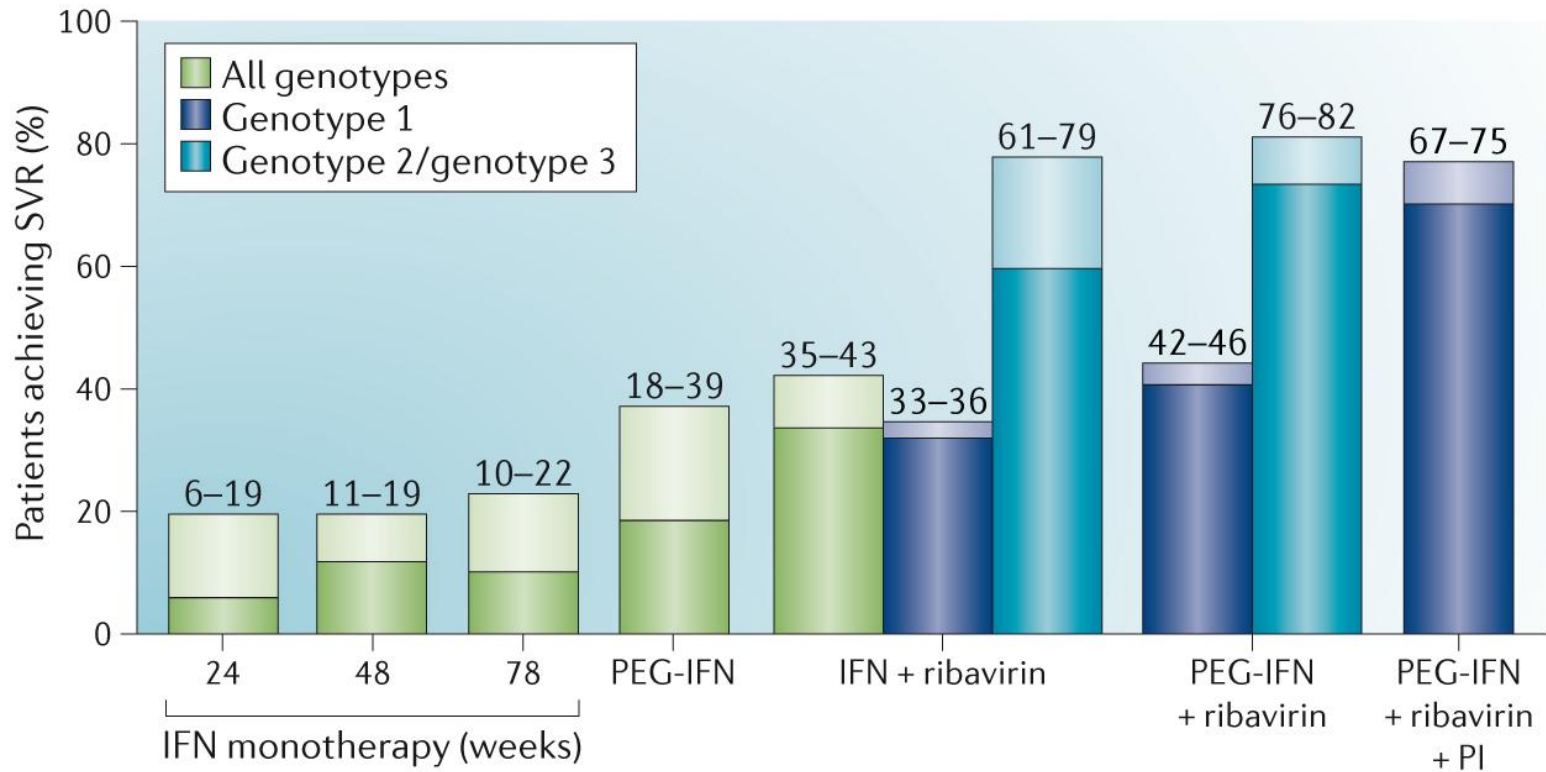
All-cause mortality

Liver-related mortality



SVR = sustained virological response

Evolution of HCV treatment



DAA = direct-acting antiviral; IFN = interferon; PEG-IFN = pegylated interferon; PI = protease inhibitor

Everson et al. J Hepatol 2013;58:#1423 S573; Gane et al. J Hepatol 2013;58:#14 S6; Kowdley et al. J Hepatol 2013;58:#3 S2; Manns & von Hahn. Nat Rev Drug Discov. 2013;doi10.1038/nrd4050; Rockstroh. NATAP conference report, available at: http://www.natap.org/2013/EASL/EASL_106.htm

DAA classes provide building blocks for new HCV treatment regimens

NS3/4A protease inhibitors

- Viral enzyme inhibitors

NS5A inhibitors

- Inhibit viral replication but precise function unknown

Nucleoside NS5B polymerase inhibitors

- Bind to NS5B active site leading to chain termination of viral genome

Non-nucleoside NS5B polymerase inhibitors

- Bind to NS5B protein outside active site causing conformational change

What will we need in order to eradicate HCV?

- Regimen(s) that are highly efficacious, have optimal tolerability and require minimal monitoring is a given
- Will some special groups (eg previous null responders, cirrhotics etc) remain resistant?
- Will we need different regimens for different viral genotypes?
- Will cost mean that different areas of the world will use different regimens
- Screening programmes will be crucial

DAA classes provide building blocks for new HCV treatment regimens

NS3/4A protease inhibitors

- Viral enzyme

Approved

Boceprevir
Telaprevir
Simeprevir

NS5A inhibitors

- Inhibit viral RNA replication
• Precise function unknown

Nucleoside NS5B polymerase inhibitors

- Bind to NS5B active site leading to chain termination of viral RNA

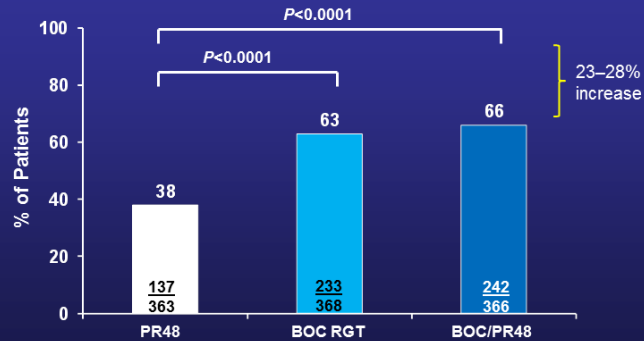
Sofosbuvir

Non-nucleoside NS5B polymerase inhibitors

- Bind to NS5B protein outside active site causing conformational change

BOC and TVR Registration Studies

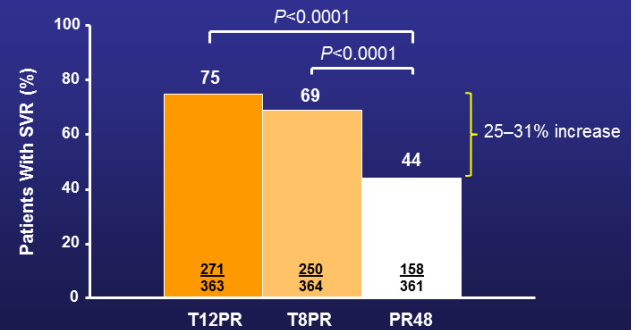
SPRINT-2: SVR Rates



Poordad F. et al. *N Engl J Med.* 2011; 364:1195-1206.

23

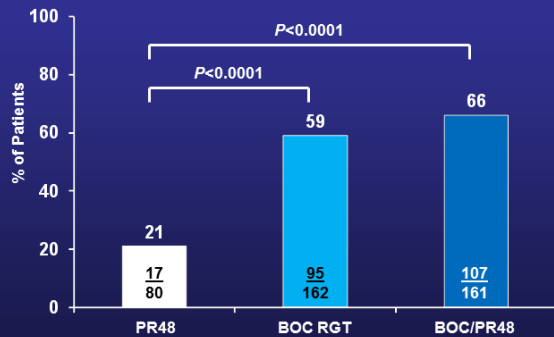
ADVANCE: SVR Rates



Jacobson IM et al. Presented at the American Association for the Study of Liver Diseases Annual Meeting, November 4-8, 2010, Boston, MA. Abstract 211.

27

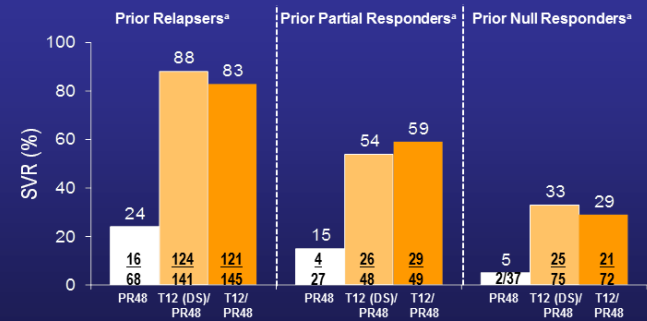
RESPOND-2 Boceprevir SVR Rates by ITT



Bacon B et al. *N Engl J Med.* 2011;364:1207-1217.

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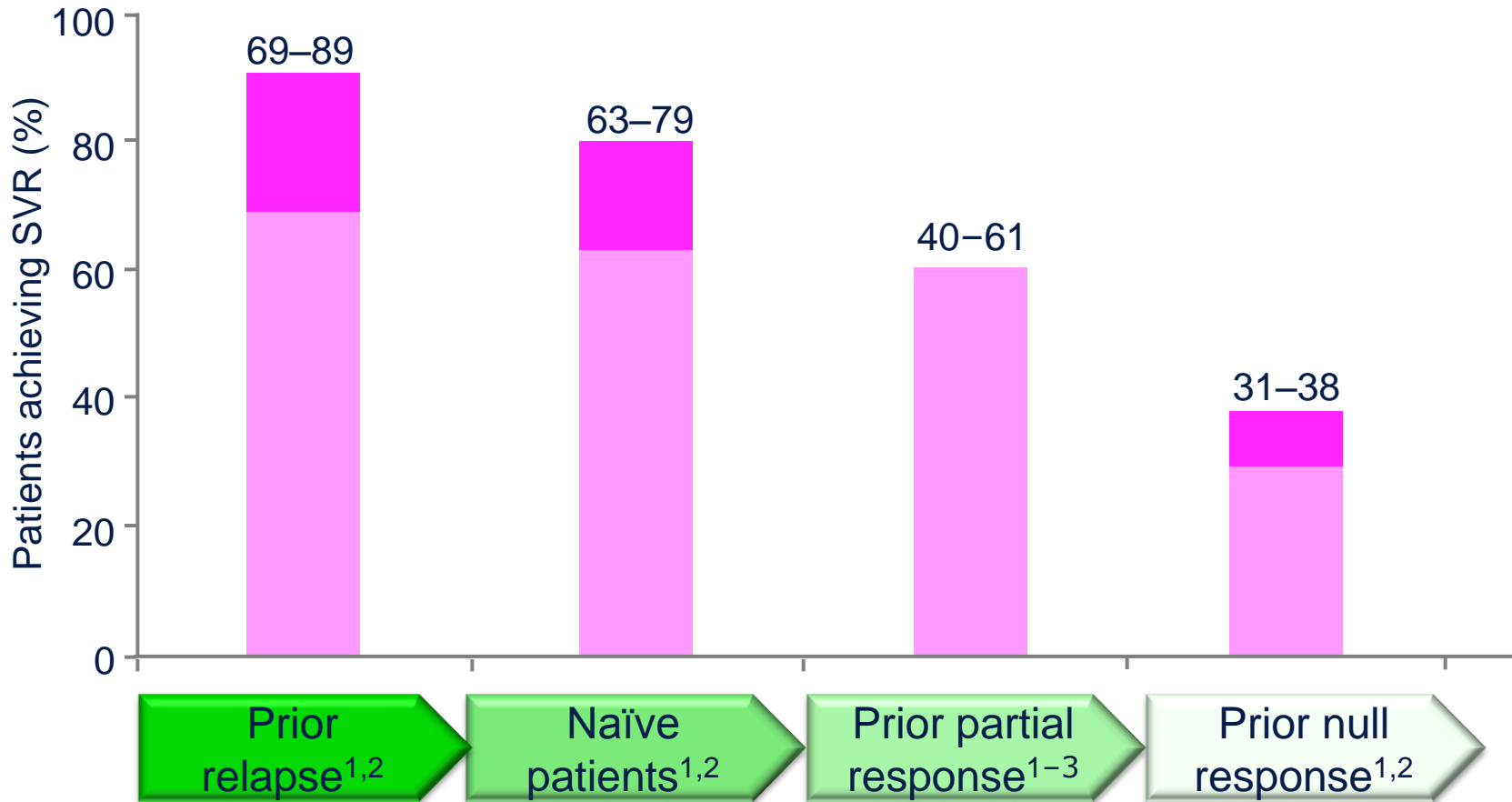
REALIZE: SVR in Prior Partial Responders, Null Responders, and Relapsers



* $P<0.0001$ T12/PR48 or T12 (DS)/PR48 vs PR48.

Zeuzem S et al. Presented at the European Association for the Study of the Liver Annual Meeting, March 30-April 3, 2011, Berlin, Germany.

First-generation protease inhibitors: SVR depends on response to PEG-IFN/RBV

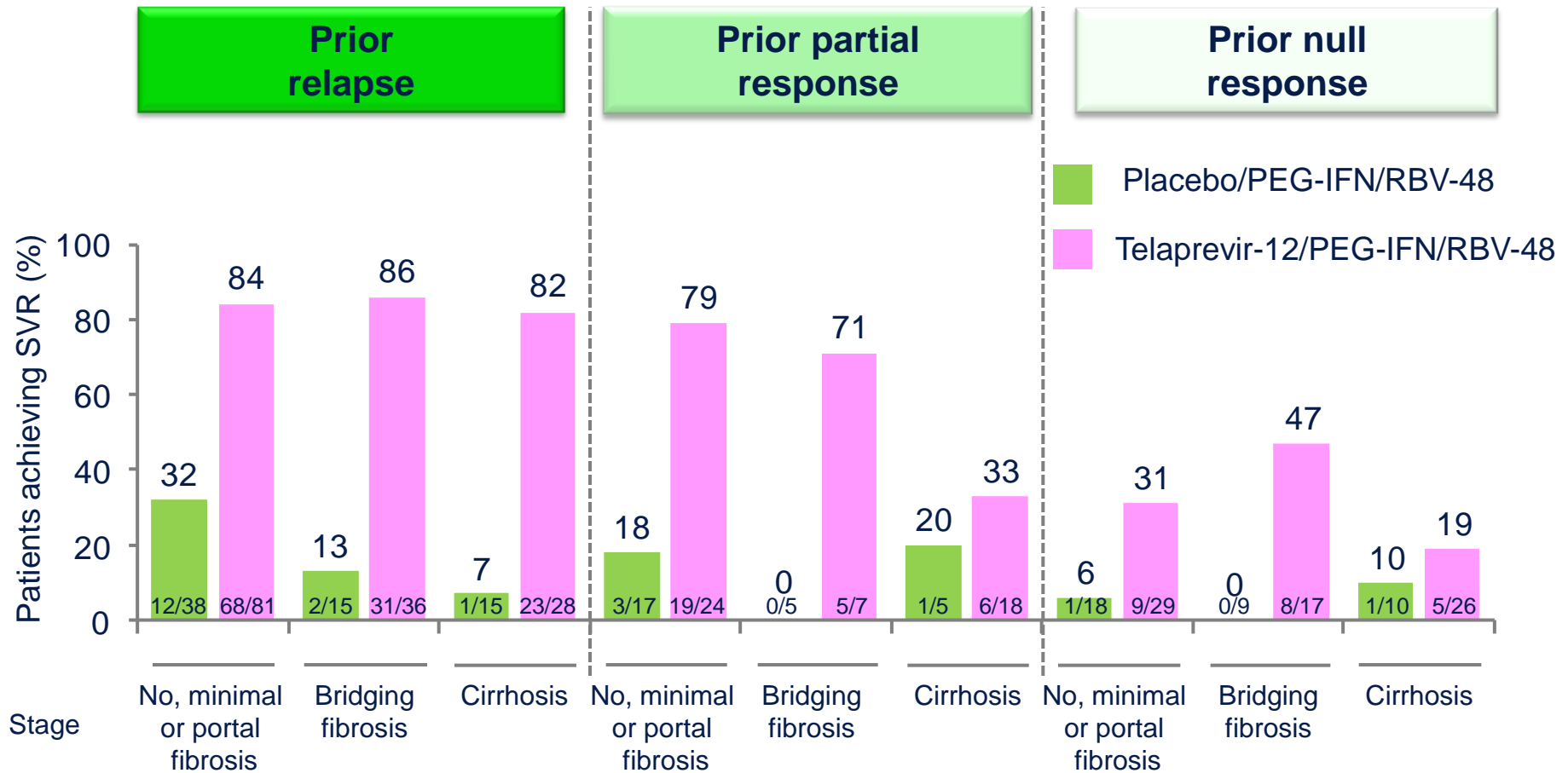


1. Victrelis SmPC Jun 2013

2. Incivo SmPC May 2013

3. Bacon et al. N Engl J Med 2011;364:1207–17

REALIZE (telaprevir): SVR in patients with fibrosis



Challenges with current PI's

Dosing schedule¹⁻⁴

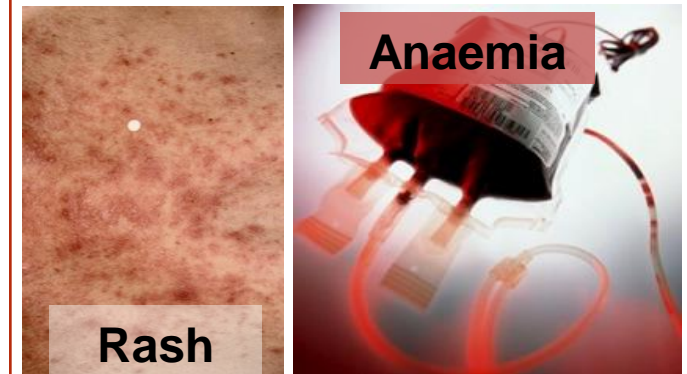
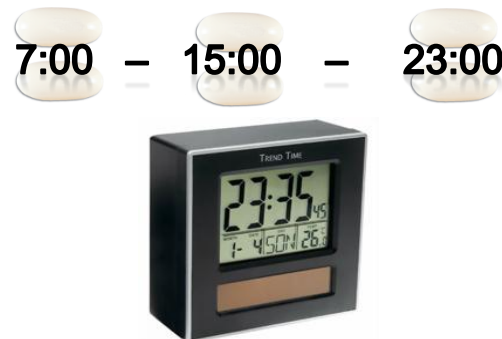
- 8–19 pills per day
- Strict 8-hour regimen
- Intake with meal (20g fat; telaprevir)
- Drug–drug interactions

Efficacy^{1,2}

- Limited in partial response null responders/patients with cirrhosis
- Mainly limited to GT1
- Viral resistance
- Limited data on re-treatment after previous PI exposure

Adverse events^{1,2,5}

- Anaemia
- Rash/dysgeusia
- Diarrhoea
- Many SAEs in patients with cirrhosis



GT = genotype; SAE = serious adverse event

CUPIC*: SVR12 and the risk of severe complications (multivariate analysis)[‡]

		Platelet count ≤100,000/mm ³	Platelet count >100,000/mm ³
Albumin <35 g/L	N	37	31
	Complications, n (%)	19 (51.4%)	5 (16.1%)
	SVR12, n (%)	10 (27.0%)	8 (29.0%)
Albumin ≥35 g/L	N	74	306
	Complications, n (%)	9 (12.2%)	19 (6.2%)
	SVR12, n (%)	27 (36.5%)	168 (54.9%)

*CUPIC is an early access cohort for treatment-experienced patients with F4 fibrosis/cirrhosis

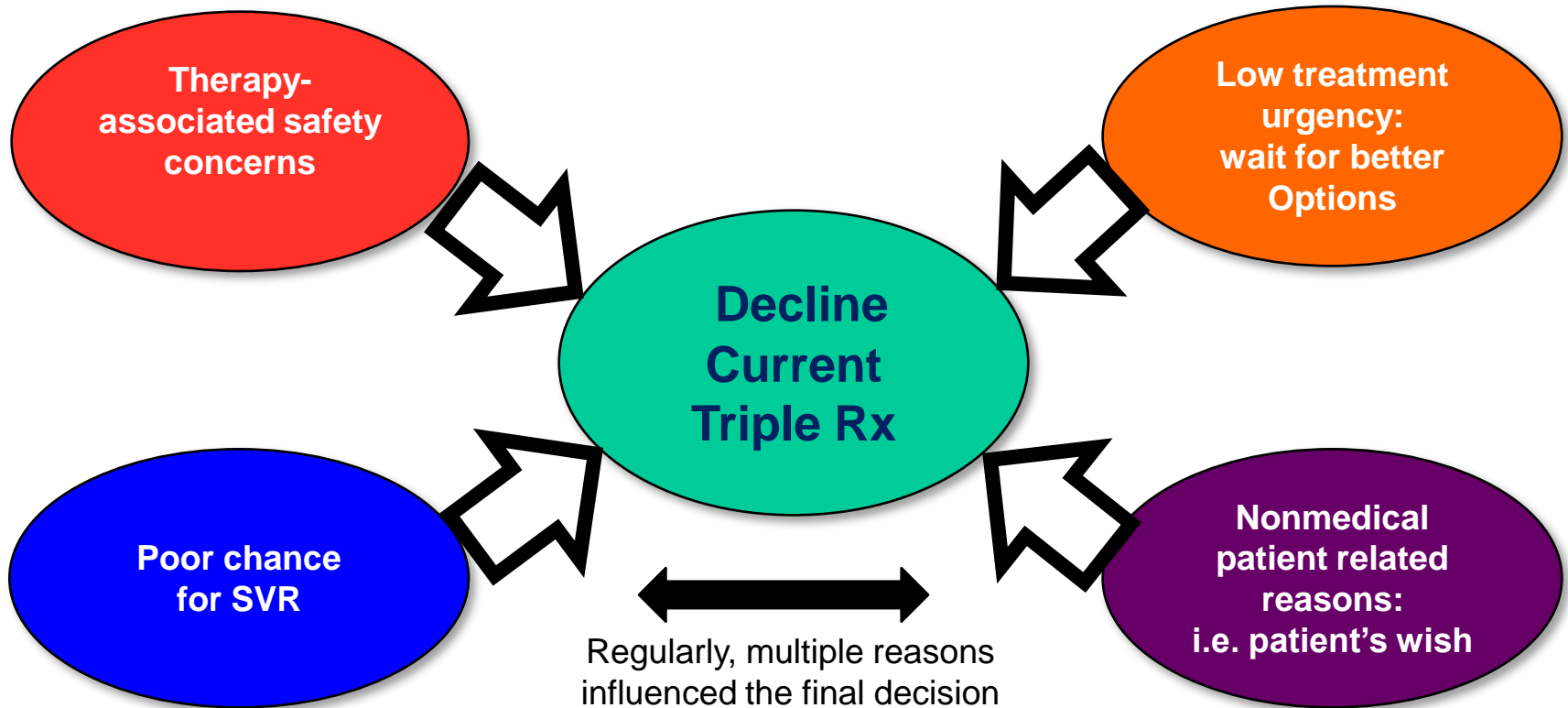
[‡]Missing data for 69 patients

Safety and efficacy stratified by risk profile in 'real' patients with cirrhosis

	Group A (n=7) Platelets <110/nl AND Child-Pugh >5	Group B (n=16) Platelets <110/nl OR Child-Pugh >5	Group C (n=20*) Platelets ≥110/nl AND Child-Pugh >5
Treatment failure	100% (n=7/7)	69% (n=11/16)	30% (n=6/20)
SAE	57% (n=4/7)	63% (n=10/16)	25% (n=5/20)
Either SAE or treatment failure	100%	94%	50%

- Almost every patient (96%; n=22/23) with Child-Pugh score >5 and/or baseline platelets <110/nl (group A/B) experienced either treatment failure and or ≥1 SAE until end of treatment
- Only remaining patient experienced relapse during further follow-up

Why are patients delaying treatment?



Populations with unmet need despite current PI's

- Non genotype 1
- Patients with cirrhosis
 - Most in need, rarely studied, reduced response rates
- Patients with HIV co-infection
 - Will low CD4 count patients respond?
- Post-liver-transplant patients
 - Huge unmet need, poor response
- Patients with renal disease
 - Dosing regimens to be determined
- PI treatment-experienced patients

Challenges with current PI's and requirements for future DAAs

Dosing schedule¹⁻⁴

- 8–19 pills per day
- Strict 8-hour regimen
- Intake with meal (20g fat; telaprevir)
- Drug–drug interactions

Efficacy^{1,2}

- Limited in partial response null responders/patients with cirrhosis
- Mainly limited to GT1
- Viral resistance
- Limited data on re-treatment after previous PI exposure

Adverse events^{1,2,5}

- Anaemia
- Rash/dysgeusia
- Diarrhoea
- Many SAEs in patients with cirrhosis

Challenges with current protease inhibitor regimens and requirements for future DAAs

Dosing schedule¹⁻⁴

- 8–19 pills per day

Efficacy^{1,2}

- Limited in partial response population

Adverse events^{1,2,5}

- Anaemia

What do we need in the future?

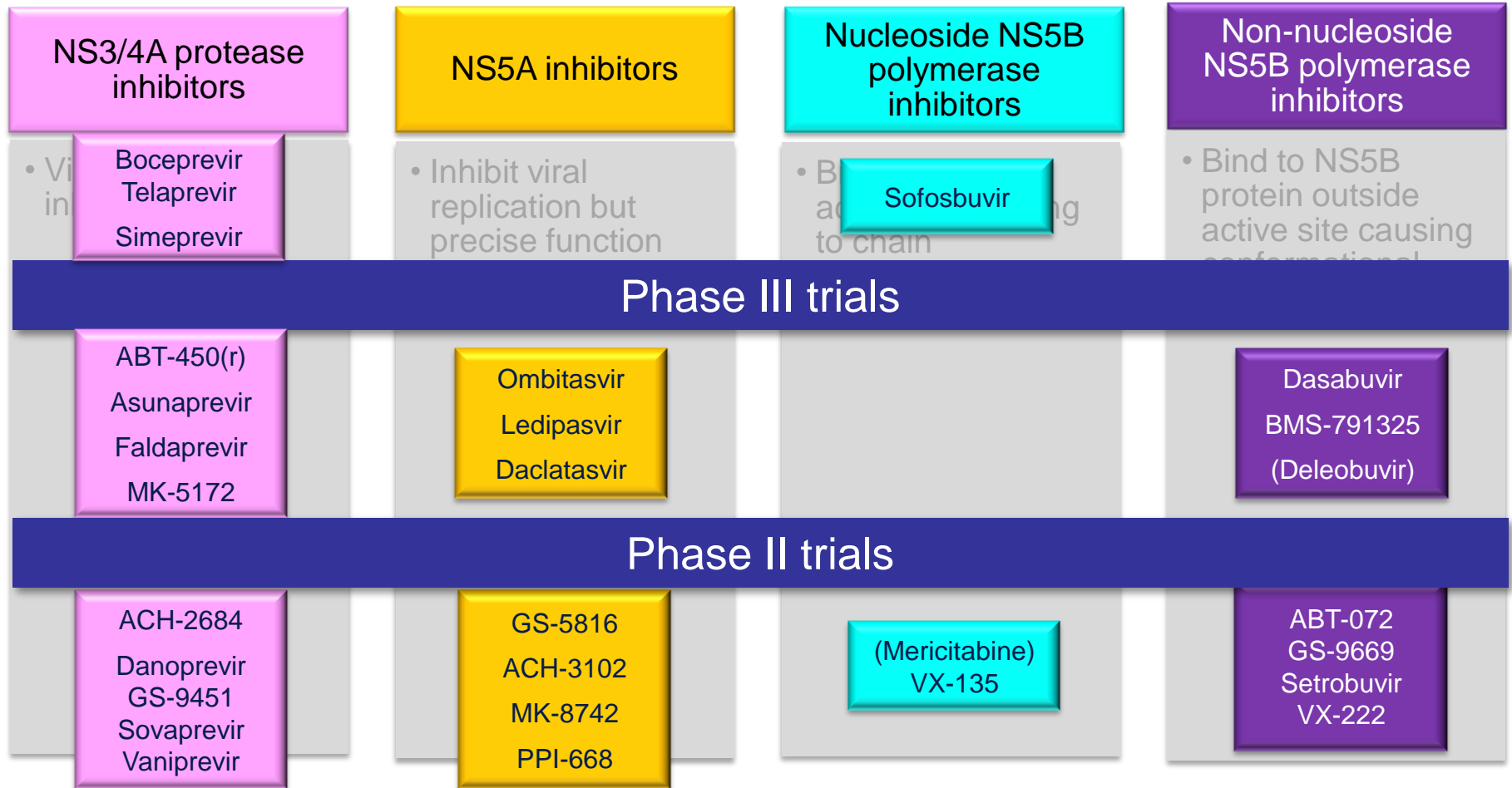
treatment after previous PI exposure

- Easier dosing schedule (once daily)
- Fewer DDI's
- Shorter duration

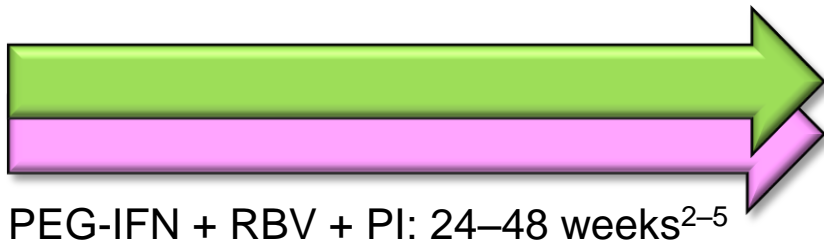
- Regimens with
 - High potency
 - Pan-genotypic
 - High barrier to resistance

- Better tolerability

DAA classes provide building blocks for new HCV treatment regimens



Treatment duration: how short could it be?



Expected for all-oral DAAs in development: : 8–12–24 weeks^{6–9}

1. EASL. J Hepatol 55:245–64; 2. Poordad et al. N Engl J Med 2011;364:1195–206;
3. Bacon et al. N Engl J Med 2011;364:1207–7; 4. Jacobson et al. N Engl J Med 2011;364:2405–16;
5. Zeuzem et al. N Engl J Med 2011;364:2417–28; 6. Gane et al. J Hepatol 2013;58:#14 S6;
7. Kowdley et al. J Hepatol 2013;58:#3 S2; 8. Everson et al. J Hepatol 2013;58:#1423 S573;
9. Rockstroh. NATAP conference report, available at: http://www.natap.org/2013/EASL/EASL_106.htm

HCV clinical trials overview

- As of Feb 2014 there were over 400 open studies in HCV¹
 - To date, many have evaluated only small numbers of patients^{2–4}
 - Studies of GT1 are most common, but other subtypes are increasingly being studied
- There are many new DAA regimens with PEG-IFN + RBV which offer potential for further reduced treatment duration and higher SVR^{5–8}
- Multiple all-oral DAA regimens without PEG-IFN are being assessed in Phase III trials^{9–15}, some excluding RBV, others including a PI booster
 - Dual DAA combinations
 - Triple DAA combinations

1. Clinical.trials.gov; 2. Lok et al. N Eng J Med 2012;366:216–24; 3. Poordad et al. N Eng J Med 2013;368:45–53; 4. Gane et al. J Hepatol 2013;58(S1) S6; 5. Ferenci et al. J Hepatol 2013;58(S1) S569; 6. Jacobson et al. J Hepatol 2013;58(S1) S574; 7. Manns et al. J Hepatol 2013;58(S1) S568; 8. Lawitz et al. N Eng J Med 2013;368:1878–87; 9. Sulkowski et al. J Hepatol 2013;58(S1) S570; 10. Jacobson et al. J Hepatol 2013;58(S1) S574; 11. Lok et al. N Eng J Med 2012;366:216–24; 12. Poordad et al. N Eng J Med 2013;368:45–53; 13. Gane et al. J Hepatol 2013;58(S1) S6; 14. Kowdley et al. J Hepatol 2013;58(S1) S2; 15. Everson et al. J Hepatol 2013;58(S1) S573

The Evolution of Treatment

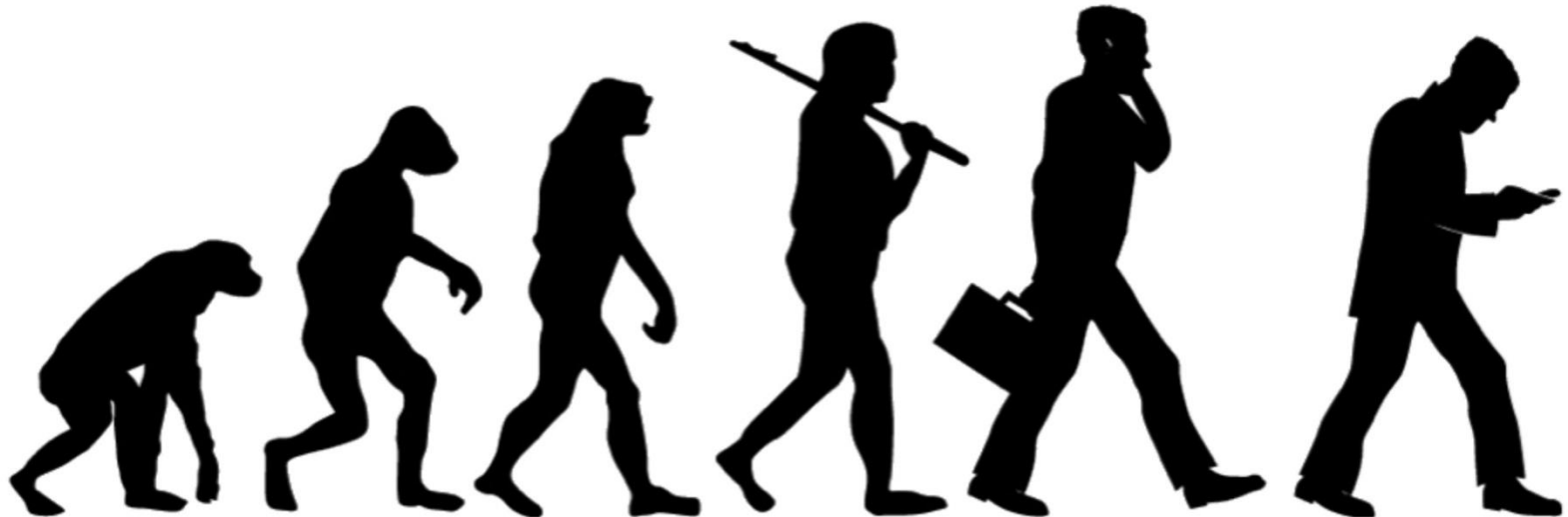
PegINF
+
ribavirin

PegINF
+
ribavirin
+
PI

DAA
+
ribavirin

DAA
+
DAA

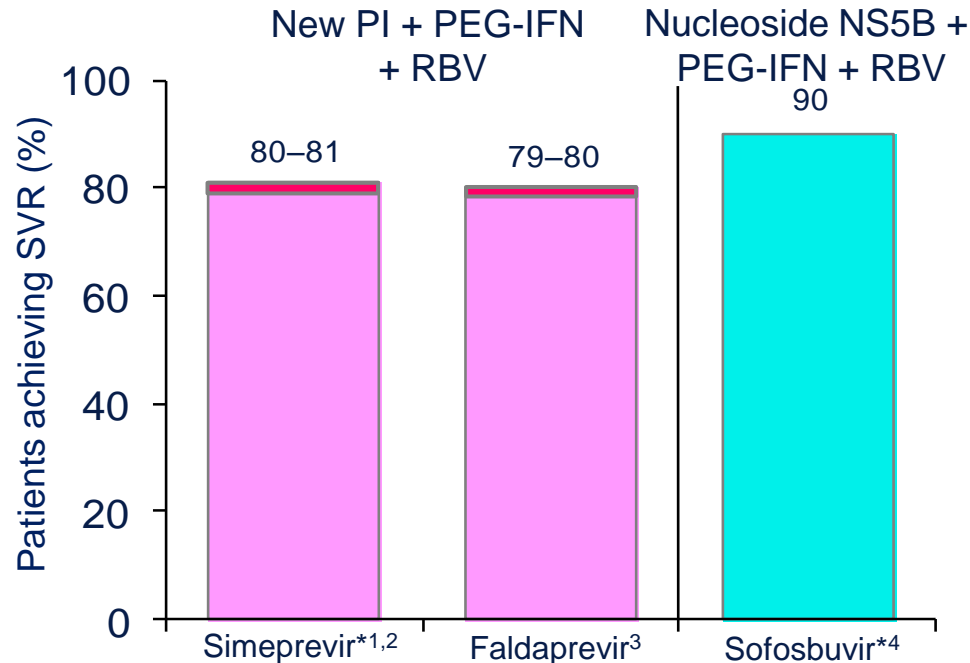
DAA
+
DAA
+
DAA



Treatment options for GT1

SVR at Week 12 (Phase II trials): new DAAs with PEG-IFN + RBV

Data from different studies
Range of values reported; lower
bar represents lower value



DAA duration (weeks):	12	12–24	12
PEG-IFN + RBV duration (weeks):	48	48	12
RGT patients with SVR12 (%)†:	86–91	86–89	N/A

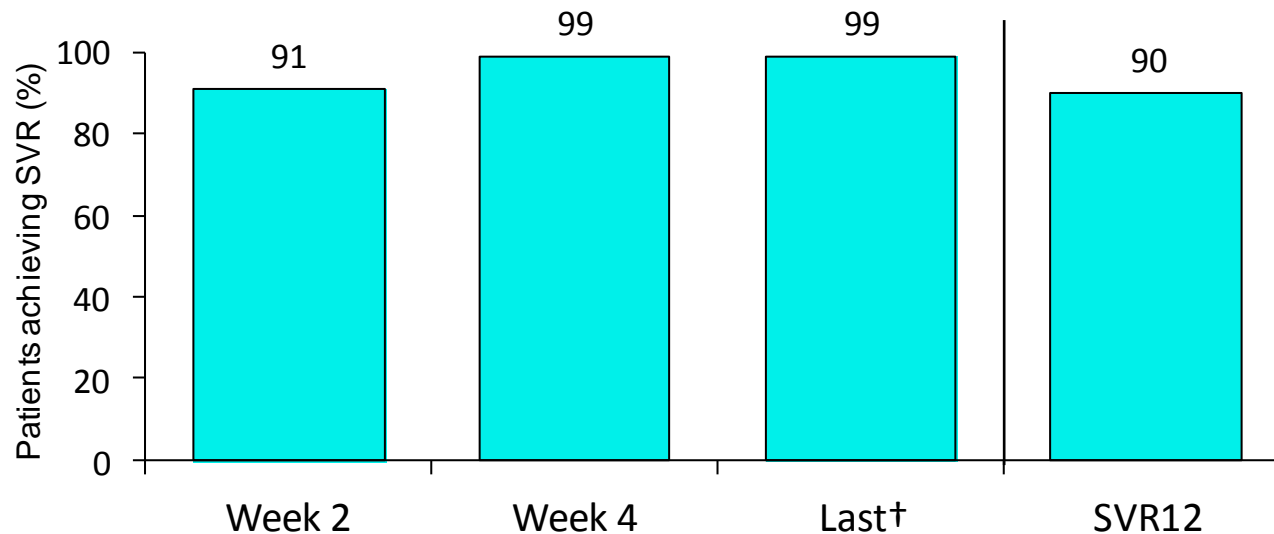
*RBV dosed according to weight⁵

†RGT: treatment stopped after 24 weeks of PEG-IFN + RBV

RGT = response-guided therapy; SVR = sustained virological response

Nucleoside NS5B inhibitor with PEG-IFN + RBV

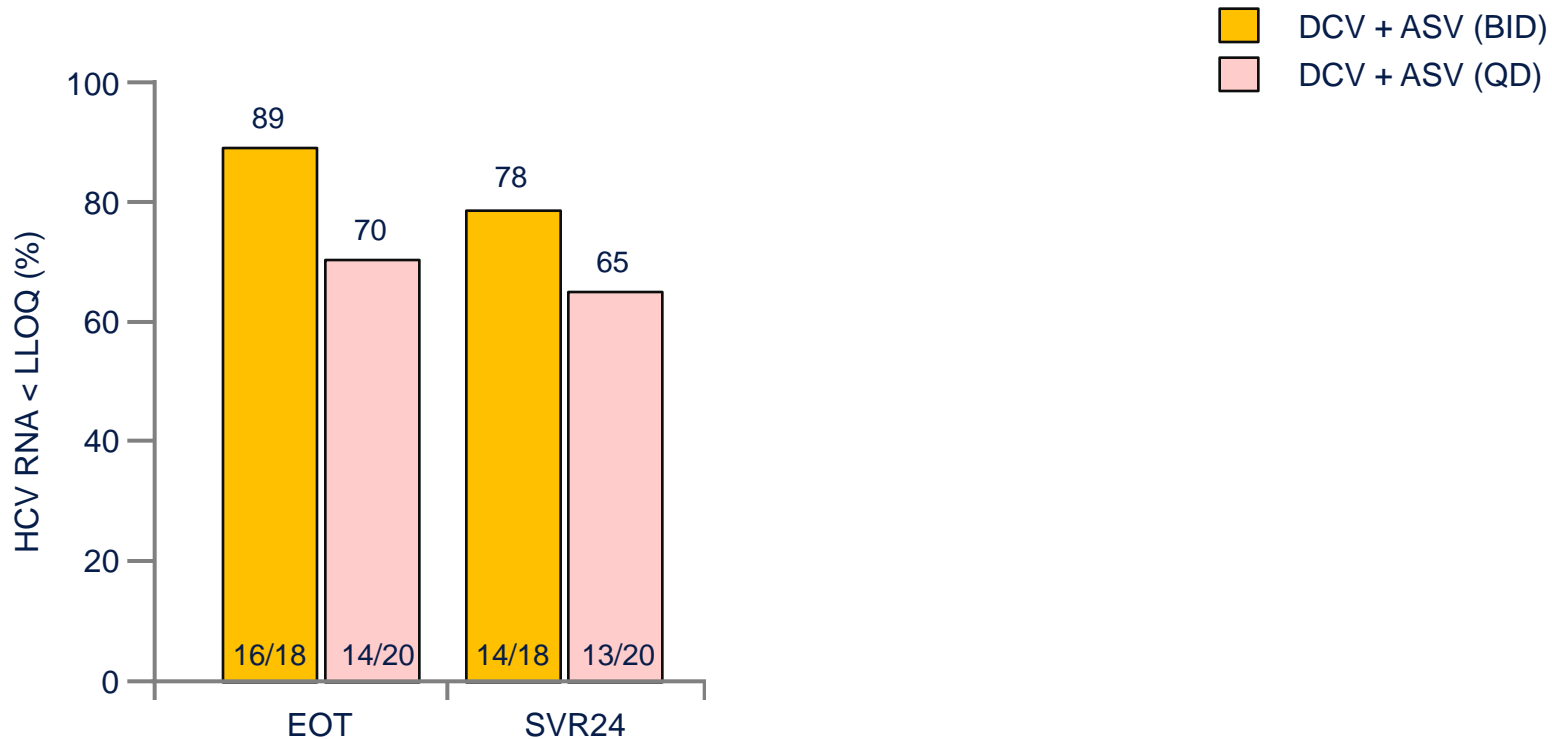
- NEUTRINO Phase III trial (n=327)
 - Sofosbuvir plus PEG-IFN + RBV* for 12 weeks
 - Treatment naïve, GT1 (89%), 4, 5 or 6
 - 17% had compensated cirrhosis



*Dose administered according to body weight

†Last observed measurement

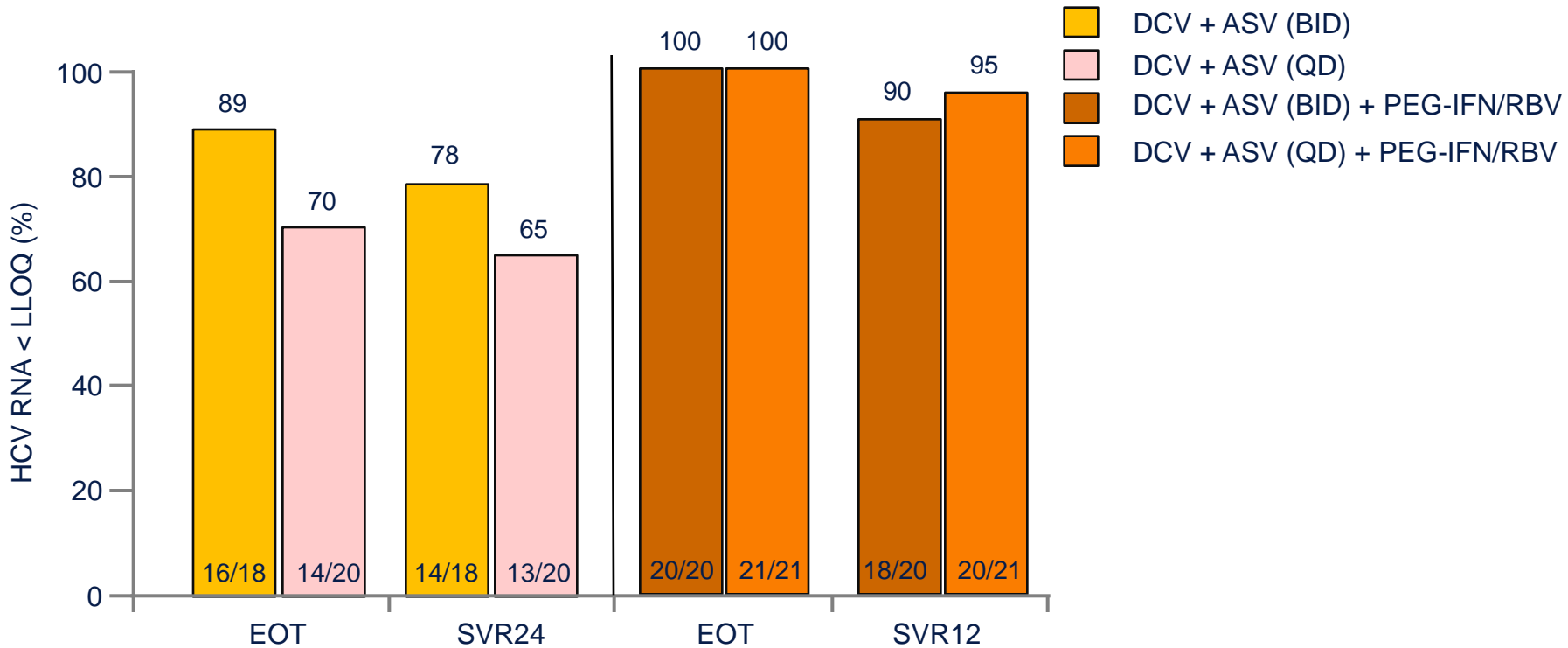
Daclatasvir + Asunaprevir ± PEG-IFN/RBV in null responders



- All GT1b patients responded
- All regimens generally well tolerated

ASV = asunaprevir; BID = twice daily; DCV = daclatasvir; QD = once daily

Daclatasvir + asunaprevir ± PEG-IFN or RBV in null responders



- ▲ All GT1b patients responded
- ▲ All regimens generally well tolerated

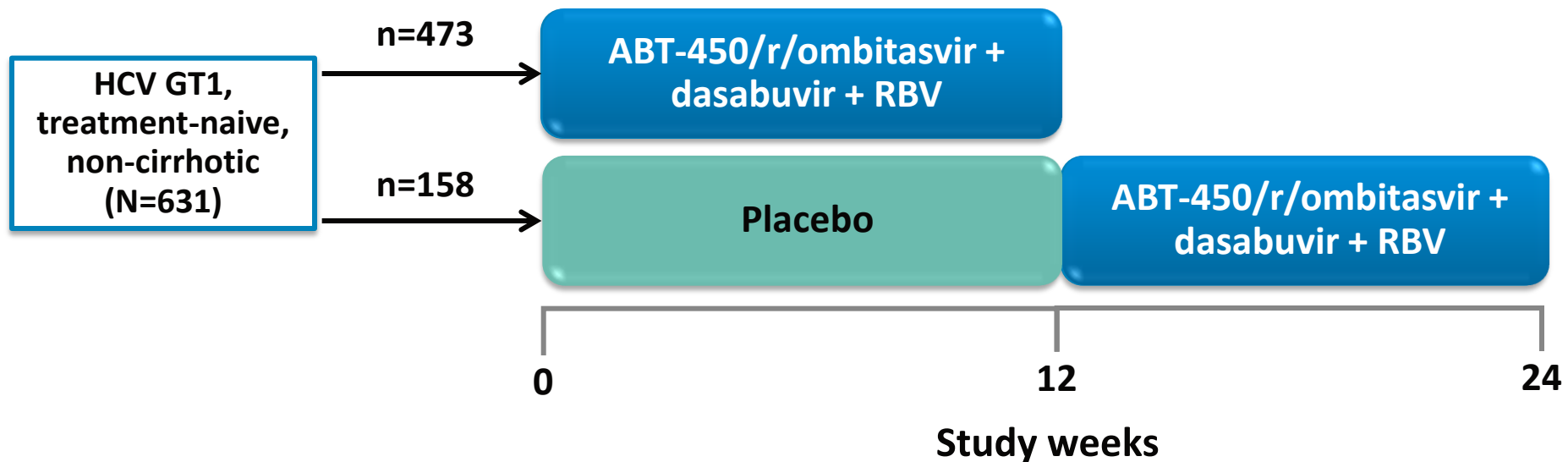
ASV = asunaprevir; BID = twice daily; DCV = daclatasvir; QD = once daily

IFN-free, all-oral DAA regimens

SAPPHIRE-I: GT1, treatment-naive, non-cirrhotic patients

Study design

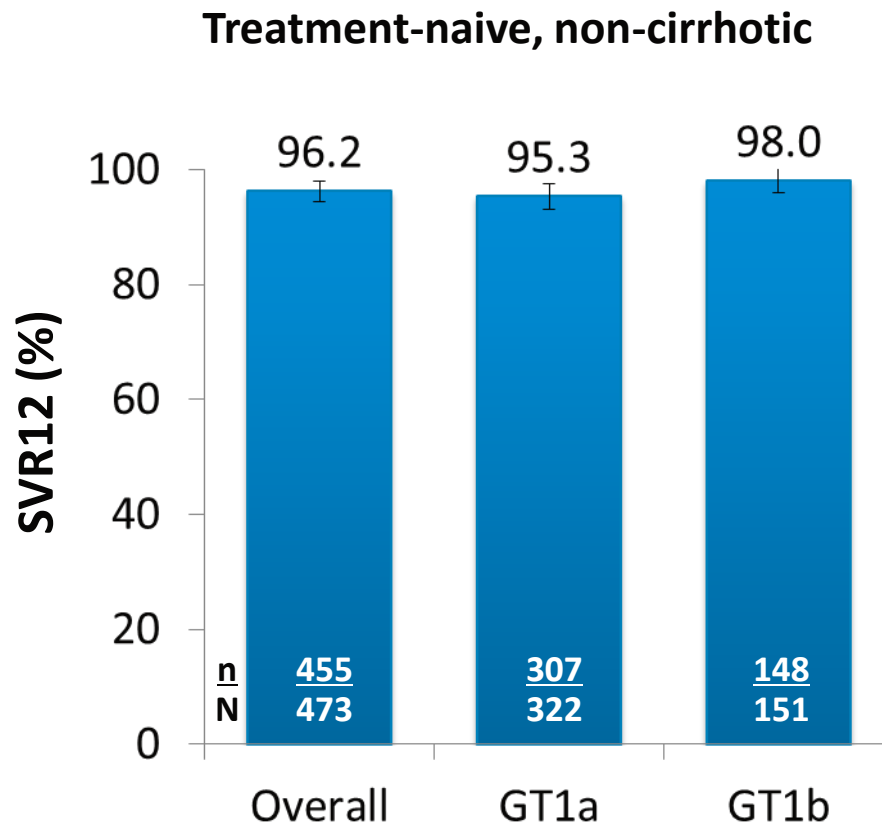
ABT-450/r/ombitasvir + dasabuvir + RBV



ABT-450/r/ombitasvir (ABT-267) = 150/100/25 mg QD co-formulated; dasabuvir (ABT-333) = 250 mg BID; RBV = 1000–1200 mg daily according to body weight.

Feld JJ, et al. *New Engl J Med* 2014; **370**:1594–1603.

SAPPHIRE-I: GT1, treatment-naive, non-cirrhotic patients SVR12 rates by HCV GT1 subtype*



* Data for 3-DAA + RBV Arm only;
Error bars: 95% CI.

Feld JJ, et al. *New Engl J Med* 2014; **370**:1594–1603.

SAPPHIRE-I: GT1, treatment-naive, non-cirrhotic patients

Adverse events occurring in $\geq 10\%$ of patients

Event, n (%)	3D + RBV (n=473)	Placebo (n=158)	Δ	P-value
Any AE	414 (87.5)	116 (73.4)	14.1	<0.05
Fatigue	164 (34.7)	45 (28.5)	6.2	NS
Headache	156 (33.0)	42 (26.6)	6.4	NS
Nausea	112 (23.7)	21 (13.3)	10.4	<0.05
Pruritus	80 (16.9)	6 (3.8)	13.1	<0.05
Insomnia	66 (14.0)	12 (7.6)	6.4	<0.05
Diarrhea	65 (13.7)	11 (7.0)	6.7	<0.05
Asthenia	57 (12.1)	6 (3.8)	8.3	<0.05
Rash	51 (10.8)	9 (5.7)	5.1	NS

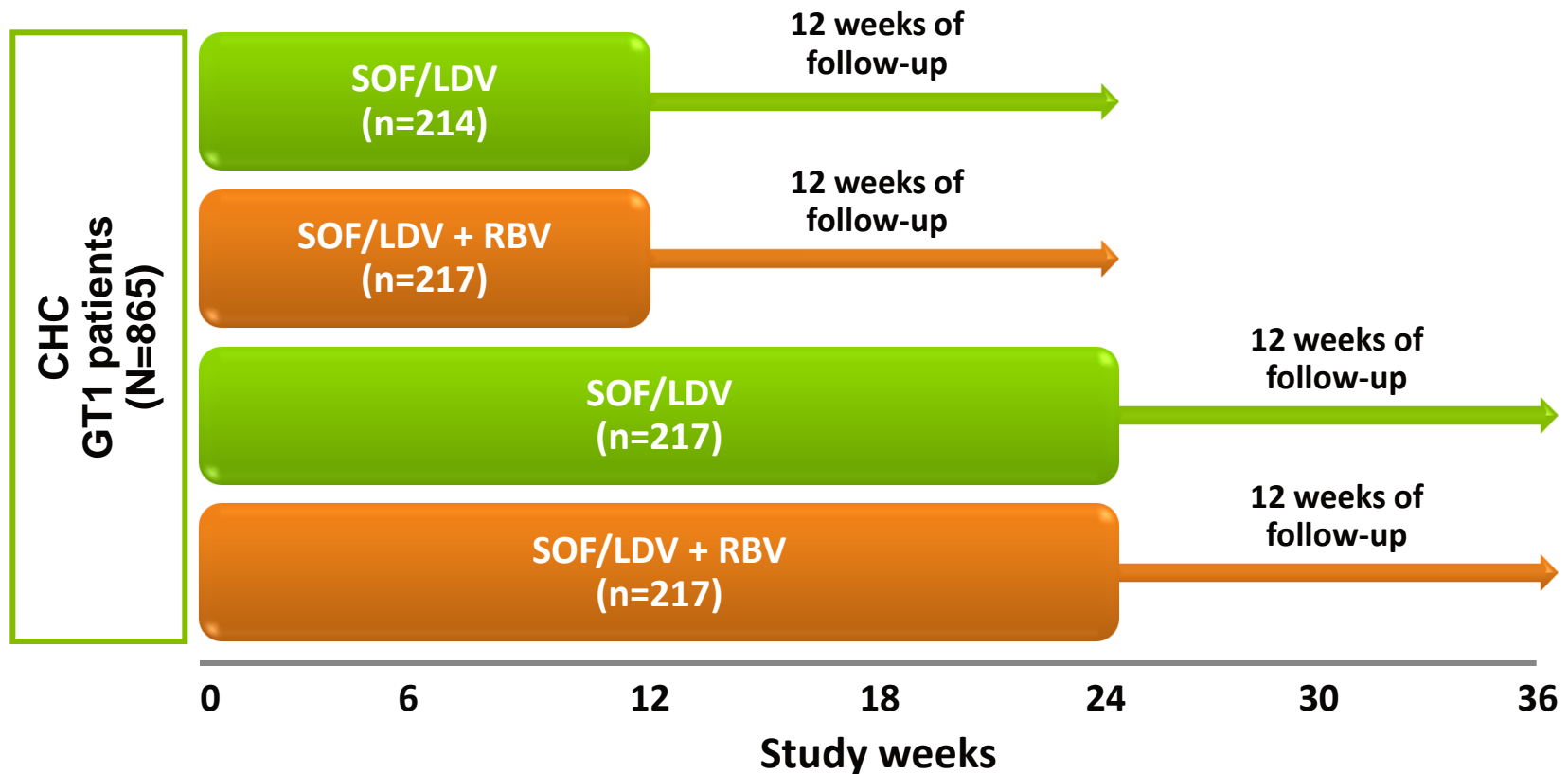
- AEs were generally mild
- Low (0.6%) rate of discontinuation due to AEs in each treatment group
- Serious AEs occurred in 2.1% of 3D + RBV recipients

NS = not significant.

Feld JJ, et al. *New Engl J Med* 2014; **370**:1594–1603.

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

Study design

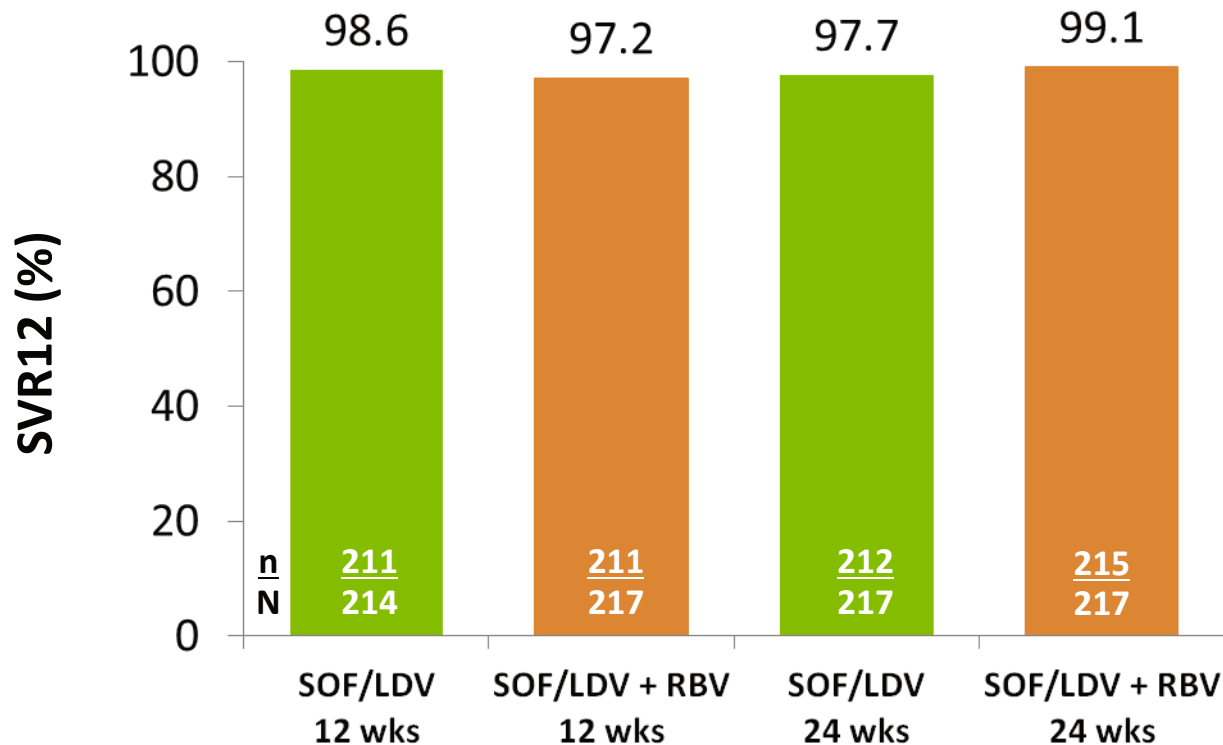


- Including 136 (15.7%) patients with cirrhosis

SOF = 400 mg/day; LDV = 90 mg/day;
RBV = 1000–1200 mg daily according to body weight.

Afdhal N, et al. *New Engl J Med* 2014; online DOI: 10.1056/NEJMoa1402454.

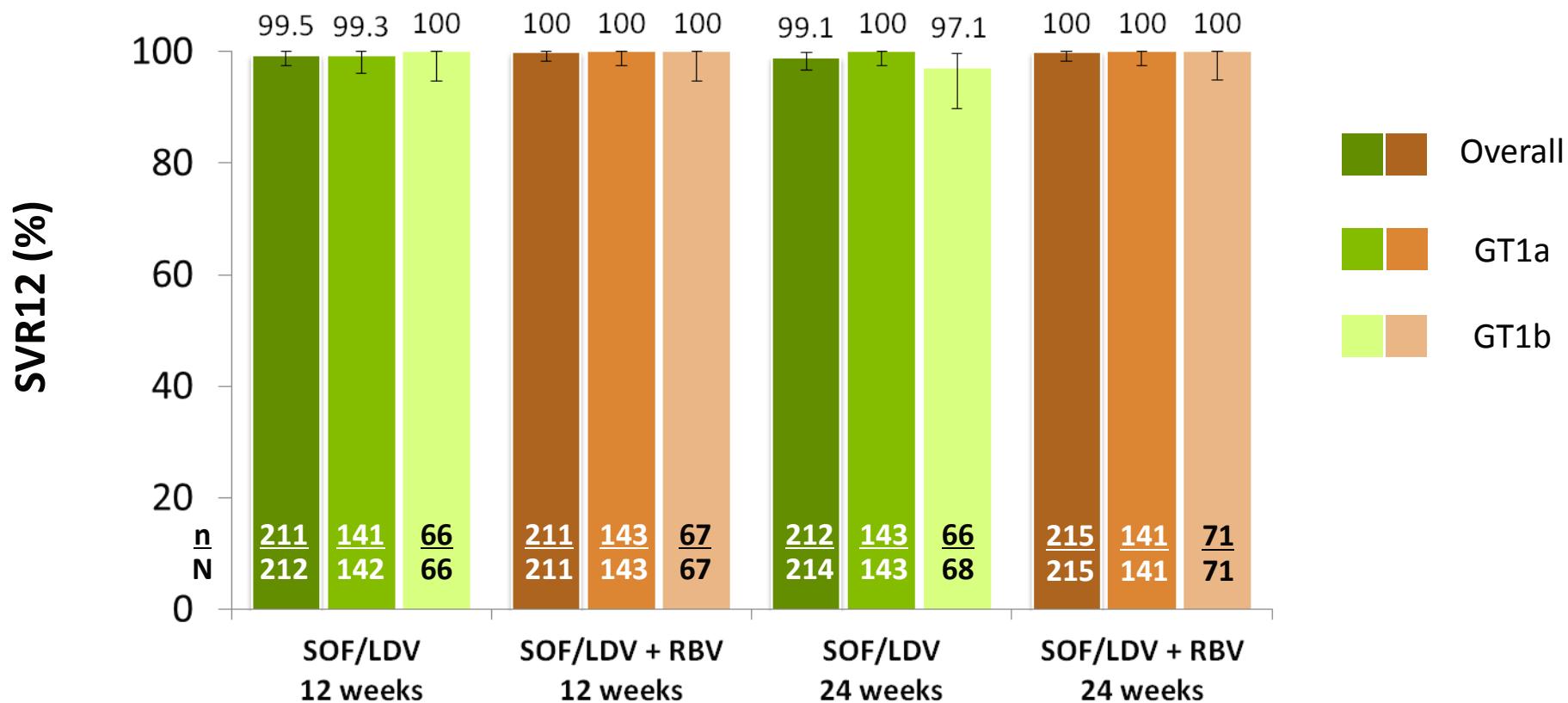
ION-1: SOF/LDV ± RBV in GT1 treatment-naive patients SVR12 rates in the ITT population (N=865)



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

SVR12 rates by genotype

SVR12 rates in the mITT population (N=852): subgroup results do not include patients who withdrew consent or who were lost to follow-up

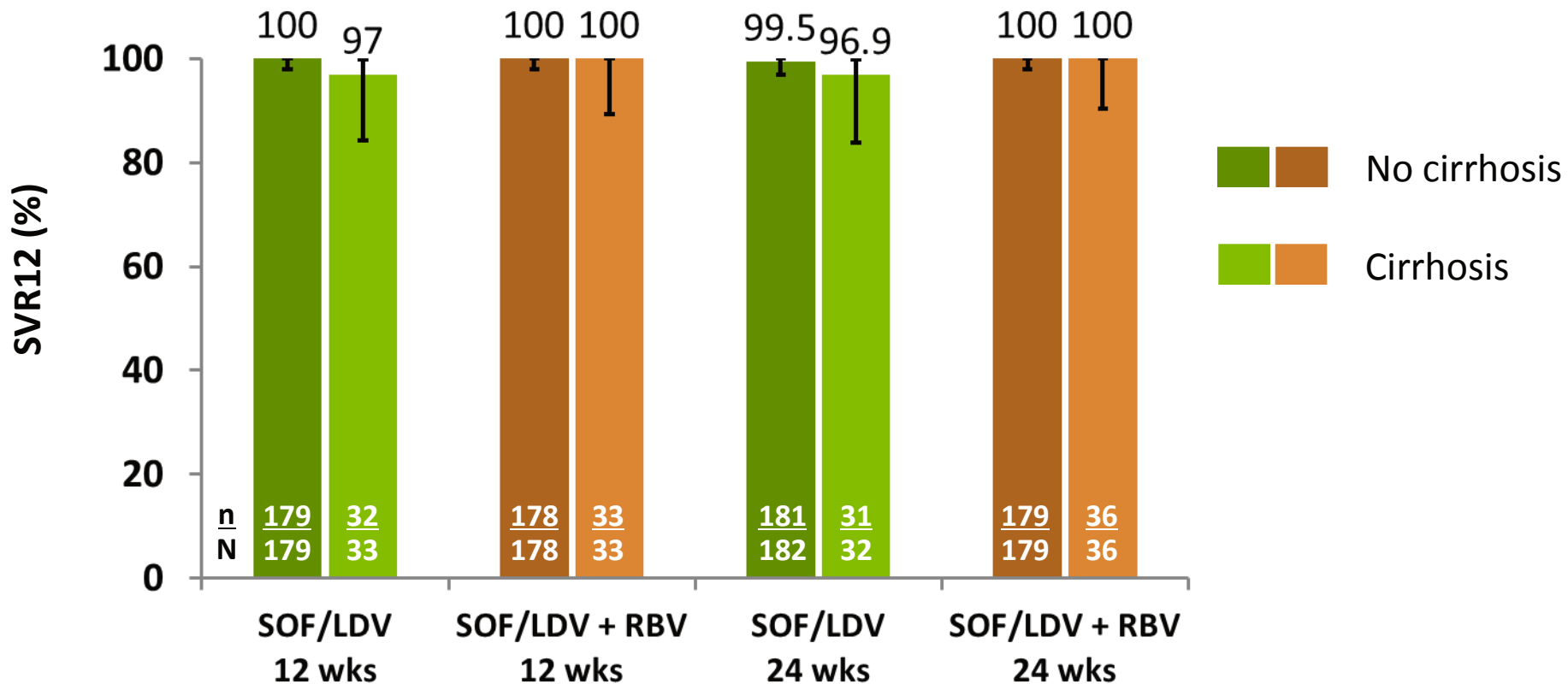


Eleven patients achieved SVR12, but were not sub-genotyped; Error bars: 95% CI.

Afdhal N, et al. *New Engl J Med* 2014; online DOI: 10.1056/NEJMoa1402454.

ION-1: SVR rates* in GT1, treatment-naive, cirrhotic patients (subgroup analysis)

15.7% (136/865) of patients enrolled had cirrhosis



* Subgroup results do not include patients who withdrew consent or were lost to follow-up.

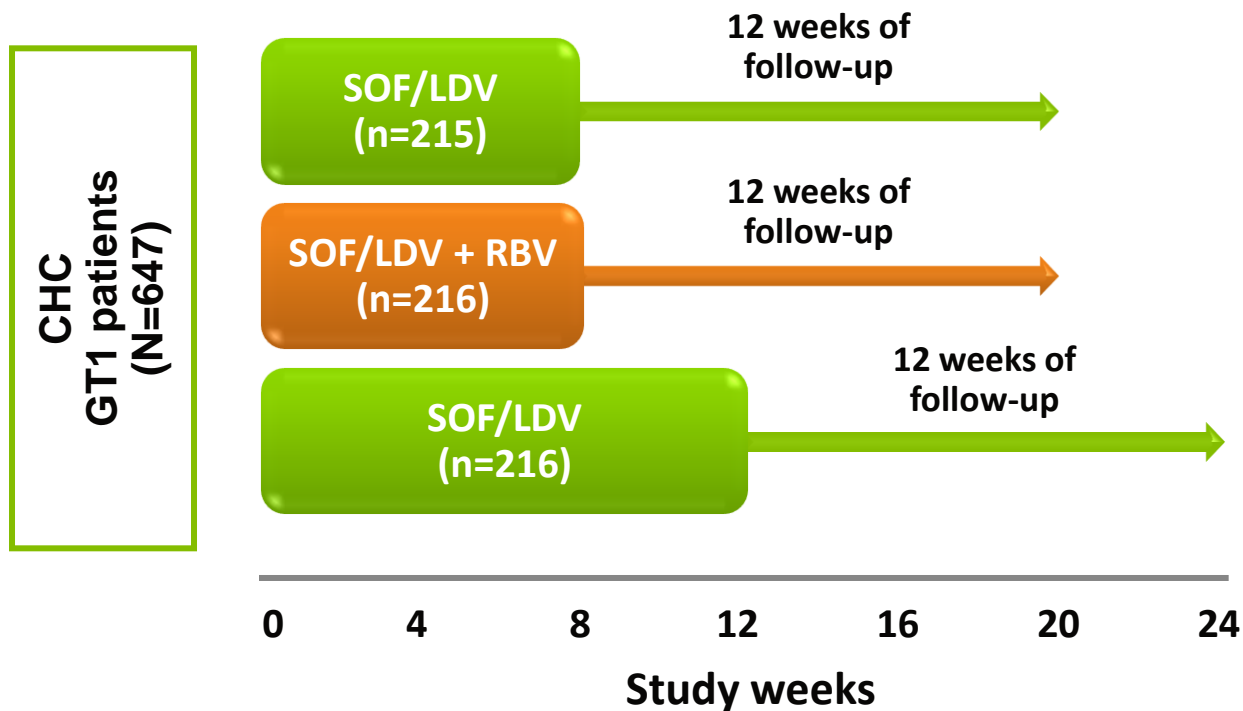
Afdhal N, et al. *New Engl J Med* 2014; online DOI: 10.1056/NEJMoa1402454.

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

Safety data

	SOF/LDV 12 weeks (N=214)	SOF/LDV + RBV 12 weeks (N=217)	SOF/LDV 24 weeks (N=217)	SOF/LDV + RBV 24 weeks (N=217)
Patients, n (%)				
Treatment discontinuations	0	0	4 (2)	6 (3)
Serious AEs	1 (<1)	7 (3)	18 (8)	7 (3)
Any AE	169 (79)	185 (85)	178 (82)	200 (92)
AEs in >15% of patients				
Fatigue	44 (21)	79 (36)	53 (24)	82 (38)
Headache	53 (25)	49 (23)	54 (25)	65 (30)
Insomnia	17 (8)	45 (21)	26 (12)	47 (22)
Nausea	24 (11)	37 (17)	29 (13)	32 (15)
Hemoglobin level <10 g/dL	0	20 (9)	0	16 (7)

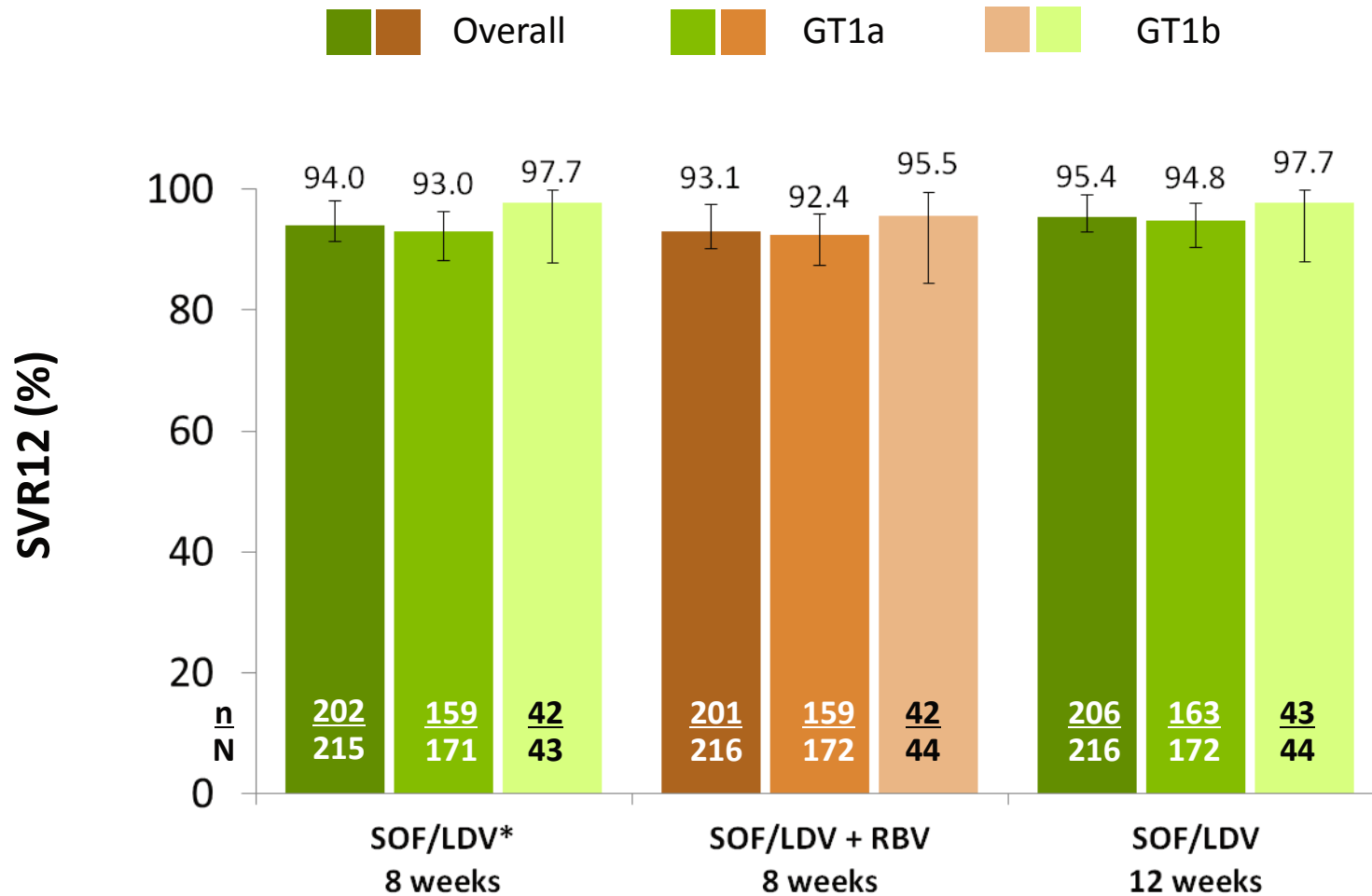
ION-3: Phase III SOF/LDV ± RBV in GT1, treatment-naive, non-cirrhotic patients – study design



SOF = 400 mg/day; LDV = 90 mg/day;
RBV = 1000–1200 mg daily according to body weight.

Kowdley KV, *et al.* *New Engl J Med* 2014; online DOI: 10.1056/NEJMoa1402355.

ION-3: Phase III SOF/LDV ± RBV in GT1, treatment-naive, non-cirrhotic patients – SVR12 rates



* One patient achieved SVR12, but was not subgenotyped; Error bars: 95% CI.

Kowdley KV, et al. *New Engl J Med* 2014; online DOI: 10.1056/NEJMoa1402355.

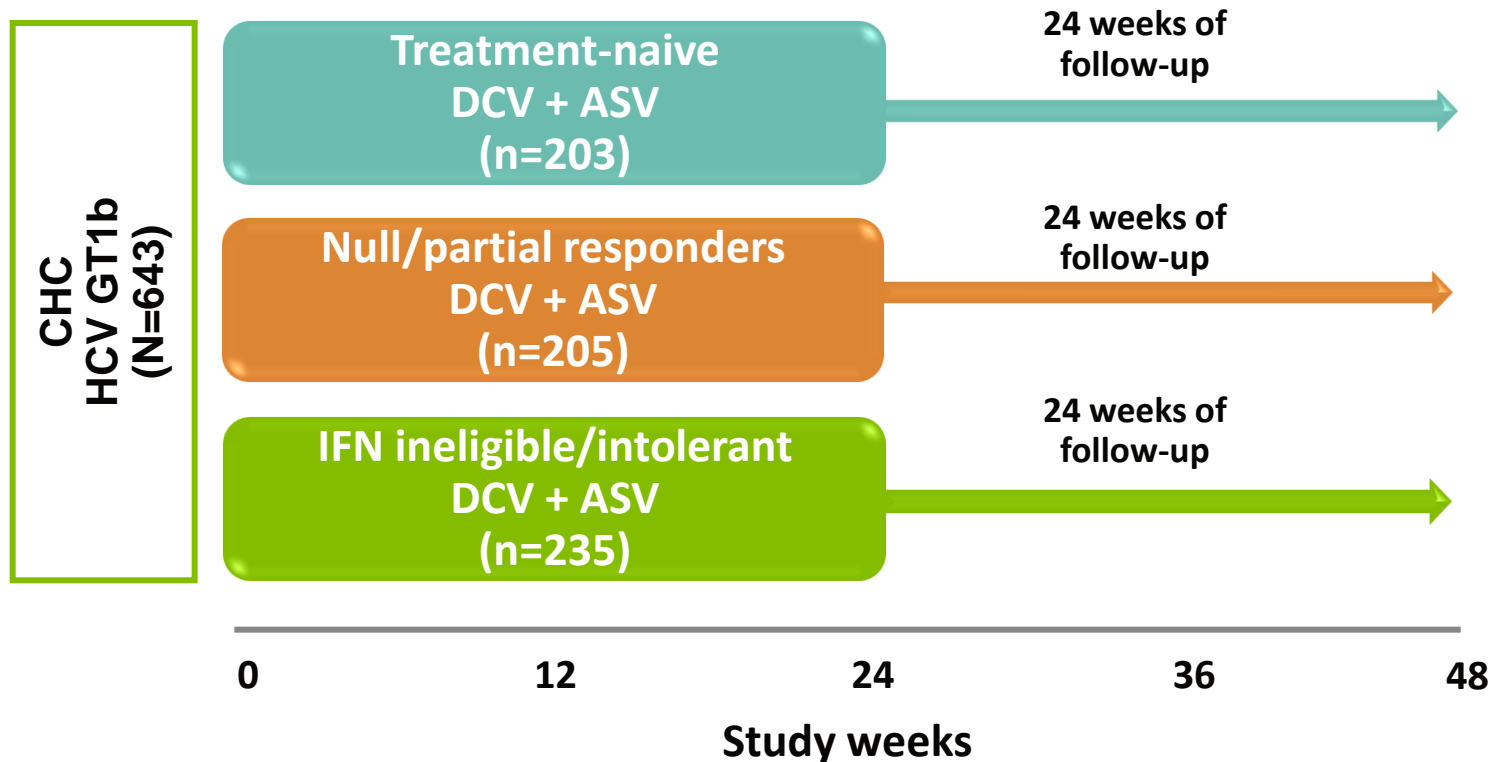
ION-3: Phase III SOF/LDV ± RBV in GT1, treatment-naive, non-cirrhotic patients – safety data

Patients, n (%)	SOF/LDV	SOF/LDV + RBV	SOF/LDV
	8 weeks (N=215)	8 weeks (N=216)	12 weeks (N=216)
Treatment discontinuations	0	1 (<1)	2 (<1)
Serious AEs	4 (2)	1 (<1)	5 (2)
Any AE	145 (67)	165 (76)	149 (69)
AEs in >10% of patients			
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)
Hemoglobin level <10 g/dL	0	11 (5)	1 (<1)

Phase III DCV + ASV for 24 weeks in patients with HCV GT1b

Study design

32.0% of patients were cirrhotic

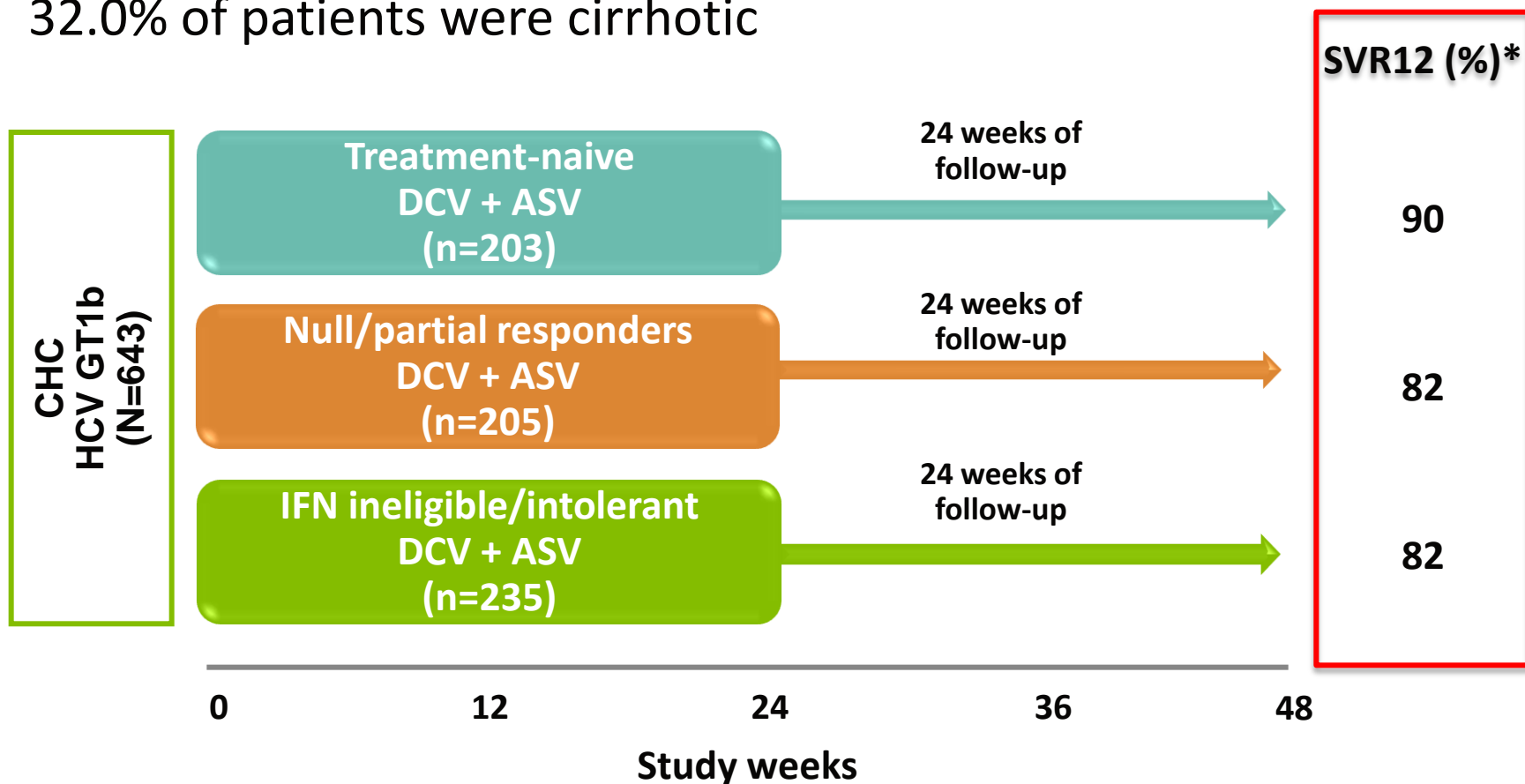


Dosing: DCV = 60 mg QD; ASV = 100 mg BID.

Manns M, et al. EASL 2014. Abstract 166 [late breaker oral presentation].

Phase III DCV + ASV for 24 weeks in patients with HCV GT1b SVR rates

32.0% of patients were cirrhotic



* Patients with missing SVR12 data counted as treatment failures;

Dosing: DCV = 60 mg QD; ASV = 100 mg BID.

Manns M, et al. EASL 2014. Abstract 166 [late breaker oral presentation].

Phase III DCV + ASV for 24 weeks in patients with HCV GT1b

Safety data

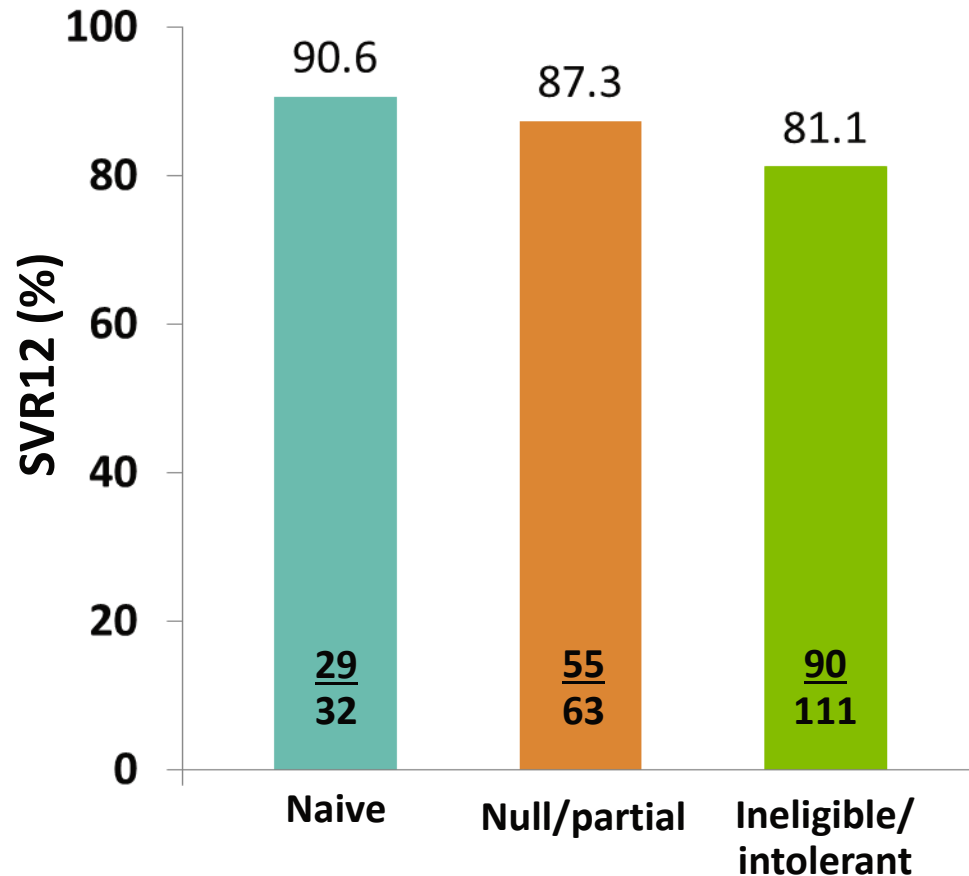
	Naive DCV + ASV (n=205)	Null/partial responders DCV + ASV (n=205)	IFN- ineligible/intolerant DCV + ASV (n=235)
Patients, n (%)			
AEs leading to discontinuation*	6 (3)	2 (1)	2 (1)
Serious AEs†	12 (6)	11 (5)	16 (7)
AEs in >10% of patients			
Headache	50 (24)	50 (24)	59 (25)
Fatigue	43 (21)	45 (22)	52 (22)
Diarrhea	24 (12)	28 (14)	51 (22)
Nausea	25 (12)	22 (11)	28 (12)
Asthenia	4 (2)	12 (6)	25 (11)
Hemoglobin level <90 g/L	0	1 (<1)	0

* Most commonly reversible ALT/AST elevations, which resolved off-treatment (7 patients; 6/7 achieved SVR12);

† One patient with confirmed Gilbert's syndrome met laboratory, but not clinical, criteria for potential drug-induced liver injury. Patient had serious AE of grade 3 increased hepatic enzyme and grade 4 ALT abnormality; patient completed treatment and achieved SVR12.

DCV + ASV therapy for 24 weeks in cirrhotic patients with HCV GT1b infection: cirrhotic subgroup analysis

Overall study (N=643)
32.0% of patients were cirrhotic



Patients, n (%)	With cirrhosis N = 207*
Serious AEs	13 (6.3)
AEs leading to discontinuation	1 (<1%)
AEs in ≥10% of patients	
Headache	51 (24.6)
Fatigue	42 (20.3)
Diarrhea	32 (15)
Nausea	22 (11)
ALT elevation, grade 3/4	3 (1.5)
AST elevation, grade 3/4	3 (1.5)

Manns M, *et al.* EASL 2014 (Abstract 166) [late breaker oral presentation];
Kao J-H, *et al.* EASL 2014 (Abstract 1300) [late breaker poster presentation].

* Includes only patients in DCV + ASV treatment arms.

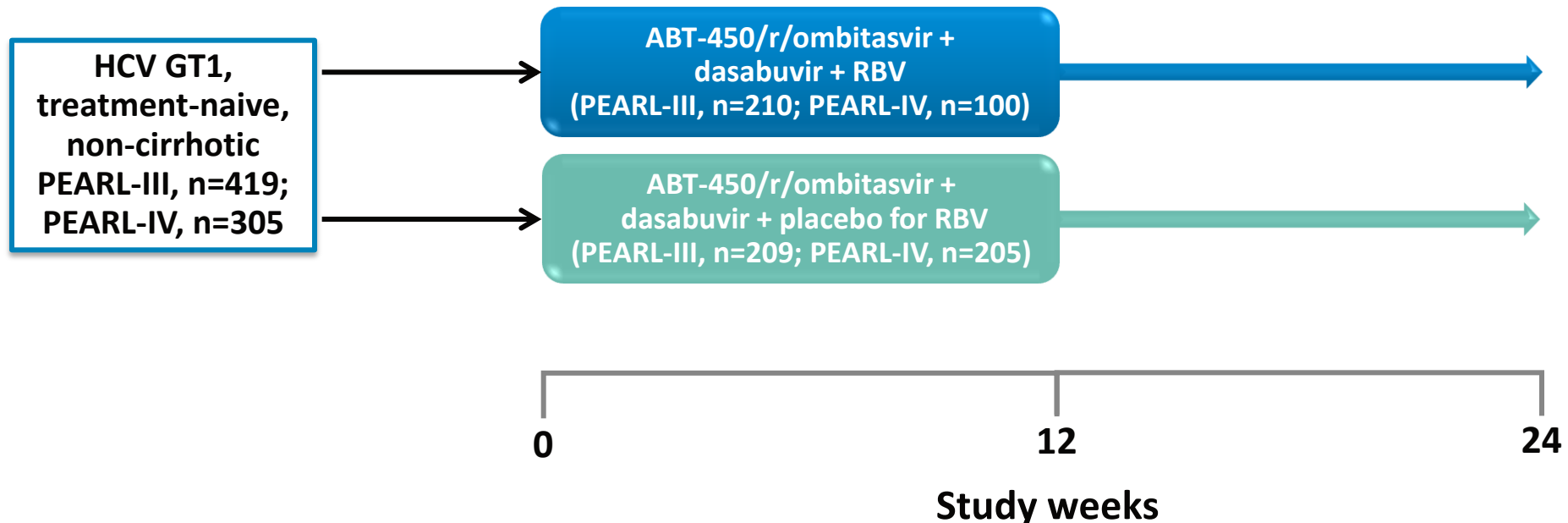
PEARL-III and -IV: GT1, treatment-naive, non-cirrhotic patients

Study design

PEARL-III: GT1b

PEARL-IV: GT1a

ABT-450/r/ombitasvir + dasabuvir ± RBV



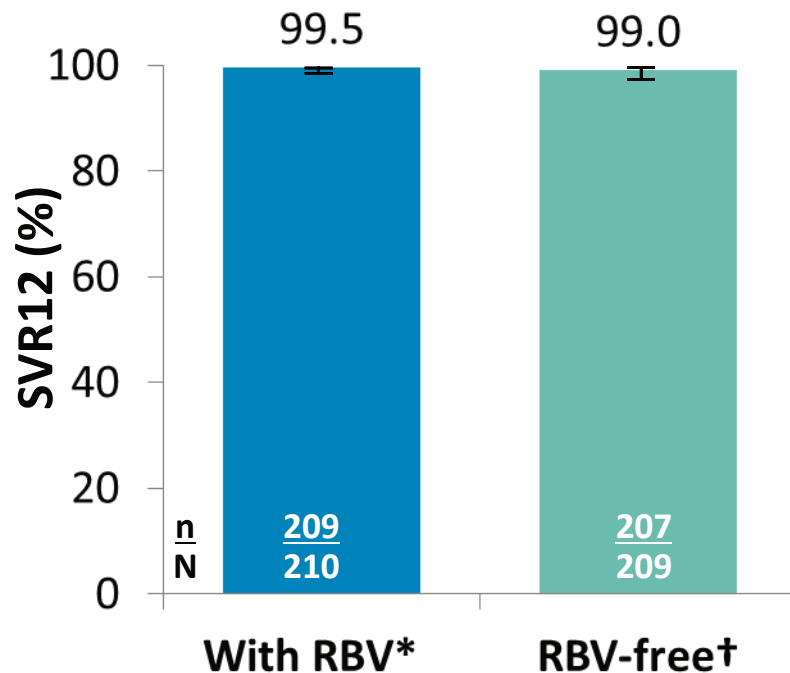
ABT-450/r/ombitasvir (ABT-267) = 150/100/25 mg QD co-formulated; dasabuvir (ABT-333) = 250 mg BID; RBV = 1000–1200 mg daily according to body weight, or matching placebo.

Ferenci P, *et al.* *New Engl J Med* 2014; online DOI: 10.1056/NEJMoa1402338.

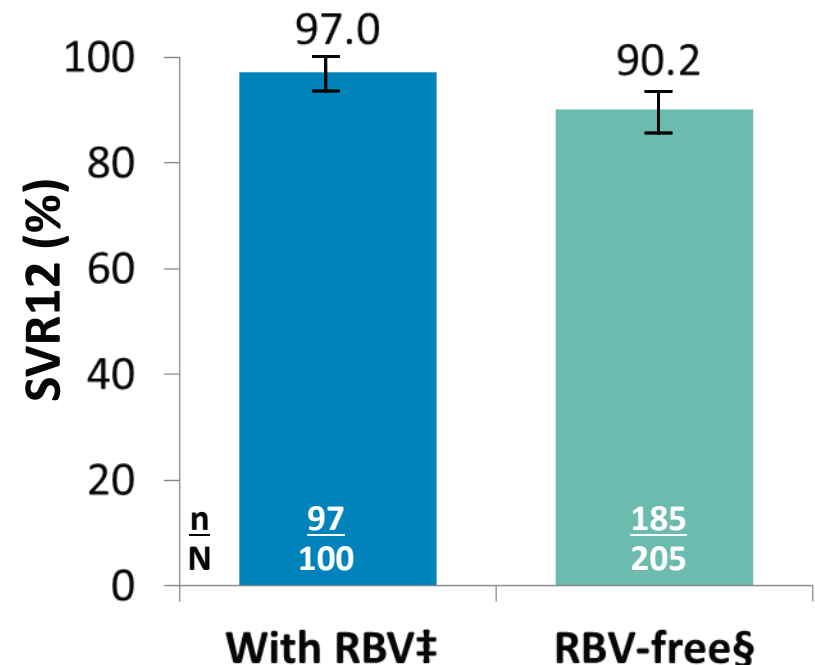
PEARL-III and -IV: GT1, treatment-naive, non-cirrhotic patients SVR12 rates

ABT-450/r/ombitasvir + dasabuvir ± RBV

PEARL-III: GT1b, treatment-naive, non-cirrhotic



PEARL-IV: GT1a, treatment-naive, non-cirrhotic



* 1 patient with virologic rebound – emergence of NS5A Y93H;

† 2 patients were lost to follow-up, but subsequently achieved an SVR24; ‡ 1 patient with virologic rebound, 1 with relapse, and 1 lost to follow-up; § 6 patients with virologic rebound, 10 with relapse, 1 lost to follow-up, and 3 discontinued treatment; Error bars: 95% CI.

Ferenci P, *et al.* *New Engl J Med* 2014; online DOI: 10.1056/NEJMoa1402338.

PEARL-III and -IV: GT1, treatment-naive, non-cirrhotic patients

Adverse events and safety summary

Patients, n (%)	PEARL-III		PEARL-IV	
	3D + RBV (N=210)	3D (N=209)	3D + RBV (N=100)	3D (N=205)
Serious AEs	4 (1.9)	4 (1.9)	3 (3.0)	1 (0.5)
AE leading to RBV dose modification†	16 (7.6)	0*	6 (6.0)	0
AE leading to study drug discontinuation	0	0	0	3 (1.5)
AEs in ≥10% of patients				
Headache	51 (24.3)	49 (23.4)	25 (25.0)	58 (28.3)
Fatigue	45 (21.4)	48 (23.0)	46 (46.0)	72 (35.1)
Pruritus	25 (11.9)	11 (5.3)*	10 (10.0)	12 (5.9)
Nausea	23 (11.0)	9 (4.3)*	21 (21.0)	28 (13.7)
Hemoglobin level <10 g/dL	19 (9.0)	0*	4 (4.0)	0*

* p≤0.05;

† All patients who had RBV dose modification achieved SVR12.

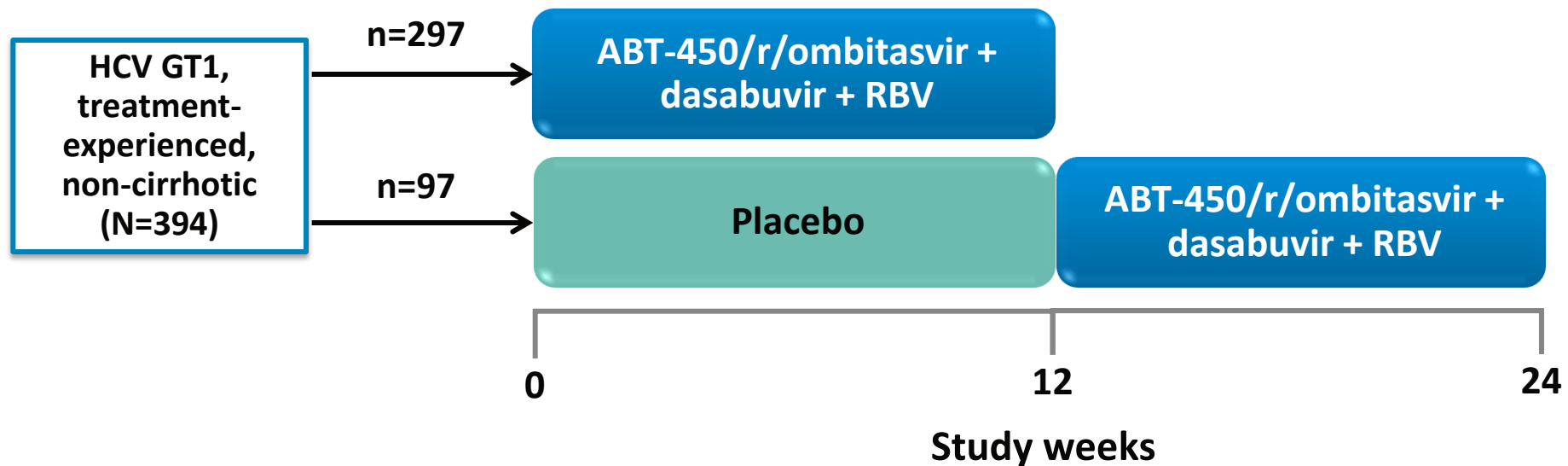
Ferenci P, et al. *New Engl J Med* 2014; online DOI: 10.1056/NEJMoa1402338.

TREATMENT-EXPERIENCED

SAPPHIRE-II: GT1, treatment-experienced, non-cirrhotic patients

Study design

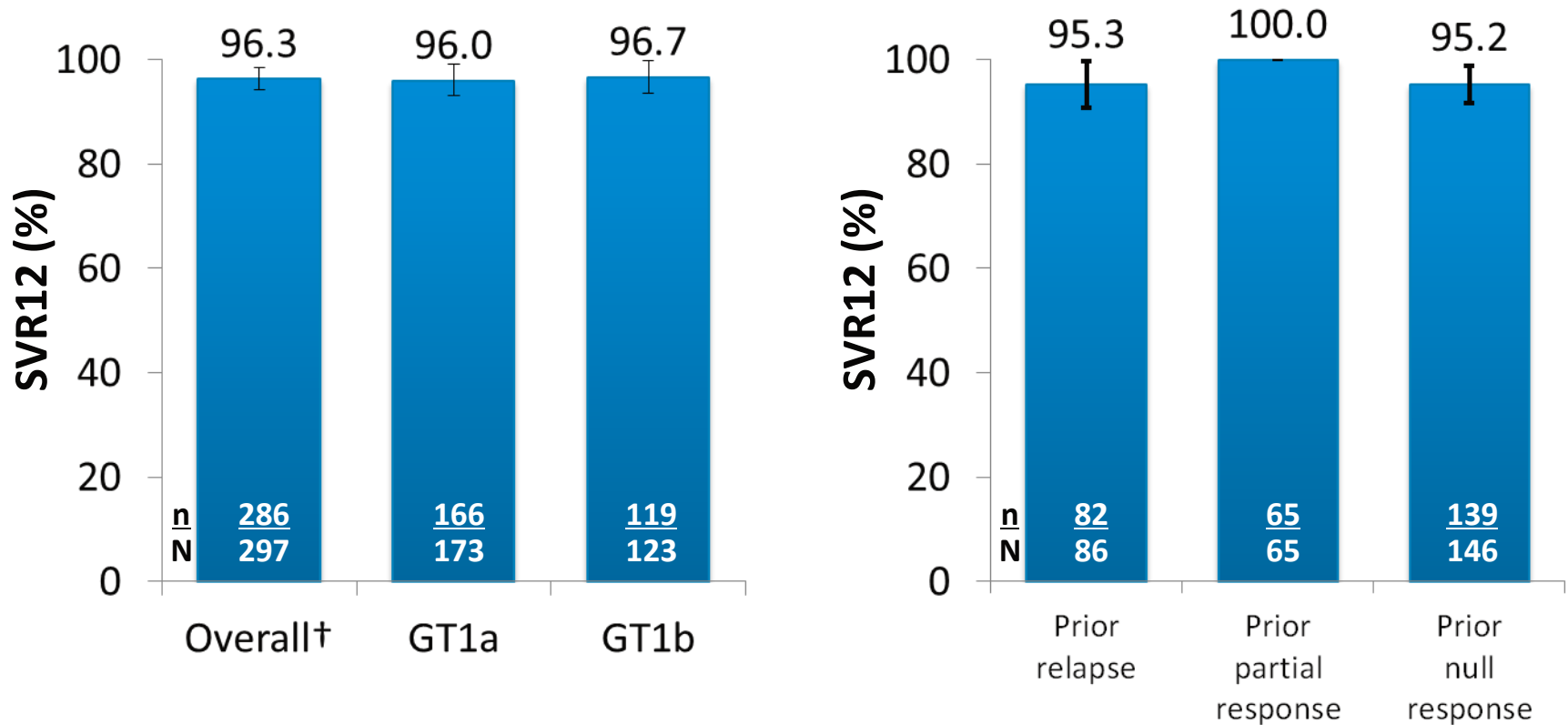
ABT-450/r/ombitasvir + dasabuvir + RBV



ABT-450/r/ombitasvir (ABT-267) = 150/100/25 mg QD co-formulated; Dasabuvir (ABT-333) = 250 mg BID; RBV = 1000–1200 mg daily according to body weight.

Zeuzem S, et al. *New Engl J Med* 2014; **370**:1604–1614.

SAPPHIRE-II: GT1, treatment-experienced, non-cirrhotic patients SVR12 rates by HCV GT1 subtype and by prior P/R response*



* Data for 3-DAA + RBV Arm only;

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

Zeuzem S, et al. *New Engl J Med* 2014; **370**:1604–1614.

SAPPHERE-II: GT1, treatment-experienced, non-cirrhotic patients

Adverse events occurring in >10% of patients

Event, n (%)	3D + RBV (N=297)	Placebo (N=97)	Δ	P-value
Any AE	271 (91.2)	80 (82.5)	8.7	<0.05
Headache	108 (36.4)	34 (35.1)	1.3	NS
Fatigue	99 (33.3)	22 (22.7)	10.6	NS
Nausea	60 (20.2)	17 (17.5)	2.7	NS
Asthenia	47 (15.8)	11 (11.3)	4.5	NS
Insomnia	42 (14.1)	7 (7.2)	6.9	NS
Pruritus	41 (13.8)	5 (5.2)	8.6	<0.05
Diarrhea	39 (13.1)	12 (12.4)	0.7	NS
Dyspnea	37 (12.5)	10 (10.3)	2.2	NS
Cough	32 (10.8)	5 (5.2)	5.6	NS
Myalgia	23 (7.7)	10 (10.3)	-2.6	NS

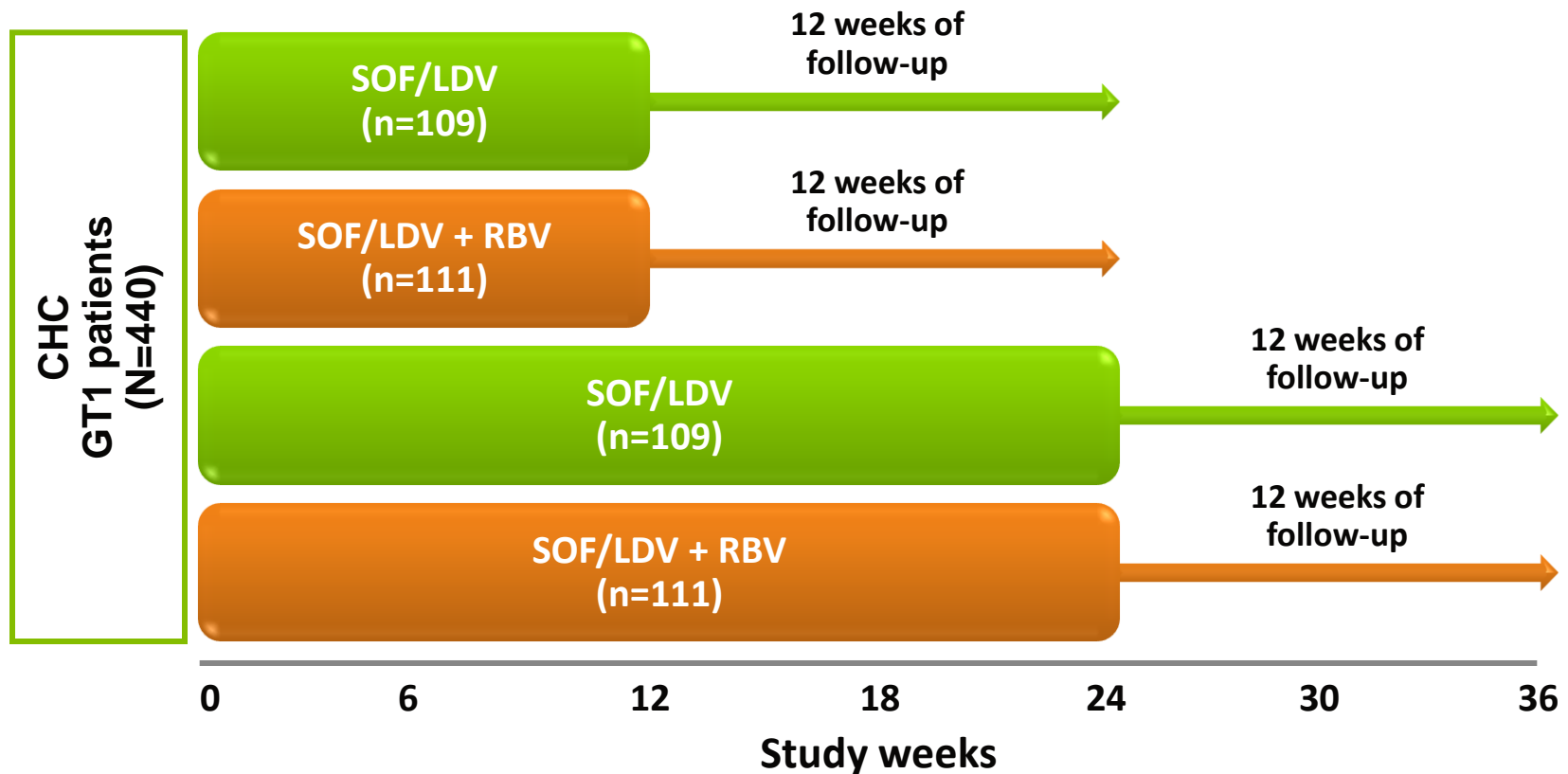
- Rate of discontinuation due to AEs was 1.0% in 3D + RBV recipients
- Serious AEs occurred in 2.0% of 3D + RBV recipients and 1.0% of placebo recipients
- No moderate or severe AEs occurred more frequently with 3D + RBV vs placebo (p>0.05)

NS = not significant.

Zeuzem S, et al. *New Engl J Med* 2014; **370**:1604–1614.

ION-2: SOF/LDV ± RBV in GT1, treatment-experienced patients

Study design

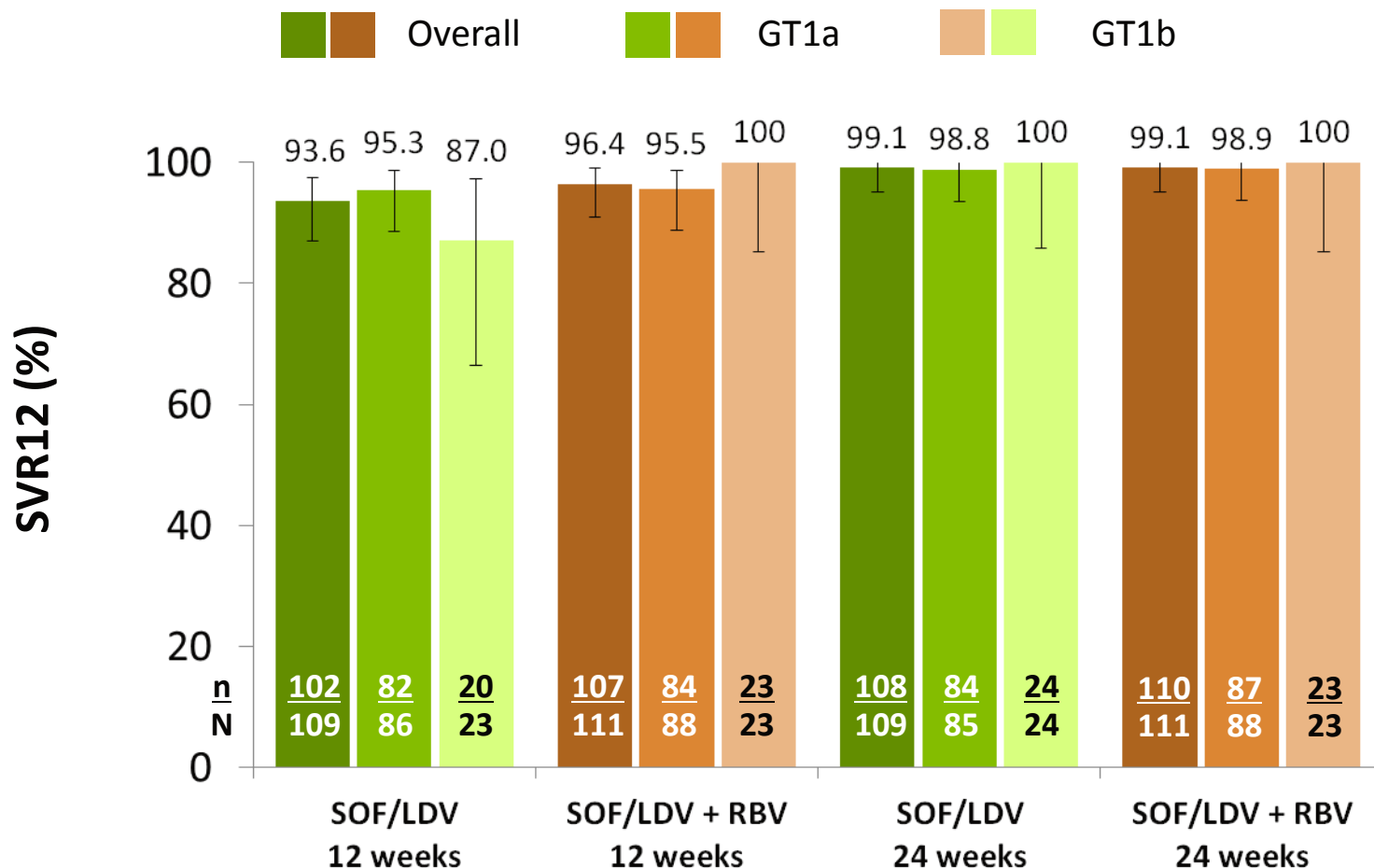


- Including 88 (20.0%) patients with cirrhosis

SOF = 400 mg/day; LDV = 90 mg/day;
RBV = 1000–1200 mg daily according to body weight.

Afdhal N, et al. *New Engl J Med* 2014; **370**:1483–1493.

ION-2: SOF/LDV ± RBV in GT1, treatment-experienced patients SVR12 rates

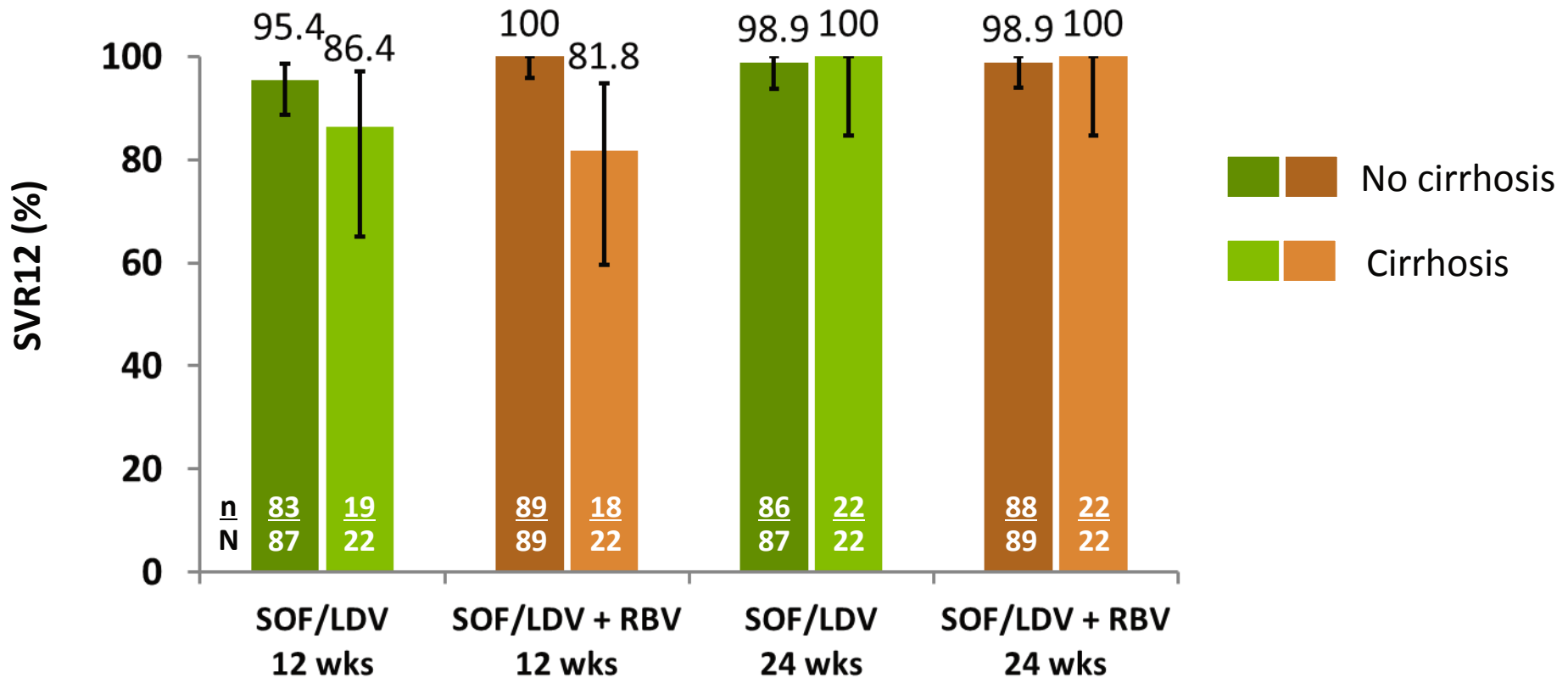


SOF = 400 mg/day; LDV = 90 mg/day;
 RBV = 1000–1200 mg daily according to body weight.
 Error bars: 95% CI.

Afdhal N, et al. *New Engl J Med* 2014; **370**:1483–1493.

ION-2: SVR rates in GT1, treatment-experienced, cirrhotic patients (subgroup analysis)

20.0% (88/440) of patients enrolled had cirrhosis



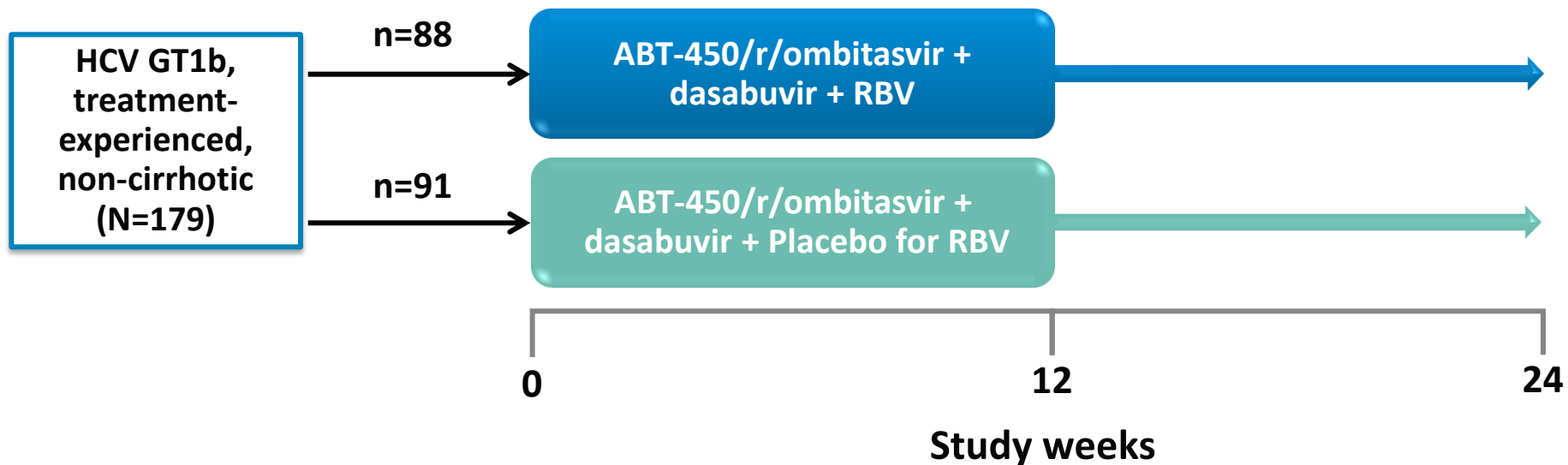
ION-2: SOF/LDV ± RBV in GT1, treatment-experienced patients

Safety data

Patients, n (%)	SOF/LDV	SOF/LDV + RBV	SOF/LDV	SOF/LDV + RBV
	12 weeks (N=109)	12 weeks (N=111)	24 weeks (N=109)	24 weeks (N=111)
Treatment discontinuations	0	0	0	0
Serious AEs	0	0	6 (6)	3 (3)
Any AE	73 (67)	96 (86)	88 (81)	100 (90)
AEs in >15% of patients				
Fatigue	23 (21)	45 (41)	26 (24)	50 (45)
Headache	28 (26)	26 (23)	25 (23)	35 (32)
Nausea	13 (12)	20 (18)	7 (6)	25 (23)
Insomnia	10 (9)	18 (16)	4 (4)	19 (17)
Arthralgia	7 (6)	13 (12)	7 (6)	17 (15)
Hemoglobin level <10 g/dL	0	2 (2)	0	9 (8)

PEARL-II: HCV GT1b, treatment-experienced, non-cirrhotic patients – study design

ABT-450/r/ombitasvir + dasabuvir ± RBV for 12 weeks

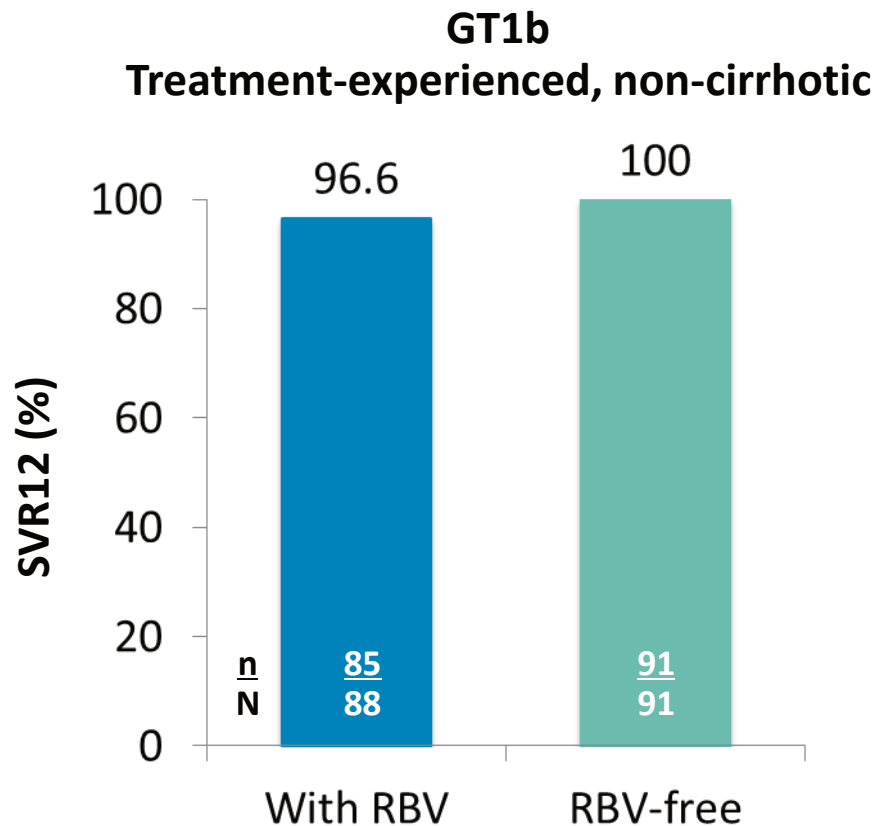


ABT-450/r/ombitasvir (ABT-267) = 150/100/25 mg QD co-formulated; dasabuvir (ABT-333) = 250 mg BID; RBV = 1000–1200 mg daily according to body weight, or matching placebo.

Andreone P, et al. DDW 2014. Abstract 5220 [oral presentation].

PEARL-II: HCV GT1b, treatment-experienced, non-cirrhotic patients – SVR12 rates

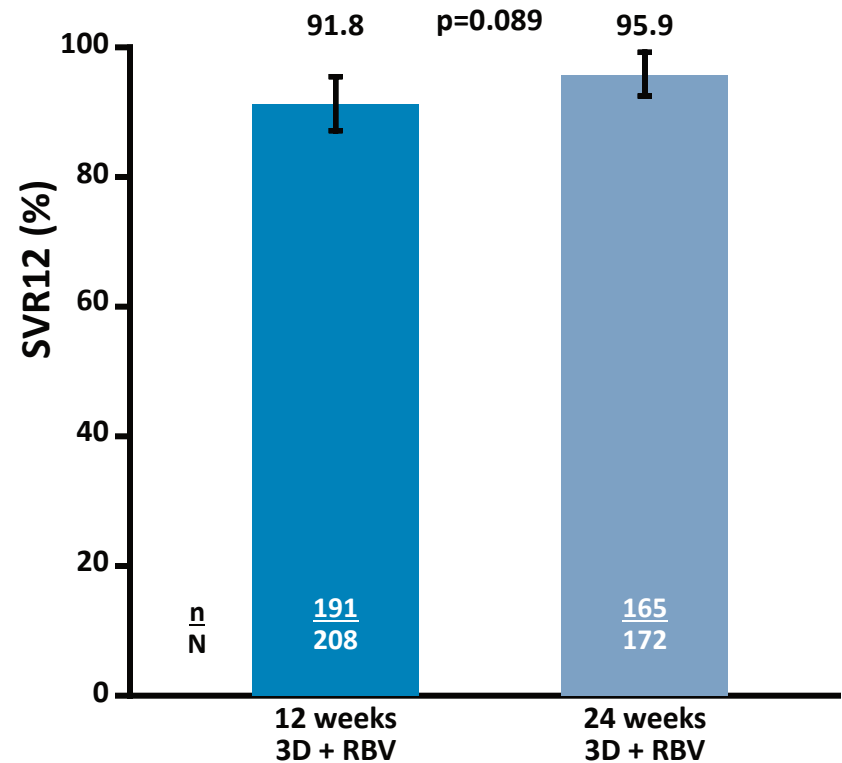
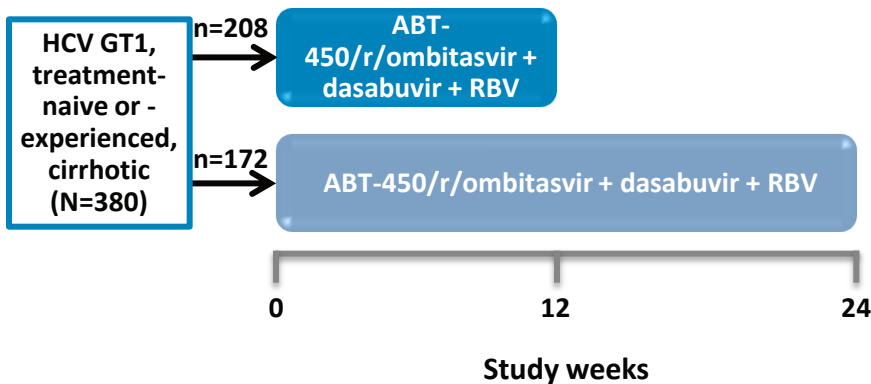
ABT-450/r/ombitasvir + dasabuvir ± RBV for 12 weeks



All-oral Treatment in patients with cirrhosis

TURQUOISE-II: GT1, treatment-naive and -experienced cirrhotic patients – study design

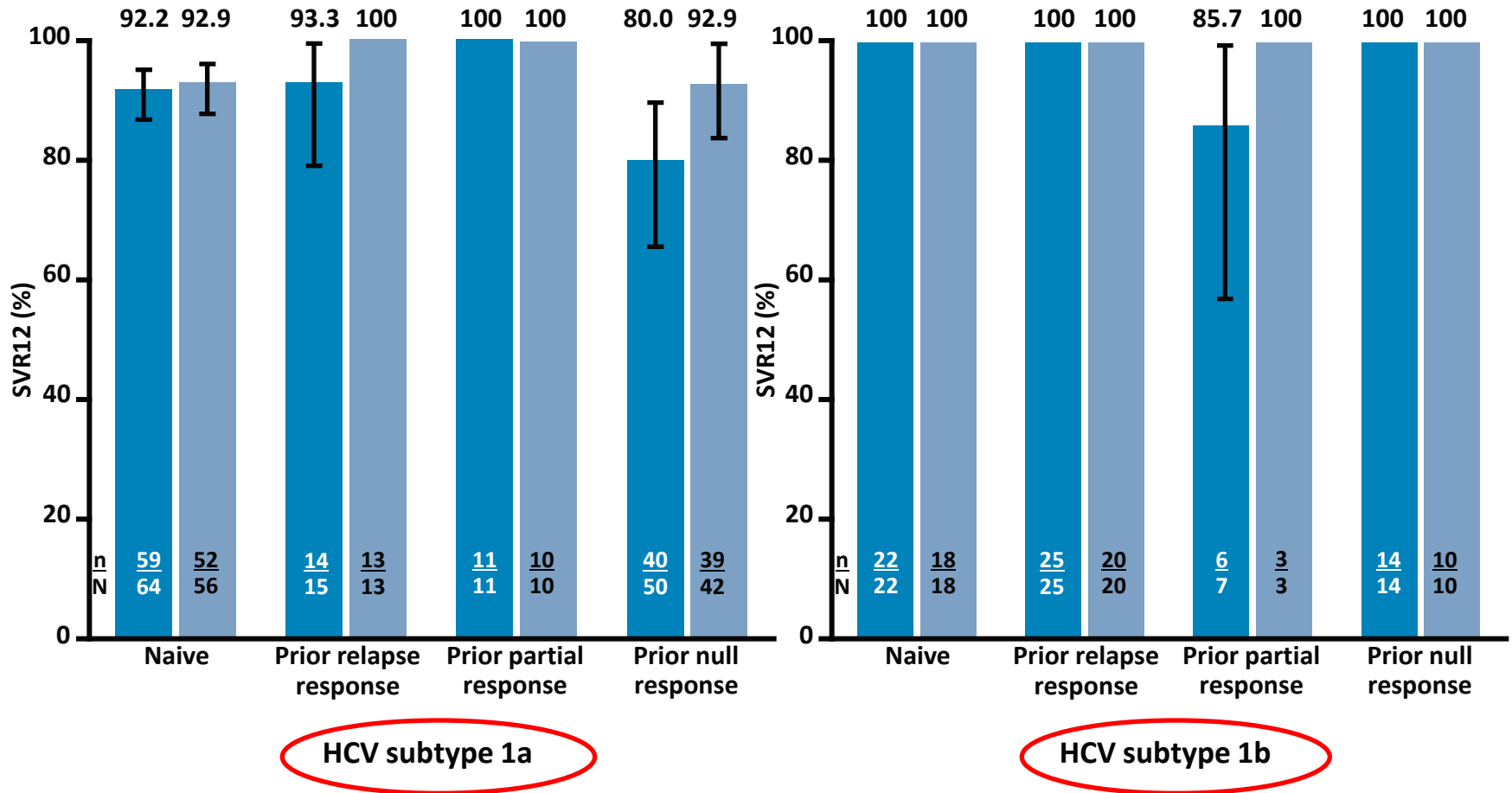
ABT-450/r/ombitasvir + dasabuvir + RBV for 12 or 24 weeks



ABT-450/r/ombitasvir (ABT-267) = 150/100 mg/25 mg QD co-formulated; dasabuvir (ABT-333) = 250 mg BID; RBV = weight-based BID.

Poordad F, et al. *N Engl J Med* 2014. Online DOI:10.1056/NEJMoa1402869.

TURQUOISE-II: SVR12 in GT1a by prior treatment response



TURQUOISE-II: safety summary in the overall population

Event, %	3D + RBV	
	12-week arm (n=208)	24-week arm (n=172)
Any AE	91.8	90.7
Serious AE	6.2	4.7
AE leading to drug discontinuation	1.9	2.3
Death*	0.5	0

Hepatic decompensation events were rare (4 patients, 1.1%)

- None were considered related to study drug

*1 patient with a non-treatment emergent death (occurring 80 days after last dose of study treatment), not attributed to 3D or RBV.

Conclusions

- HCV treatments are evolving
 - Current therapies can be optimized for some patients
 - Treatment needs remain for both patients and physicians
- Therapeutic options are emerging that will improve treatment further
 - The strength of IFN-free, all-oral therapies is key
 - May fulfil the needs of all patients
- We may have the armamentarium to eradicate HCV – forever

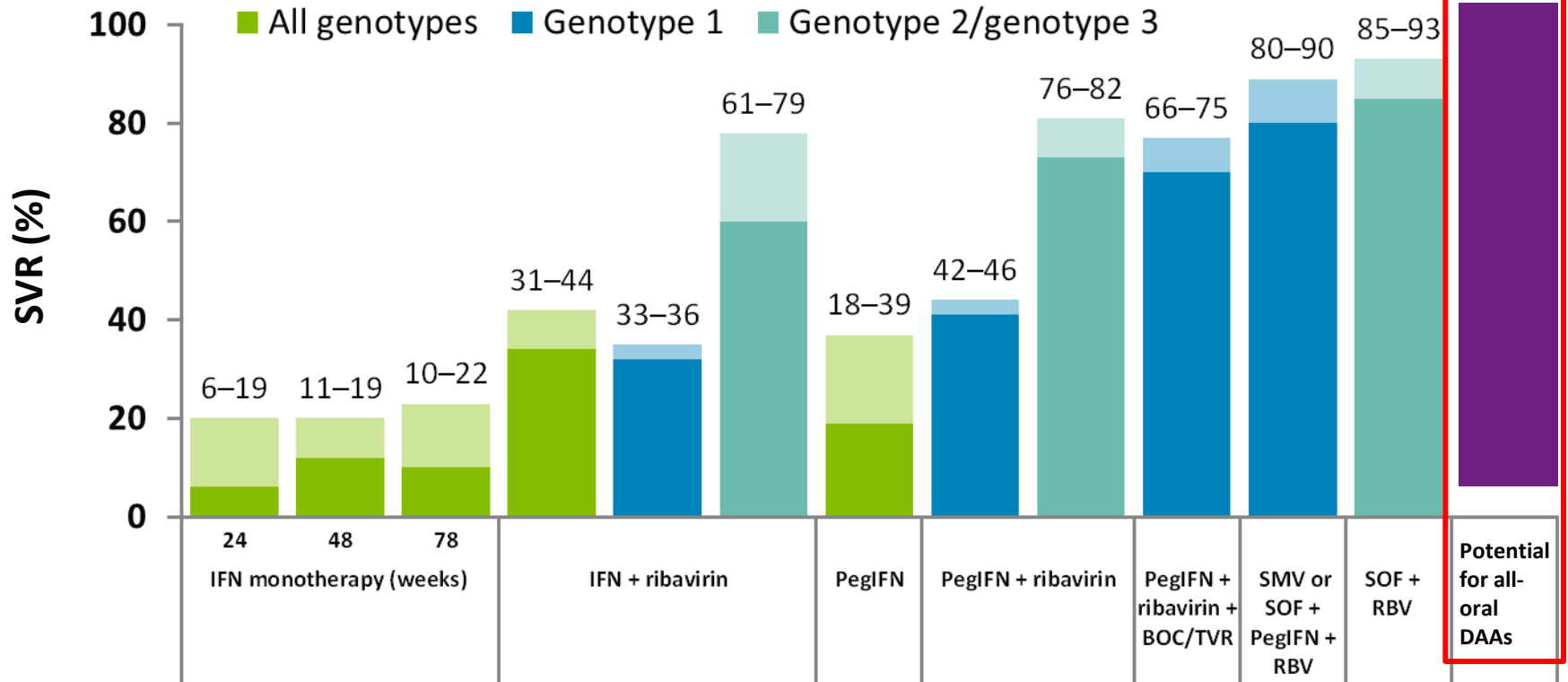
Is the next stage in the evolution of HCV treatment eradication for all patients?

1989

2011

2013

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Davis GL, et al. *N Engl J Med* 1989; **321**:1501–1506; Poynard T, et al. *N Engl J Med* 1995; **332**:1457–1462; McHutchison JG, et al. *N Engl J Med* 1998; **339**:1485–1492; Poynard T, et al. *Lancet* 1998; **352**: 1426–1432; Zeuzem S, et al. *N Engl J Med* 2000; **343**:1666–1672; Linsay KL, et al. *Hepatology* 2001; **34**:395–403; Pockros PJ, et al. *Am J Gastroenterol* 2004; **99**:1298–1305; Manns MP, et al. *Lancet* 2001; **358**:958–965; Fried MW, et al. *N Engl J Med* 2002; **347**:975–982; Poordad F, et al. *N Engl J Med* 2011; **364**:1195–1206; Jacobson IM, et al. *N Engl J Med* 2011; **364**:2405–2416; Simeprevir prescribing information, November 2013; Lawitz E, et al. *N Engl J Med* 2013; **368**:1878–1887; Zeuzem S, et al. *Hepatology* 2013; **58**(Suppl 1):733A; AbbVie press release 2014 [Accessed 25-02-14]; Gilead press release 2013 [Accessed 25-02-14]; Sulkowski MS, et al. *N Engl J Med* 2014; **370**:211–221.

THANK YOU

ACIU