Advances in HCV Treatment: Beyond Triple Therapy

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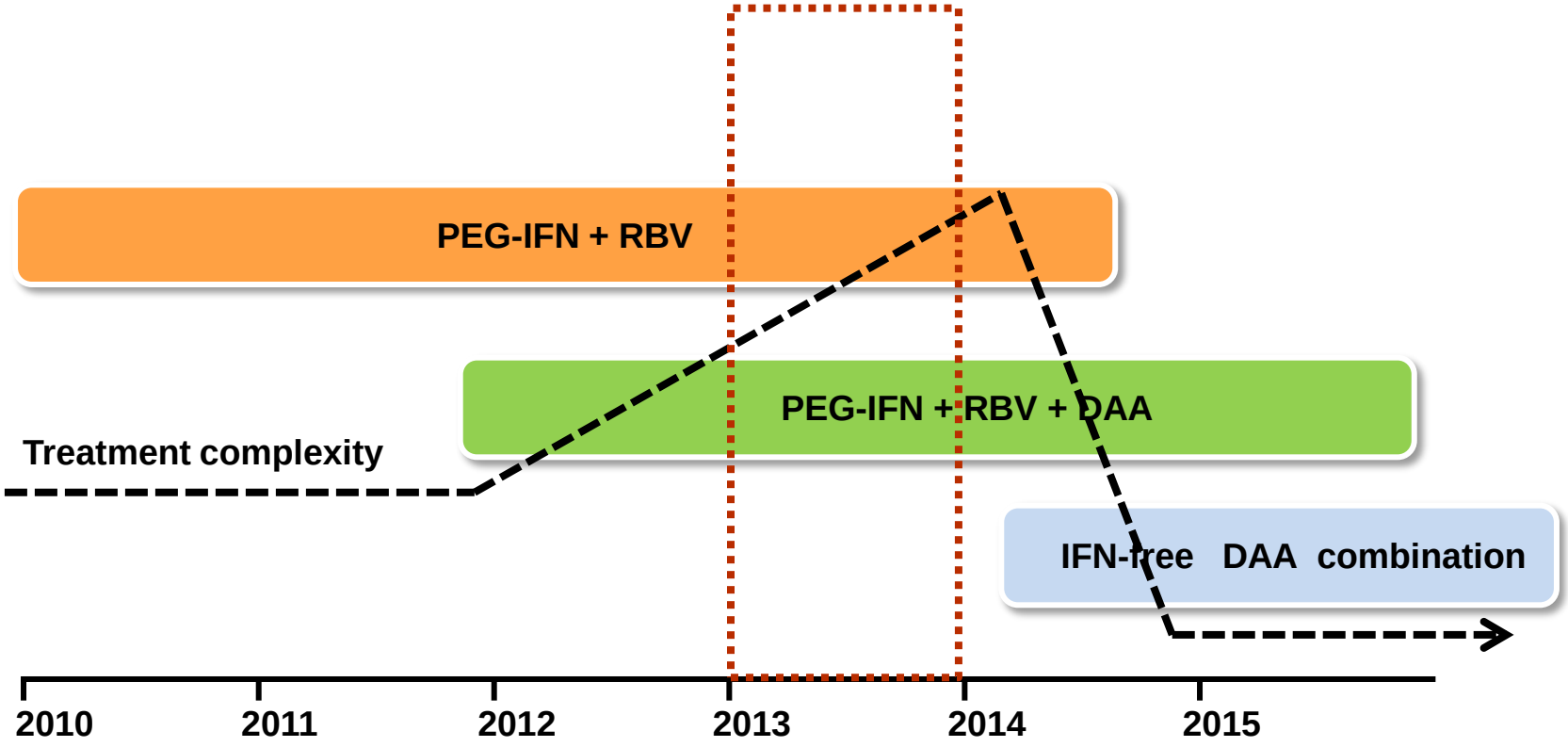
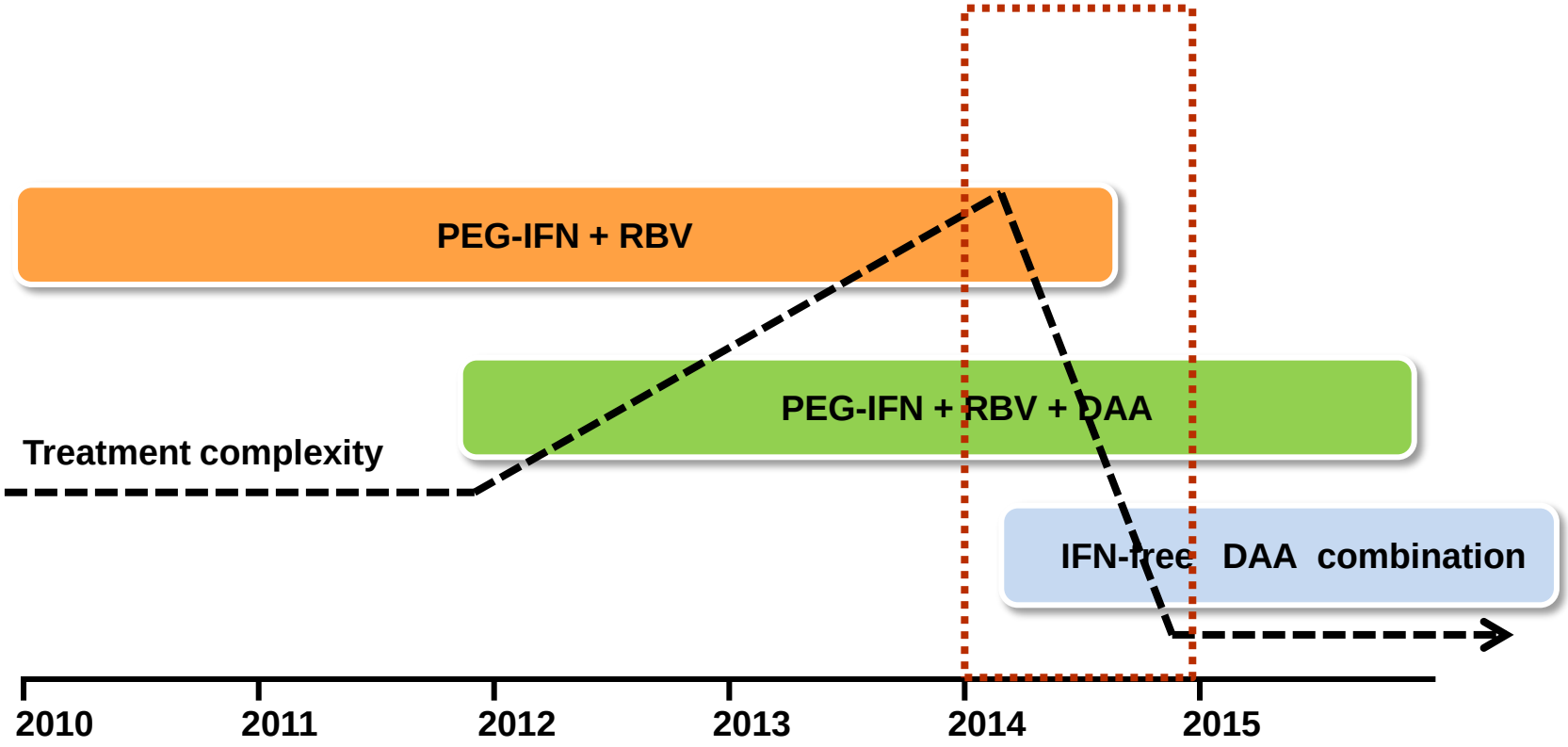
HCV TREATMENT STRATEGIES



Dore GJ. MJA 2012 (revised)

HCV TREATMENT STRATEGIES



Dore GJ. MJA 2012 (revised)

Current DAA-based therapy (TVR, BOC)

Problematic drug profiles:

- Too many additional side effects (anaemia, rash)
- Complex treatment algorithms (different stopping rules, durations)
- Drug – drug interactions (CYP 450 metabolism)

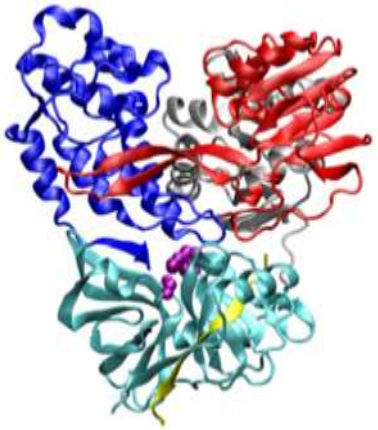
Less responsive sub-groups:

- Prior PEG-IFN/RBV “null responders”
- Advanced fibrosis (vs early liver disease)
- Genotype 1a (vs genotype 1b)

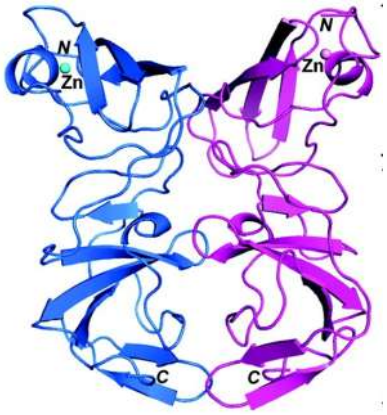
Anti-HCV Targets Include NS3 Protease, NS5B Polymerase, NS5A Replication Complex Protein and Cyclophilins

Viral targets

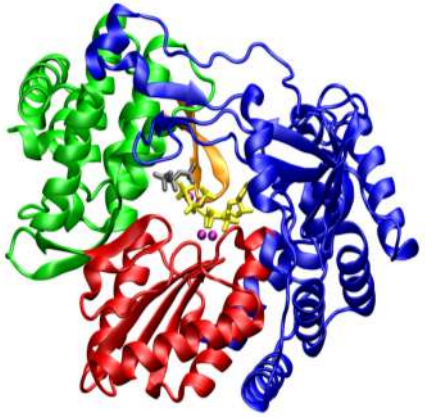
Host targets



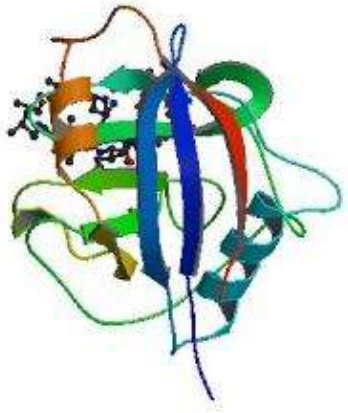
NS3: bifunctional protease/helicase



NS5A: an active component of HCV replicase



NS5B: RNA-dependent RNA polymerase



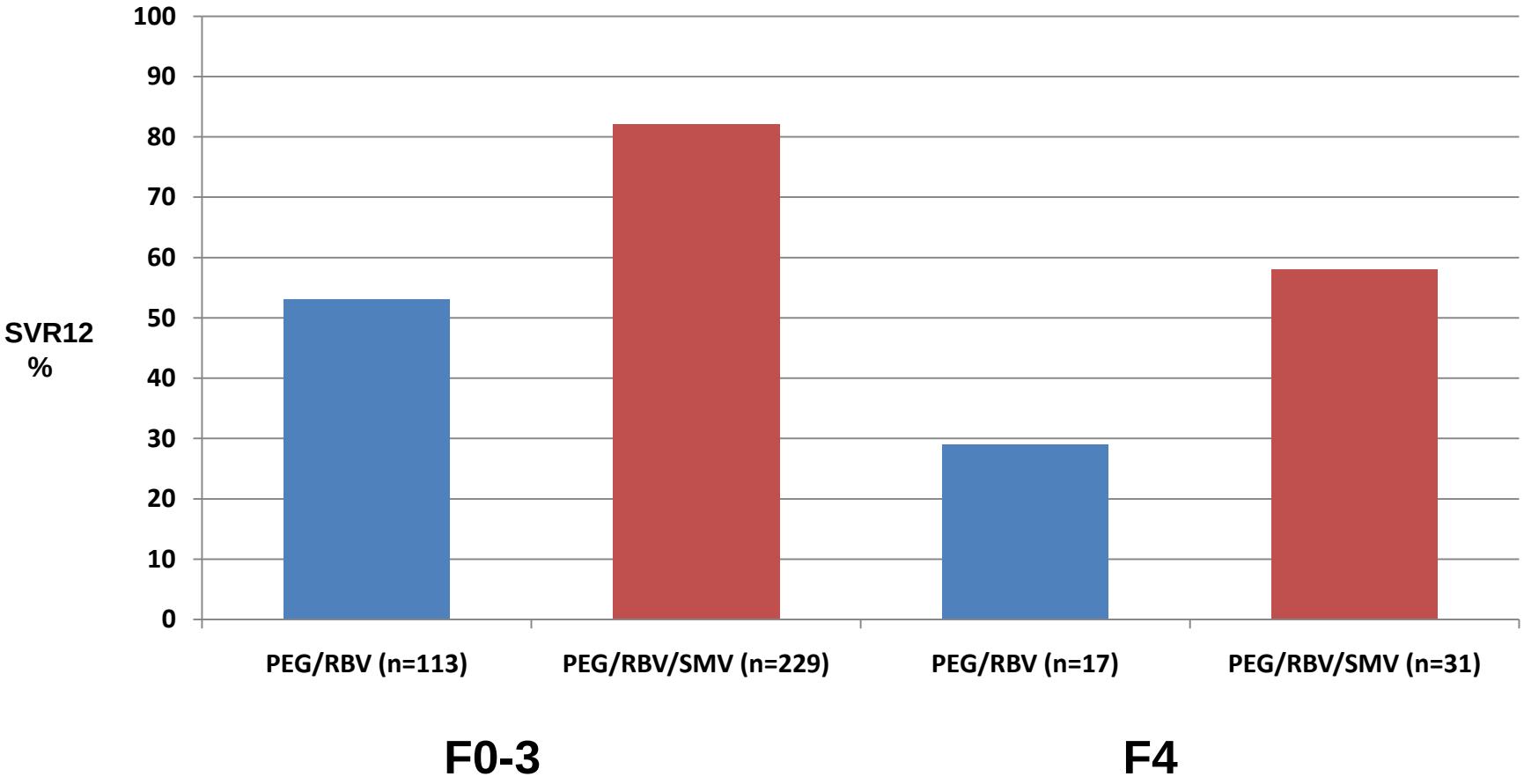
Cyclophilin A

Key recent HCV developments

- *Sofosbuvir (nucleotide analogue) best in class NS5B polymerase inhibitor*
- *Second generation PI's e.g., simeprevir: Once daily dosing, few AEs, fewer DDIs*
- *PI resistance less major clinical issue*
- *Genotype 2 and 3 are very different strains, with contrasting responsiveness to initial IFN-free DAA regimen*
- *Two potent DAAs should provide high curative rates for genotype 1, and probably other genotypes*
- *Feasible HCV treatment durations are shortening (8-12 weeks)*

QUEST-1: PEG-IFN/RBV/SIMEPREVIR (24-48 WEEKS)

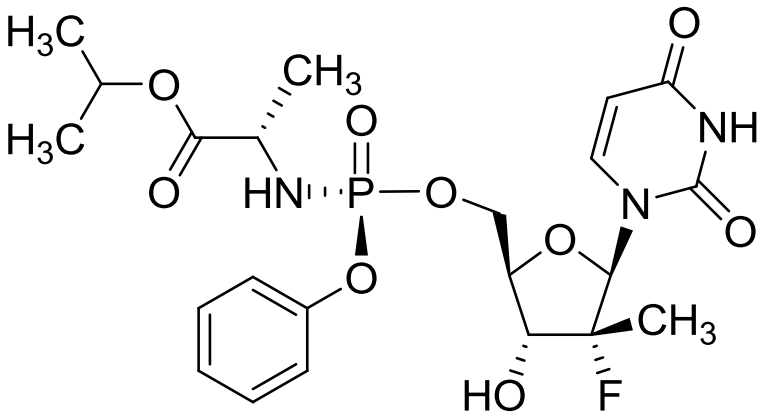
Genotype 1 treatment naïve



Jacobson I et al. EASL 2013

Sofosbuvir (SOF, GS-7977)

- HCV-specific uridine analog chain terminating polymerase inhibitor
- Potent pan-genotypic antiviral activity against HCV GT1–6
- High barrier to resistance
- Once-daily, oral, 400-mg tablet
- Favorable clinical pharmacology profile
  - No food effect
  - No significant drug interactions
- Generally safe and well-tolerated in clinical studies to date (>3,000 patients)
  - No safety signal in preclinical/clinical studies



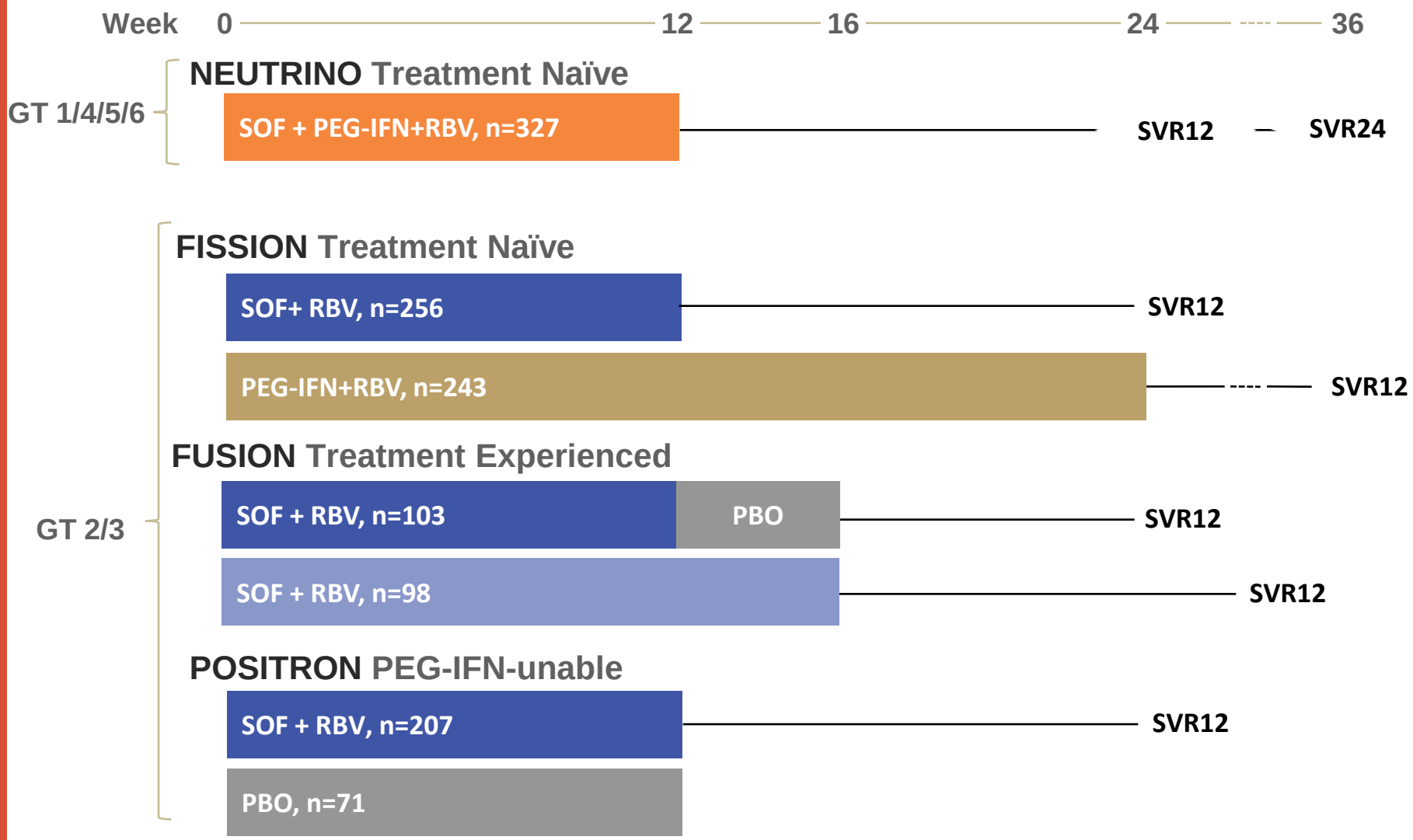
Sofosbuvir Phase 3 Studies

Study	Population	Total Patients	Percentage with Cirrhosis	Lower Limit of Platelets
NEUTRINO	GT 1,4,5,6 Treatment Naïve	327	17%	≥ 90,000/mm^3
FISSION	GT 2 & 3 Treatment Naïve	499	20%	≥ 75,000/mm^3
FUSION	GT 2 & 3 Treatment Experienced	201	34%	≥ 50,000/mm^3
POSITRON	GT 2 & 3 IFN Unable	278	15%	No Lower Limit
Total		1,302	20%	

- Expanded inclusion criteria
  - No upper limit to age or BMI, opiate replacement therapy permitted

Lawitz et al, Jacobson et al, Nelson et al, Gane et al. EASL 2013. Amsterdam, The Netherlands.

Sofosbuvir Phase 3 Studies Designs



Lawitz et al, Jacobson et al, Nelson et al, Gane et al. EASL 2013. Amsterdam, The Netherlands.

NEUTRINO: Treatment Naïve GT1,4,5,6

Primary Efficacy Endpoint: SVR 12*		
Overall	**Genotype 1**	**Genotypes 4, 5, 6**
90% (295/327)	**89% (91% SVR 24)**	**97%**

- Superiority was demonstrated compared to SVR 12 rate 60% (historic control), *P*<0.001
- SVR 12 achieved among 80% of patients with cirrhosis at baseline†
- Most common adverse events occurring in ≥20% of patients: fatigue, headache, nausea, insomnia, anemia
- Five patients (2%) discontinued due to adverse events

***All patients became HCV RNA negative with relapse accounting for all virologic failures**
†17% of patients had compensated cirrhosis at baseline

Gilead Sciences Press Release. February 4, 2013. http://www.gilead.com/pr_1780873
Lawitz E, et al. APASL 2013 LB-02

GT 2 and GT 3 Treatment-Naïve: SOF+RBV vs PEG-IFN+RBV

FISSION Summary

	Efficacy Endpoints: SVR 12		
FISSION – Treatment Naive	Overall	Genotype 2	Genotype 3
SOF + RBV x12 weeks	67%	97%	56%
PEG-IFN + RBV x24 weeks	67%	78%	63%

- SOF+RBV as an "All Oral Regimen" for 12 weeks resulted in
  - Overall, non-inferior results compared to 24 weeks of PEG-IFN+RBV
    - Significantly better response for GT2
  - No resistance detected in SOF+RBV in any patient
  - SOF+RBV was well-tolerated
    - Less discontinuations due to AEs (1% vs 11%)
    - Significantly fewer AEs as compared with PEG-IFN+RBV
    - Safety profile consistent with RBV

Gane E, et al. EASL 2013. Amsterdam, The Netherlands. Oral #5.
Lawitz E, et al. *N Engl J Med.* 2013;368:1878-1887.

GT2/3 Treatment-Experienced: SOF+RBV 12 vs 16 weeks

FUSION Summary

	Efficacy Endpoints: SVR 12		
FUSION – Treatment Experienced	Overall	Genotype 2	Genotype 3
SOF + RBV x12 weeks	50%*	86%	30%
SOF + RBV x16 weeks	73%*	94%	62%

Superiority was demonstrated compared with a predefined historical control SVR rate of 25%; *$P < 0.001$ for both arms

- SOF+RBV as an "All Oral Regimen" for 12 or 16 weeks resulted in
  - Significantly better response compared to standard of care
  - No resistance detected in SOF+RBV in any patient
  - SOF+RBV was well-tolerated
    - No discontinuation due to AEs in either arm
    - No additional toxicities with 4 more weeks of therapy
    - Safety profile consistent with RBV

Nelson DR, et al. EASL 2013. Amsterdam, The Netherlands. Oral #6.
Jacobson IM, et al. *N Engl J Med.* 2013;368:1867-1877.

GT 2 and GT 3 IFN-Unable: SOF+RBV x 12 weeks

POSITRON Summary

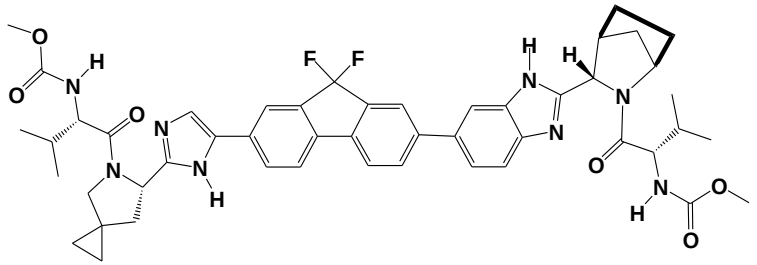
	Efficacy Endpoints: SVR 12		
POSITRON – IFN Unable	Overall	Genotype 2	Genotype 3
SOF + RBV x12 weeks	78%	93%	61%
Placebo	0%	0%	0%

- SOF+RBV for 12 weeks showed efficacy and tolerability in the majority of GT 2 and 3 patients with no current treatment options
  - No resistance detected in SOF+RBV in any patient
  - SOF+RBV was well-tolerated
    - Few discontinuations due to AEs (2% vs 4%)
    - Safety profile consistent with RBV

Jacobson I, et al. EASL 2013. Amsterdam, The Netherlands. Oral #61.
Jacobson IM, et al. *N Engl J Med.* 2013;368:1867-1877.

Ledipasvir (LDV, GS-5885) NS5a Inhibitor

- **NS5A is essential for RNA replication and post-replication assembly and secretion**
- **LDV has picomolar potency against genotype 1a and 1b HCV**

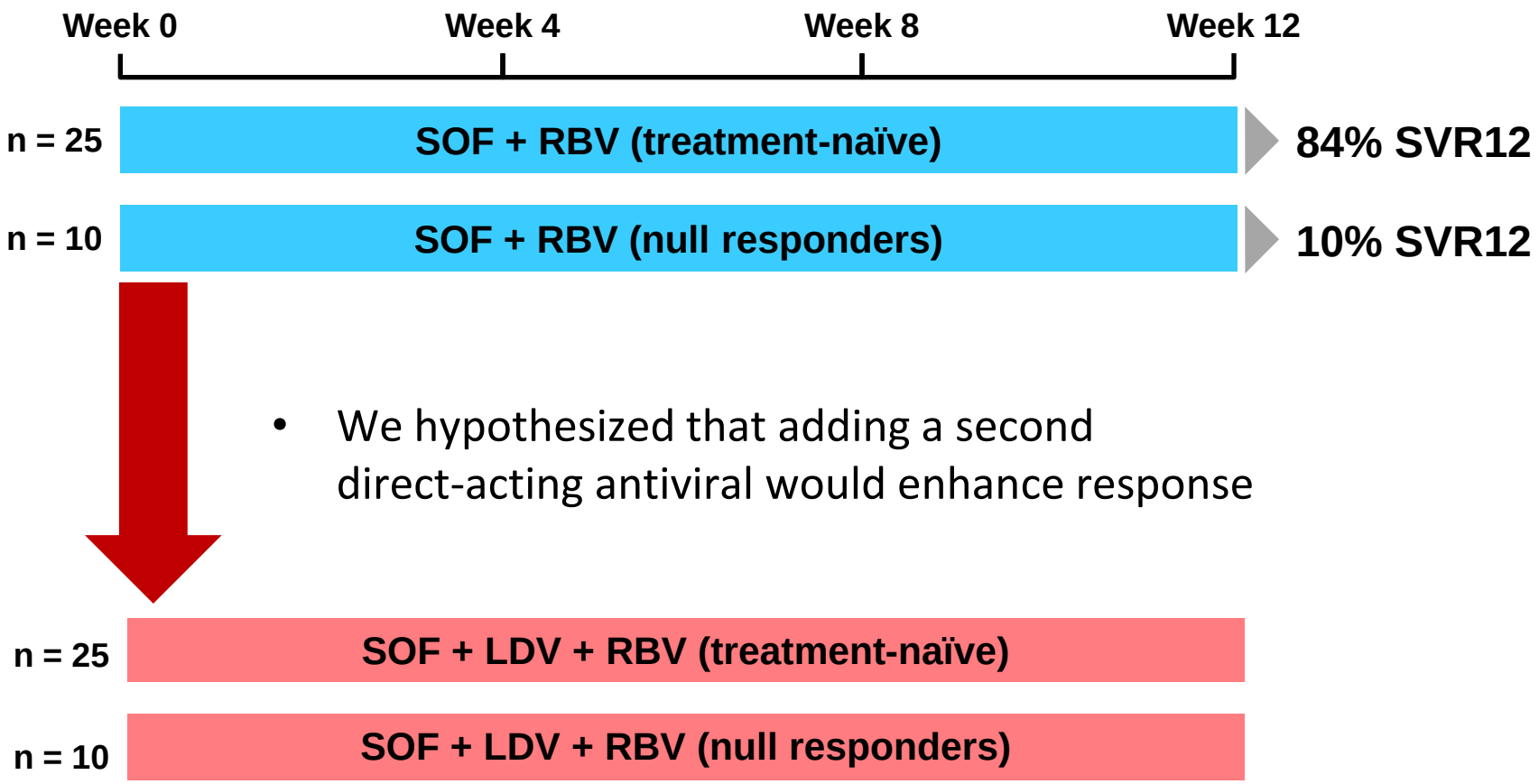


- Effective against signature NS5B-resistant mutant S282T
- Once-daily oral dosing
- Dosed in >3000 patients
- No clinically significant drug-drug interactions with sofosbuvir
- Phase 3 program with SOF/LDV fixed-dose combination tablet underway

Lawitz EJ et al, *J Hepatol* 2012; 57: 24–31; Gane EJ, et al. CROI 2013; Atlanta, GA. Oral #41LB

Phase 2: ELECTRON

Study Design: Genotype 1 Cohorts



- We hypothesized that adding a second direct-acting antiviral would enhance response

LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir

ELECTRON

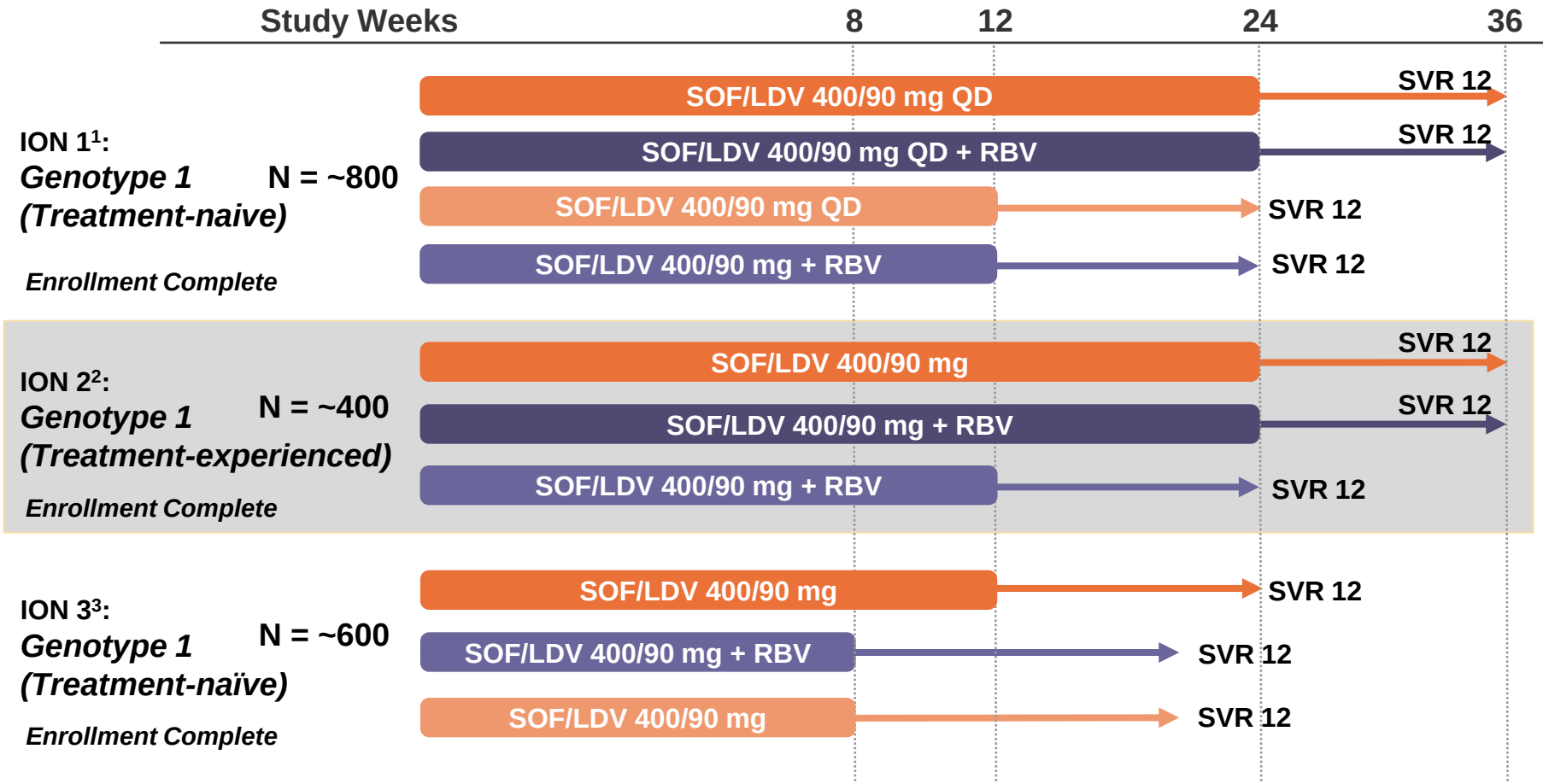
Virologic Efficacy

Patients with HCV RNA <LOD* over Time, n/N (%)

	SOF + RBV		SOF + LDV + RBV	
	Treatment-naïve (n=25)	Null responder (n=10)	Treatment-naïve (n=25)	Null responder (n=9)
Week 4	25/25 (100)	10/10 (100)	25/25 (100)	8/9 (89)
EOT	25/25 (100)	10/10 (100)	25/25 (100)	9/9 (100)
SVR4	22/25 (88)	1/10 (10)	25/25 (100)†	9/9 (100)
SVR12	21/25 (84)	1/10 (10)	25/25 (100)	9/9 (100)

*Analyzed by TaqMan® HCV Test 2.0 with limit of detection (LOD) of 15 IU/mL
†Includes 1 patient who stopped all treatment due to an SAE at week 8; this patient subsequently achieved SVR24
EOT, end of treatment; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir

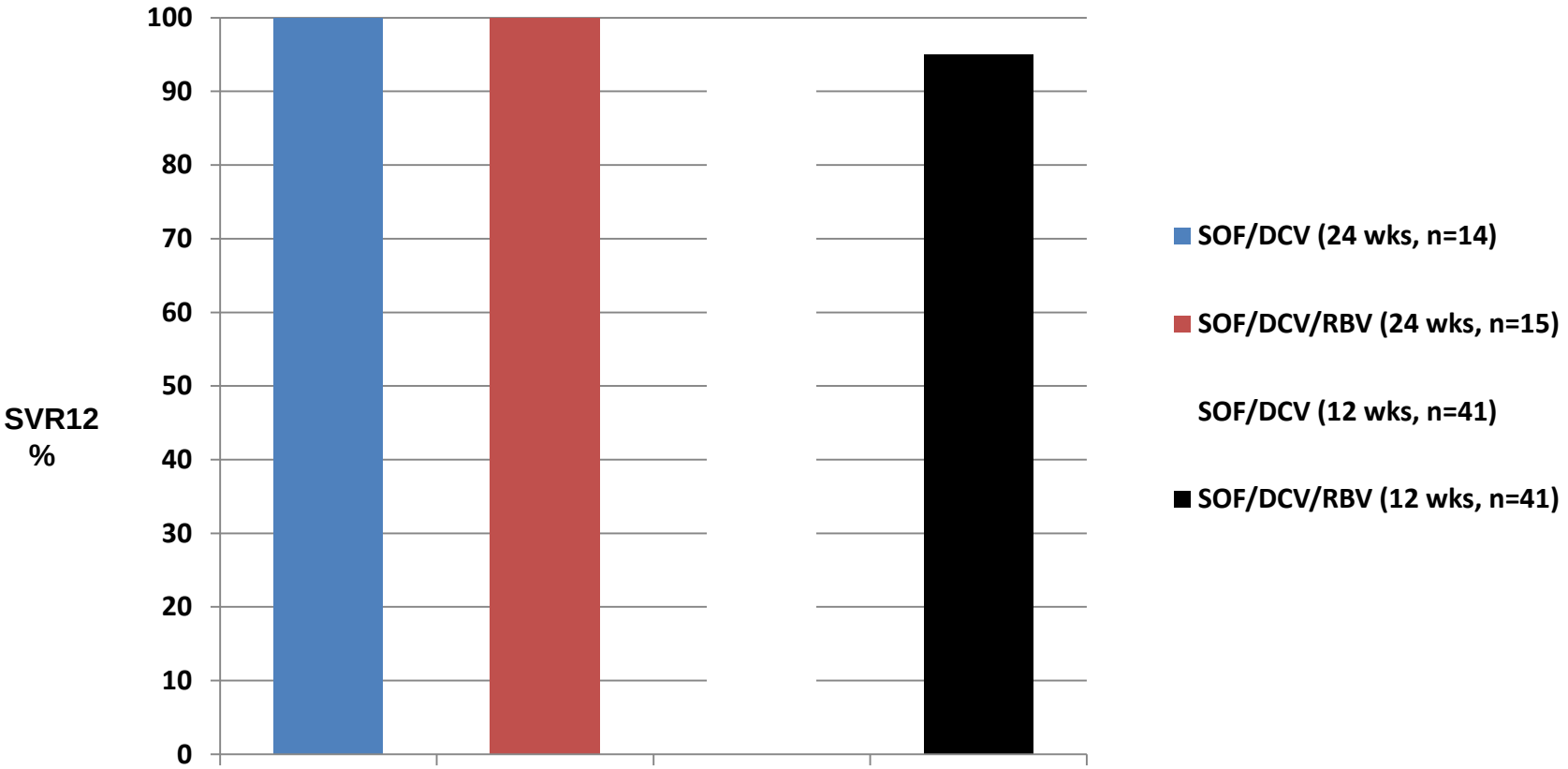
SOF/LDV Phase 3: Genotype 1



1. http://www.clinicaltrials.gov/ct2/show/NCT01768286?term=ION+1+sofosbuvir&rank=1. Accessed May 24, 2013.
2. http://www.clinicaltrials.gov/ct2/show/NCT01768286?term=ION+2+sofosbuvir&rank=1. Accessed February 28, 2013.
3. http://www.clinicaltrials.gov/ct2/show/NCT01851330?term=ION3+sofosbuvir&rank=1. Accessed May 24, 2013.

DUAL DAA (SOFOSBUVIR/DACLATASVIR)

Genotype 1, treatment naive

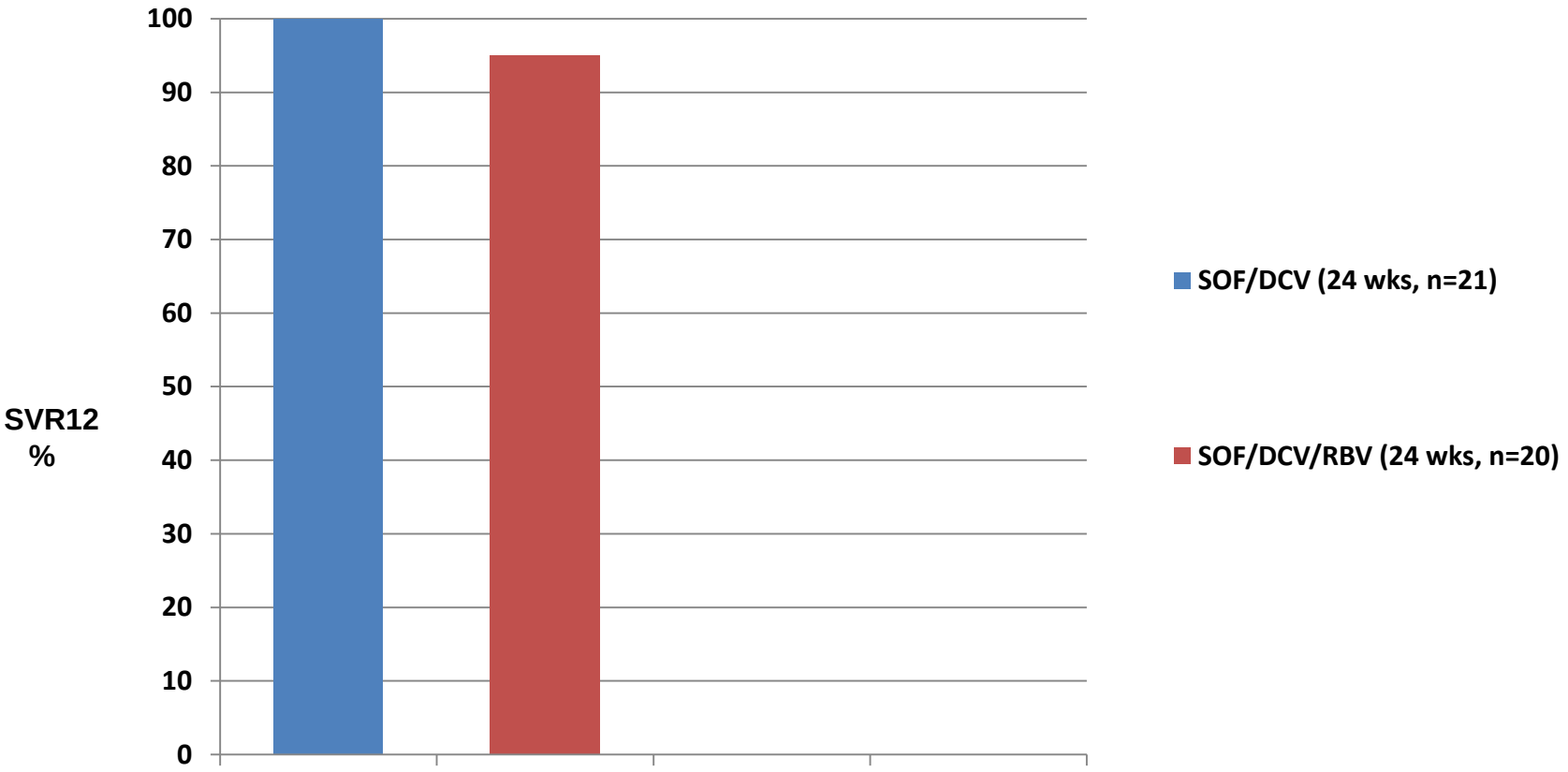


Non-cirrhotic, ~70% non-CC, ~GT1a 70%;
No cases of virological breakthrough or relapse

Sulkowski M et al. AASLD 2012

DUAL DAA (SOFOSBUVIR/DACLATASVIR)

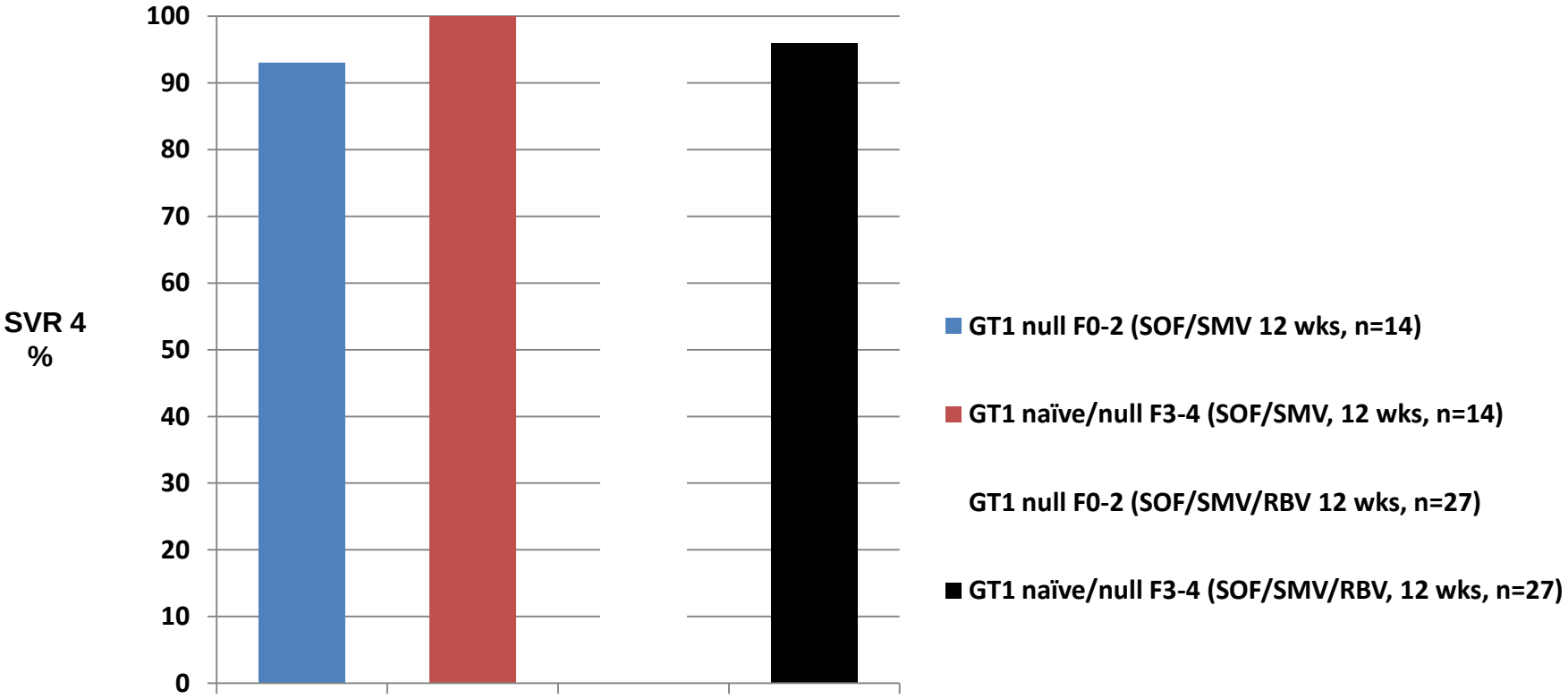
Genotype 1, treatment experienced (TVR or BOC virological failure)



Non-cirrhotic, 97% non-CC, GT1a 80%; 46% PI resistance
No cases of virological breakthrough or relapse

DUAL DAA (SOFOSBUVIR/SIMEPREVIR) (COSMOS)

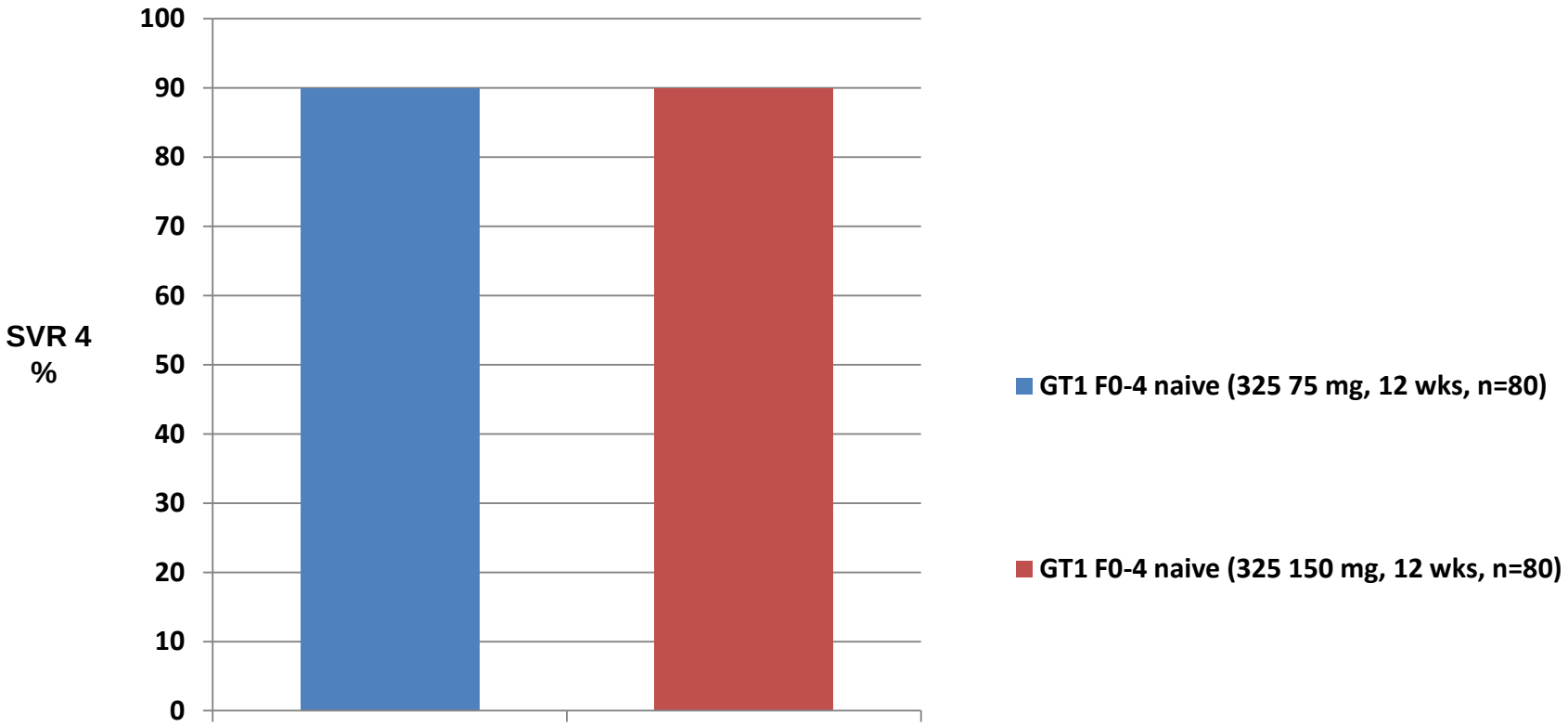
Genotype 1, treatment naive and experienced



Jacobson I, et al. AASLD 2013

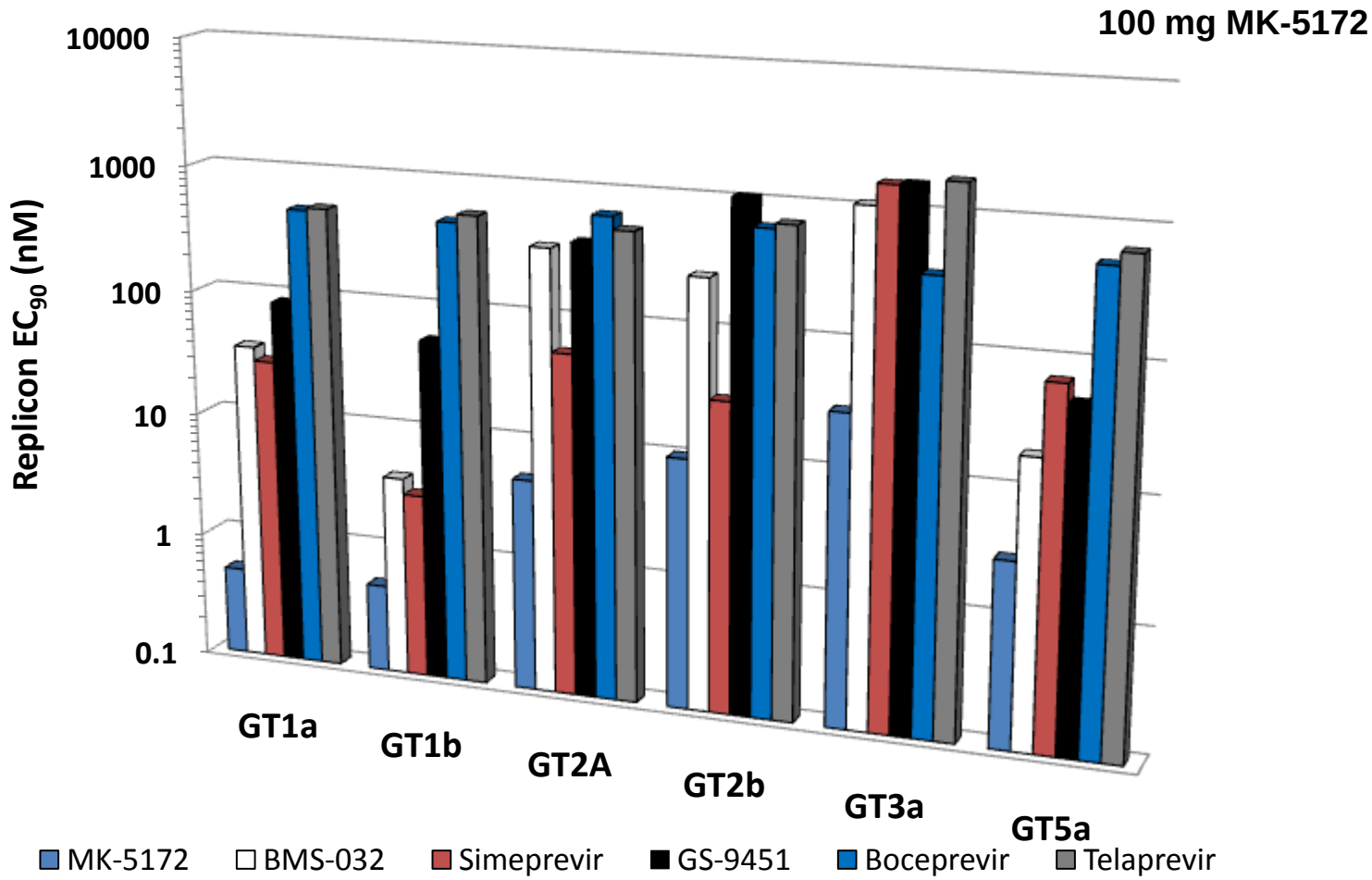
TRIPLE DAA (ASUNAPREVIR/DACLATASVIR/BMS-791325)

Genotype 1, treatment naive



Everson G, et al. AASLD 2013

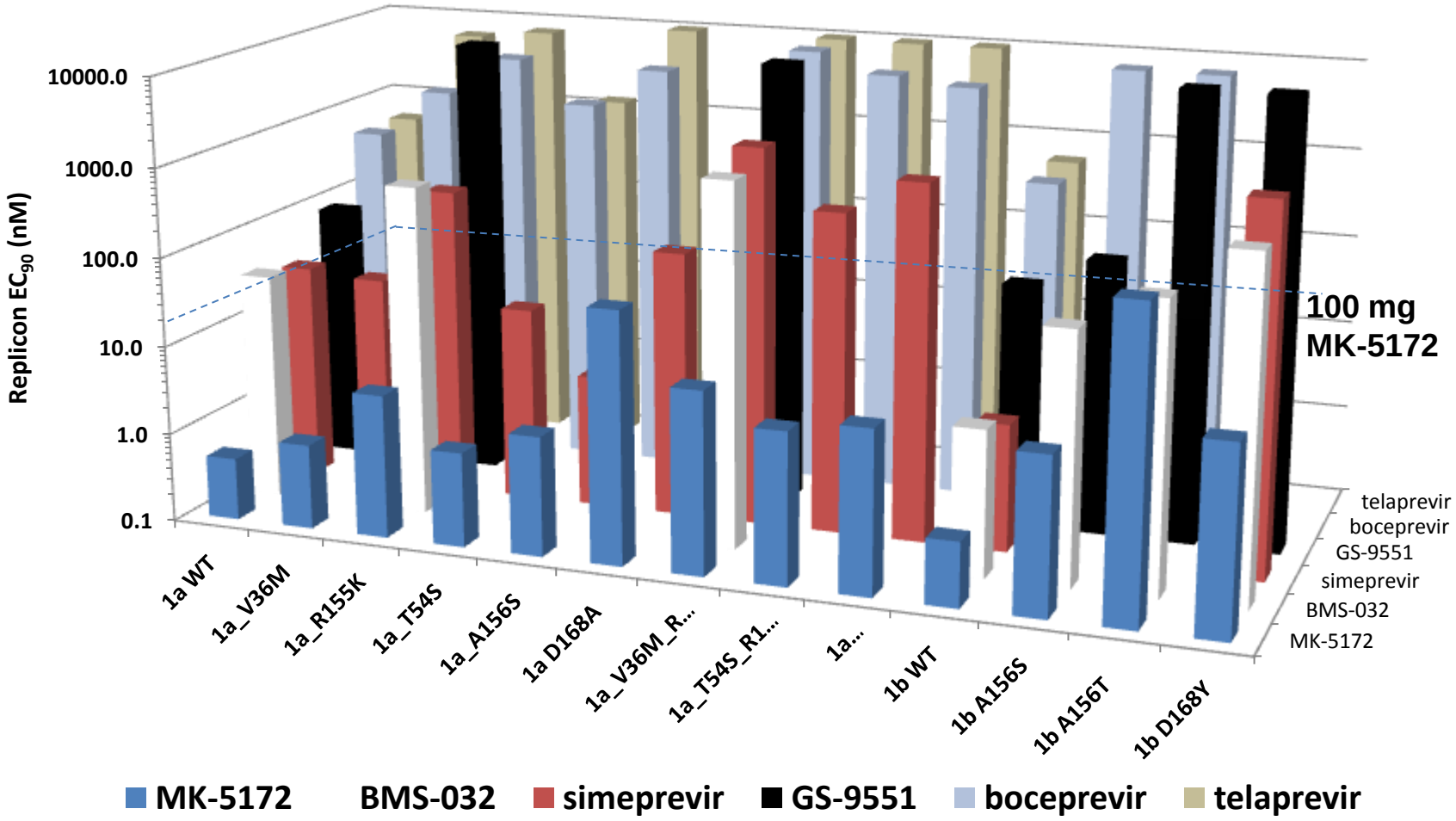
Genotype Activities of Protease Inhibitors *in vitro*



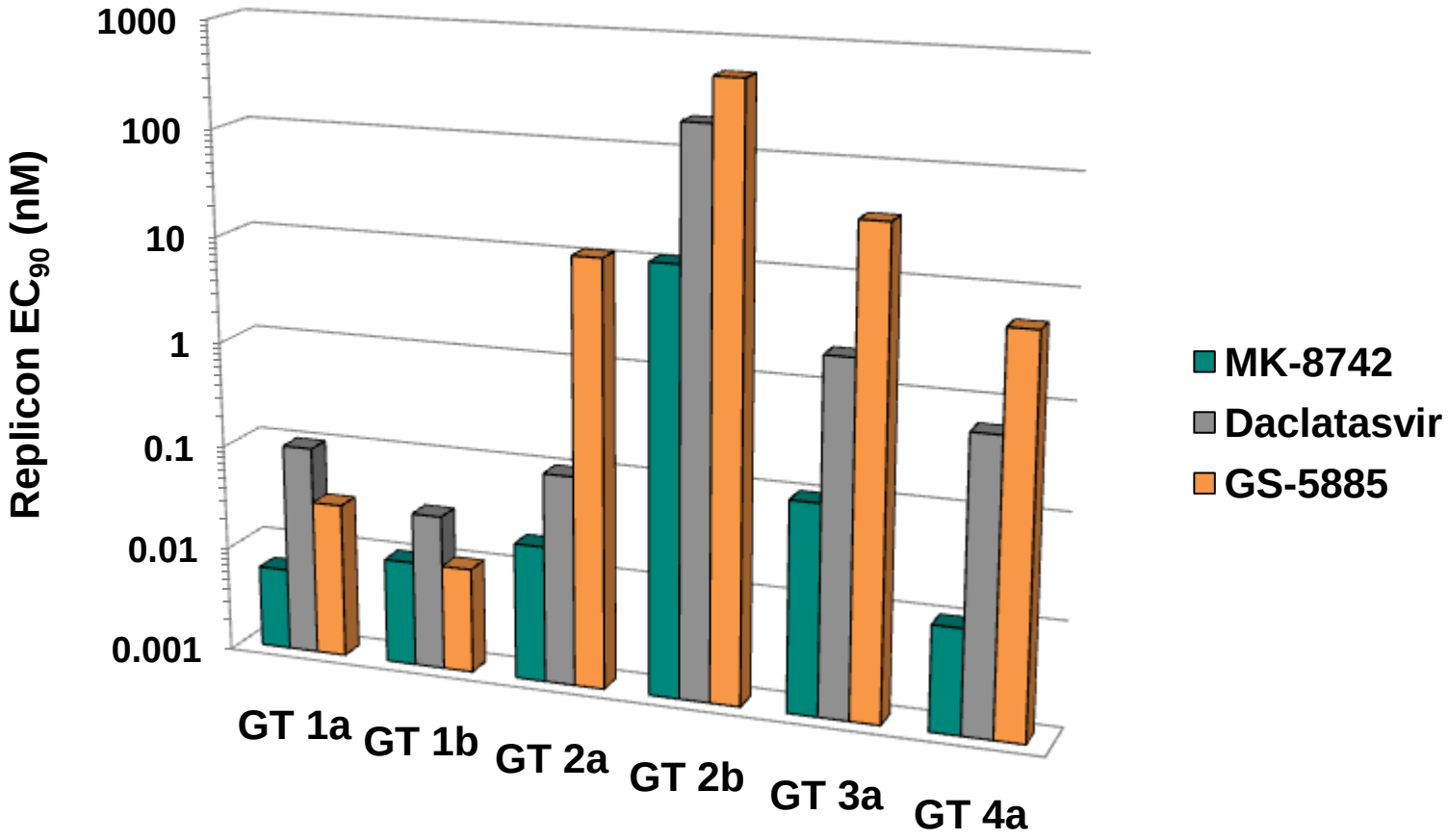
GT 2 – 5 are chimeric replicons containing NS3 from the respective genotypes

- Potent activities against GT 1, 2 and 5

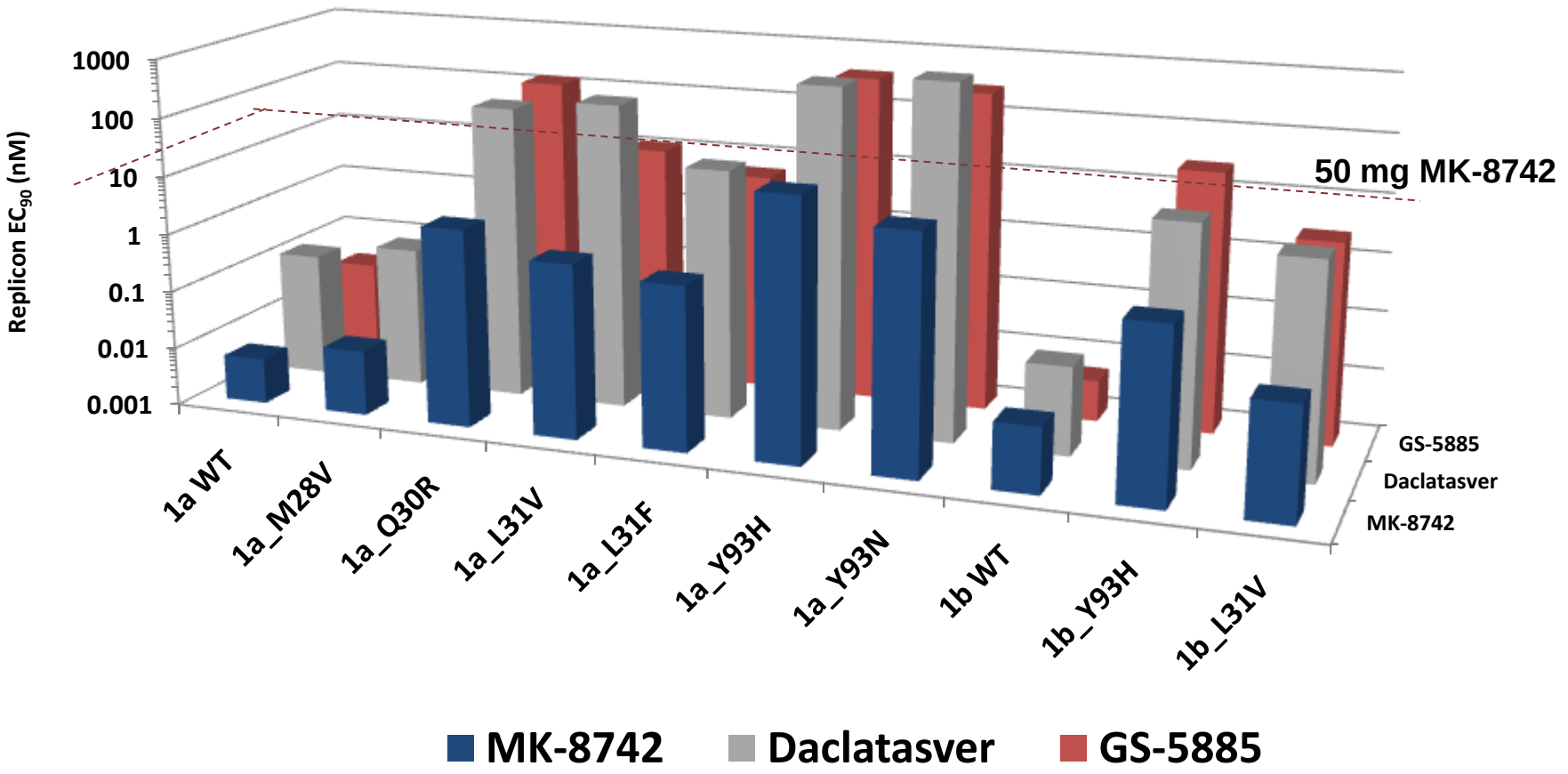
MK-5172: Enhanced Activity against RAVs Associated with 1st Gen PI Treatment Failure



Genotype Activities of NS5A Inhibitors



MK-8742 Demonstrates Improved Potency Against Resistant Variants Selected in the Clinic



AVIATOR

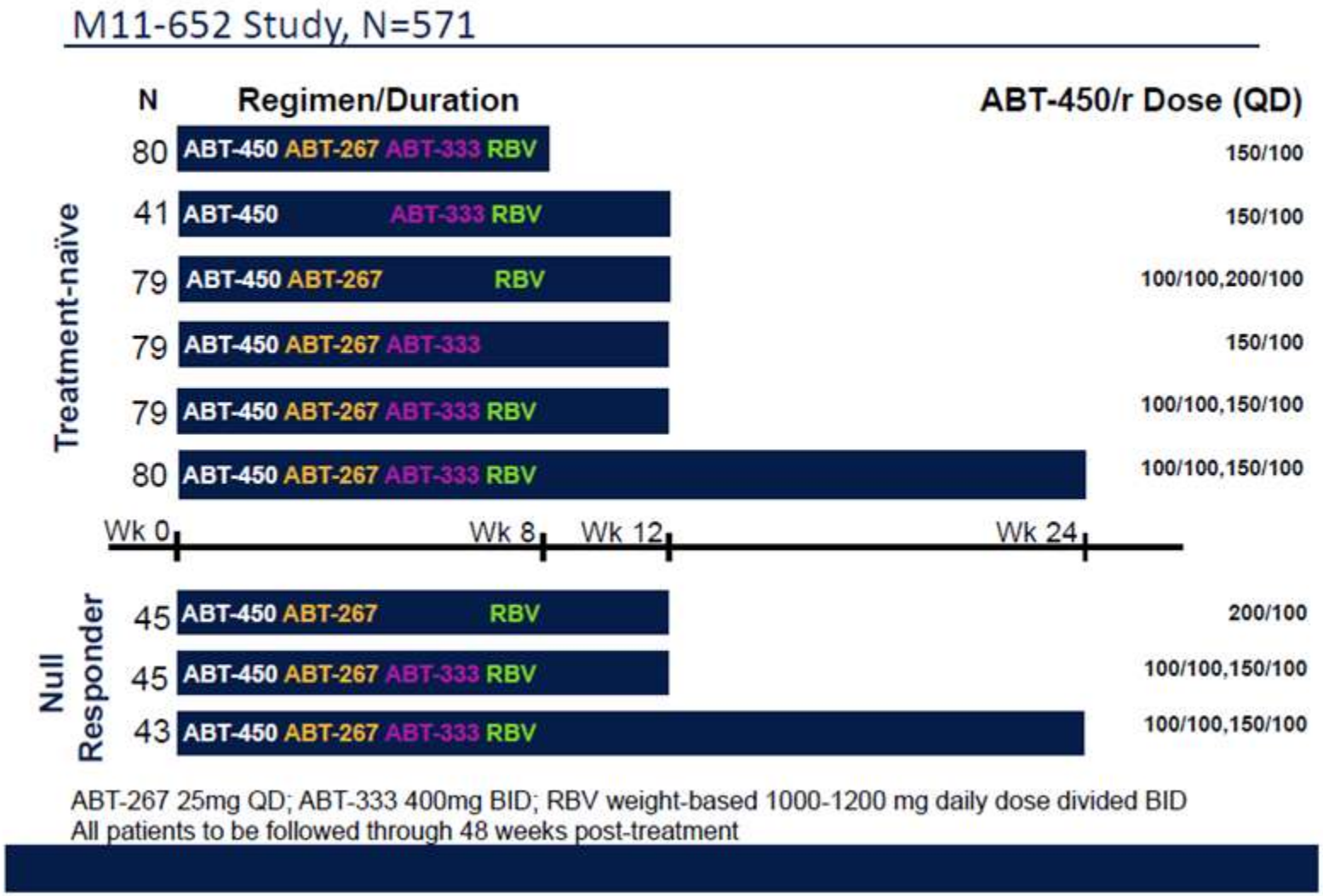
Trial Design

- **AVIATOR** is a randomized, open-label, multicenter Phase 2 study to evaluate the antiviral activity and safety of interferon-free regimens of ABT-450/r, ABT-267, and ABT-333 plus ribavirin (RBV) for 8, 12 or 24 weeks in treatment-naïve and null responder patients with chronic HCV genotype 1 (GT1) infection
  - Interim analysis: 12 weeks of treatment with 3 DAAs + RBV resulted in (ITT) SVR_{12} rates of 97.5% in treatment-naïve patients and 93.3% in null responders[1]

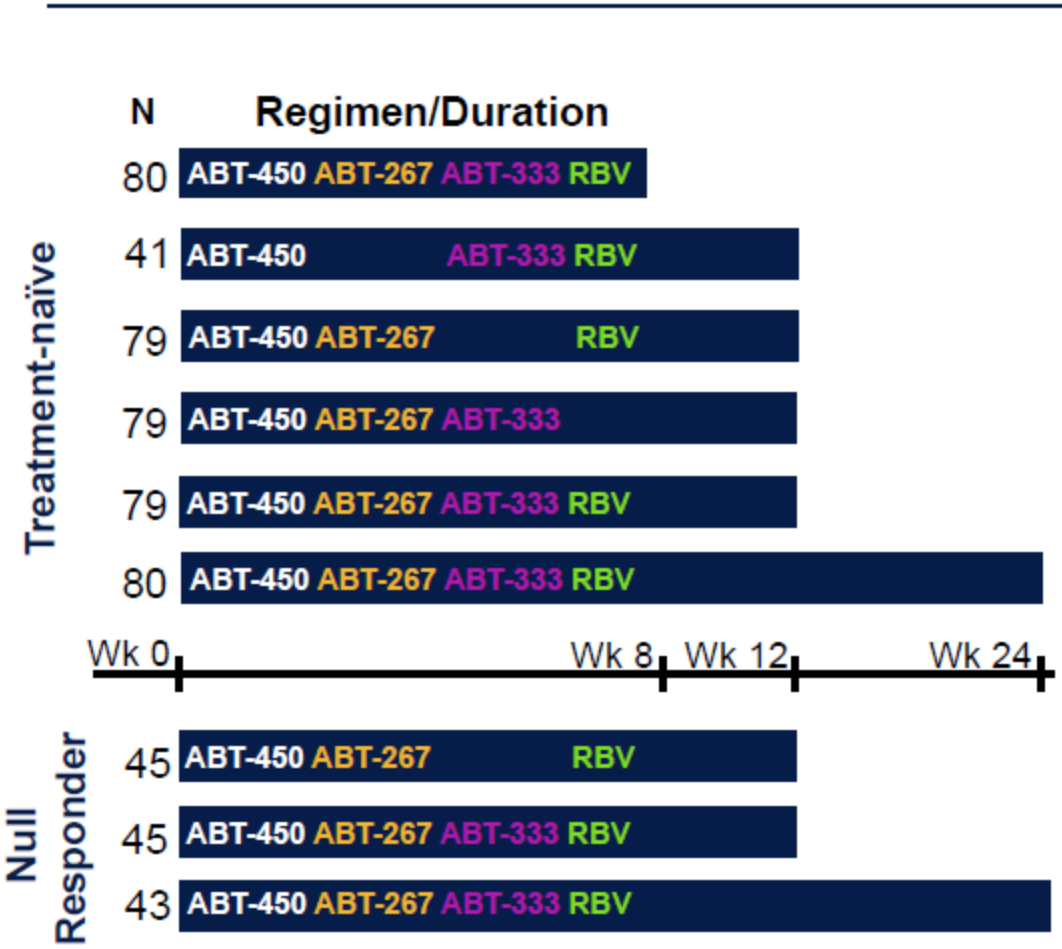
Direct Acting Anti-Viral Agents

- **ABT-450,** identified as a lead compound by AbbVie and Enanta, is a potent HCV NS3/4A protease inhibitor that is dosed once daily with ritonavir (ABT-450/r)
- **ABT-267** is an NS5A inhibitor that is dosed once daily
- **ABT-333** is a non-nucleoside polymerase inhibitor dosed twice daily

1. Kowdley, *et al.* AASLD 2012.


M11-652 Study, N=571
N
Regimen/Duration
ABT-450/r Dose (QD)
Treatment-naïve
80
ABT-450 ABT-267 ABT-333 RBV
150/100
41
ABT-450 ABT-333 RBV
150/100
79
ABT-450 ABT-267 RBV
100/100,200/100
79
ABT-450 ABT-267 ABT-333
150/100
79
ABT-450 ABT-267 ABT-333 RBV
100/100,150/100
80
ABT-450 ABT-267 ABT-333 RBV
100/100,150/100
Wk 0
Wk 8
Wk 12
Wk 24
Null Responder
45
ABT-450 ABT-267 RBV
200/100
45
ABT-450 ABT-267 ABT-333 RBV
100/100,150/100
43
ABT-450 ABT-267 ABT-333 RBV
100/100,150/100
ABT-267 25mg QD; ABT-333 400mg BID; RBV weight-based 1000-1200 mg daily dose divided BID
All patients to be followed through 48 weeks post-treatment

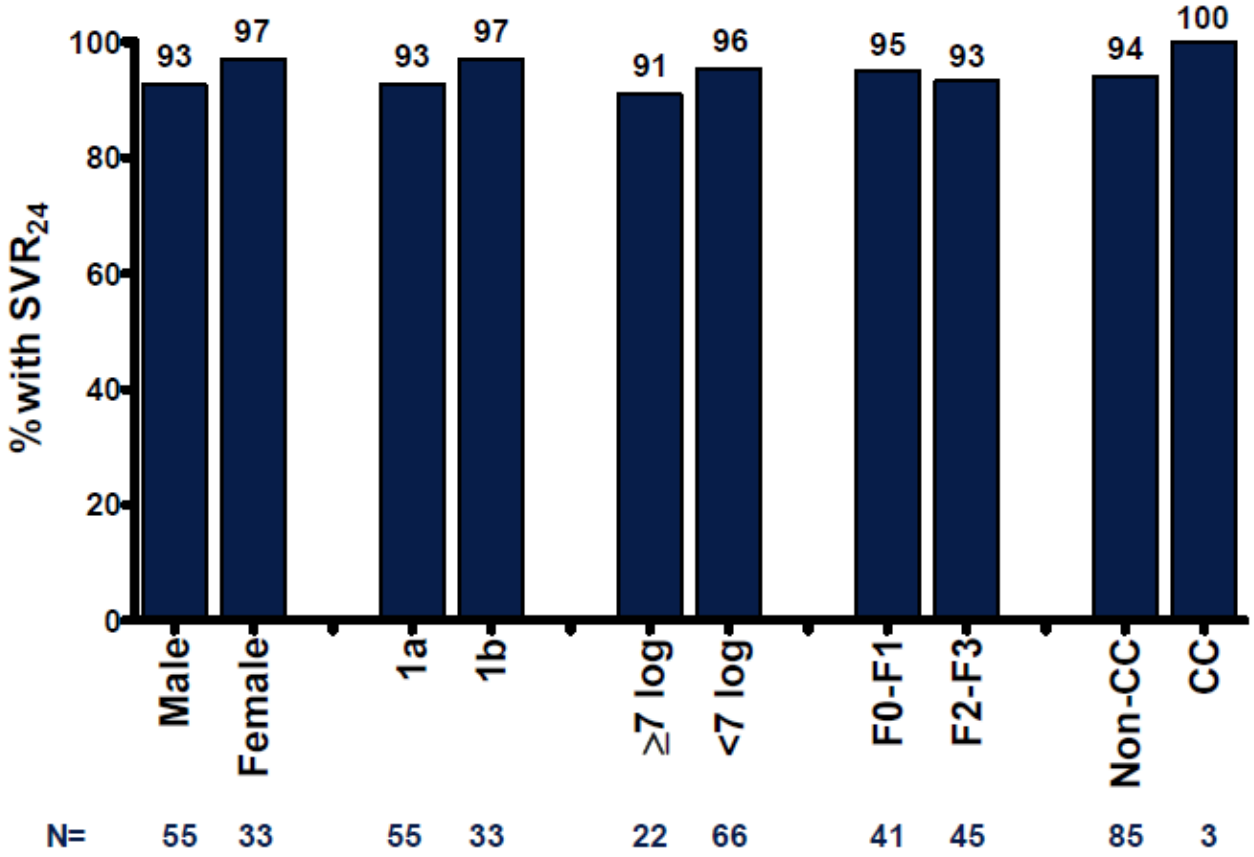
Response Rates, All Groups, N=571



SVR_{12} %	SVR_{24}* %	Breakthrough /Relapse
89	88	0 / 10
85	83	1 / 4
91	89	1 / 8
90	87	1 / 5
99	96	0 / 1
93	90	0 / 2
89	89	0 / 5
93	93	3 / 0
98	95	1 / 0

* 8 patients with SVR_{12} have not returned for >24 weeks and are counted as virologic failures for SVR_{24}; 3 patients relapsed between SVR_{12} and SVR_{24}.

SVR_{24} by Baseline Subgroups – Null Responders



Waves of HCV Development

Wave 1 2014

GT 1,4,5,6: Simplified, shorter therapy
GT 2/3: First all-oral therapy *(SOF+R)*

Wave 2

GT 1: All-oral Fixed Dose Combination therapy)

Wave 3

All-oral FDC therapy for all HCV genotypes

SOF, sofosbuvir; P, pegylated interferon; R, ribavirin; LDV, ledipasvir; FDC, fixed dose combination

HCV therapeutic development: IFN-free GT1

	Protease inhibitor	Nucleotide analogue	Non-nucleoside analogue	NS5A inhibitor	Ribavirin	Duration	Phase
Gilead					+ / -	12-24 wks	III (1a/1b)

HCV therapeutic development: IFN-free GT1

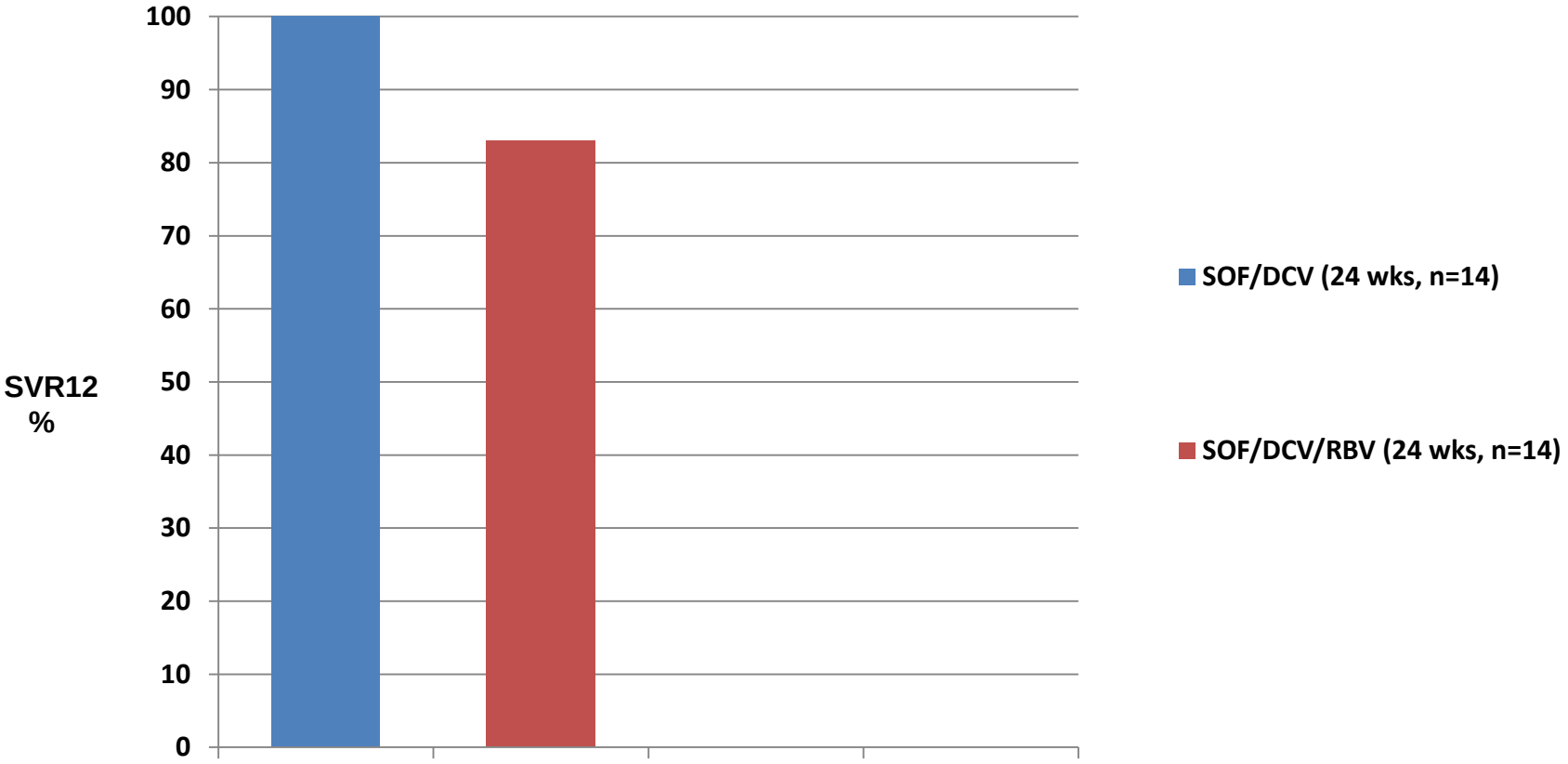
	Protease inhibitor	Nucleotide analogue	Non-nucleoside analogue	NS5A inhibitor	Ribavirin	Duration	Phase
Gilead					+ / -	12-24 wks	III (1a/1b)
BMS						12 wks	III (1a/1b)
Abbvie					+ / -	12 wks	III (1a/1b)
Boehringer						16-24 wks	III (1b)

HCV therapeutic development: IFN-free GT1

	Protease inhibitor	Nucleotide analogue	Non-nucleoside analogue	NS5A inhibitor	Ribavirin	Duration	Phase
Gilead					+ / -	12-24 wks	III (1a/1b)
BMS						12 wks	III (1a/1b)
Abbvie					+ / -	12 wks	III (1a/1b)
Boehringer						16-24 wks	III (1b)
Janssen / Vertex						12 wks	II (1a/1b)
BMS / Janssen					+ / -	12-24 wks	II (1a/1b)
BMS / Merck						12 weeks	II (1a/1b)
Vertex / BMS						12 weeks	II (1a/1b)

DUAL DAA (SOFOSBUVIR/DACLATASVIR)

Genotype 2/3, treatment naive



Non-cirrhotic, ~70% non-CC, ~GT2 60%;
No cases of virological breakthrough

Sulkowski M et al. AASLD 2012

HCV therapeutic development: IFN-free GT2/3

	Protease inhibitor	Nucleotide analogue	Non-nucleoside analogue	NS5A inhibitor	Ribavirin	Duration	Phase
Gilead						12-16 wks	FDA

HCV therapeutic development: IFN-free GT2/3

	Protease inhibitor	Nucleotide analogue	Non-nucleoside analogue	NS5A inhibitor	Ribavirin	Duration	Phase
Gilead						12-16 wks	FDA
Gilead						12-24 wks	II
Gilead						12 wks	II planning

HCV therapeutic development: IFN-free GT2/3

	Protease inhibitor	Nucleotide analogue	Non-nucleoside analogue	NS5A inhibitor	Ribavirin	Duration	Phase
Gilead						16-24 wks	FDA
Gilead						12-24 wks	II
Gilead						12 wks	II planning
? Vertex / BMS						?	?

HCV regimen timelines

Phase I (Predominantly IFN-based therapy, 2013-2014):

- PEG-IFN + RBV (GT2/3)
- PEG-IFN + RBV + TVR or BOC (GT1)
- PEG-IFN + RBV + Simeprevir (GT1/4)
- PEG-IFN + RBV + Sofosbuvir (GT1/4)
- Sofosbuvir + RBV (G2/3 naïve) (GT2/3)

Phase II (Predominantly IFN-free therapy, 2015-2016):

- PEG-IFN + RBV + Sofosbuvir (GT1/4)
- Sofosbuvir + RBV (G2/3 naïve)
- Asunaprevir + Daclatasvir (G1b)
- Sofosbuvir + Ledipasvir +/- RBV (GT1)

Phase III (Cross-genotype, comb formulations, 2017 and beyond):

- Sofosbuvir + GS-5816
- Other DAA-based regimens


Thank you !