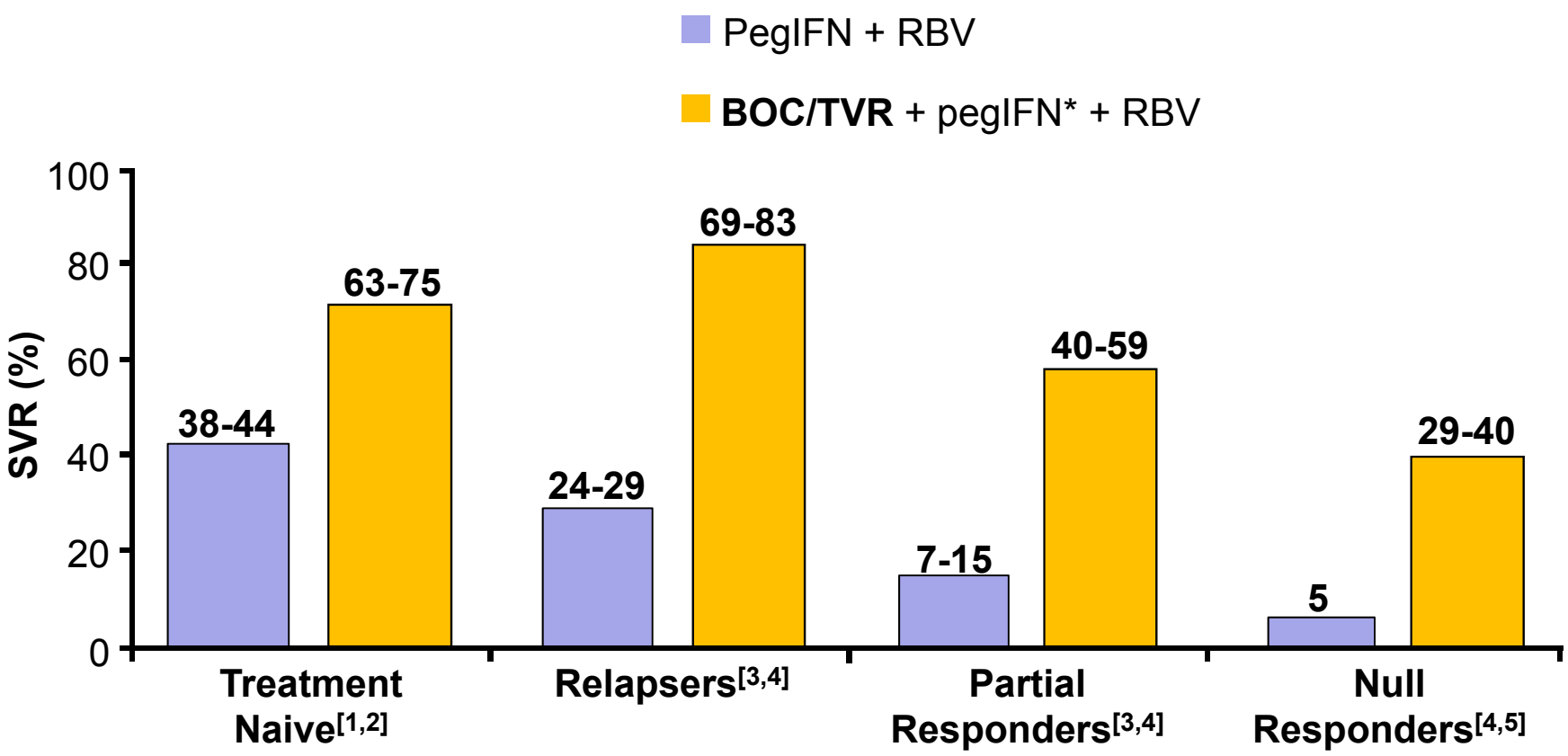
ACTUALIZACIÓN EN EL TRATAMIENTO DE LA HEPATITIS C:

Medicamentos en Investigación a medio plazo

Manuel Romero-Gómez.
Unidad Médico-Quirúrgica de Enfermedades Digestivas y ciberehd.
Hospital Universitario de Valme.
Universidad de Sevilla.

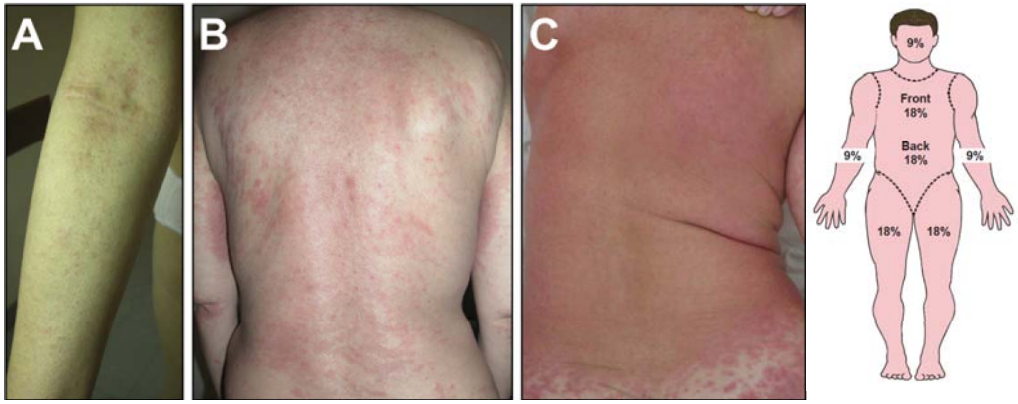
Tasas de RVS con BOC/ TVR en G1



***BOC (SCH503034) was administered with pegIFN-α2b; TVR (VX950) was administered with pegIFN-α2a.**

1. Poordad F, et al. N Engl J Med. 2011;364:1195-1206. 2. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416.
3. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217. 4. Zeuzem S, et al. N Engl J Med. 2011;364:2417-2428.
5. Bronowicki JP, et al. EASL 2012. Abstract 11.

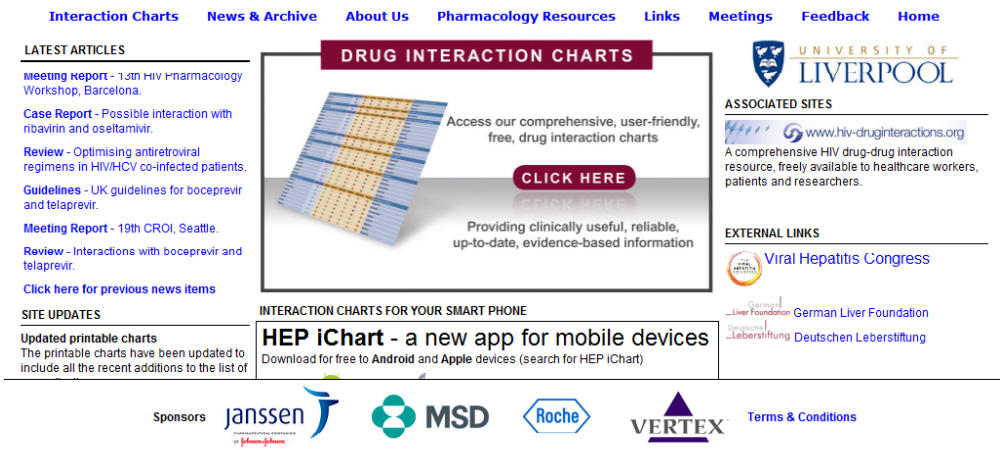
Limitaciones actuales del BOC/ TVR

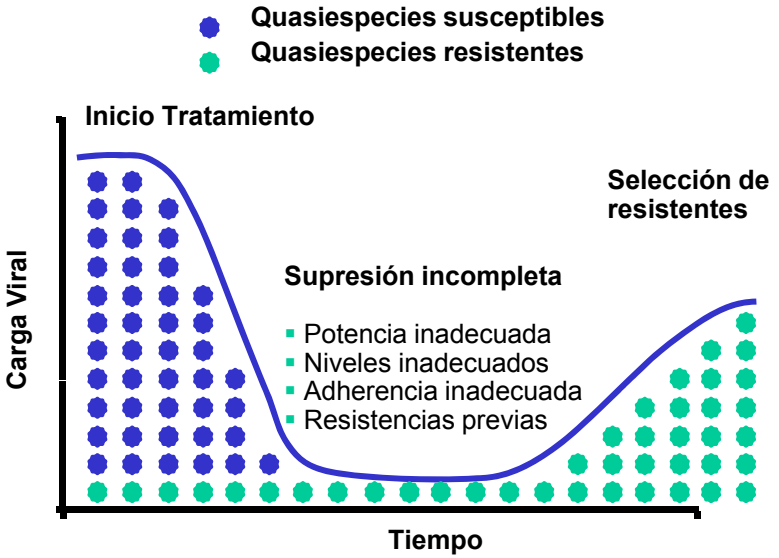


Mayor complejidad:

- **Interferón pegilado/semana**
- **11 a 18 comprimidos/dia**
  - **BOC TID: 12 comp/día**
  - **TPV TID: 6 comp/día**
  - **RBV BID: 4-6 comp/día**

http://www.hep-druginteractions.org/





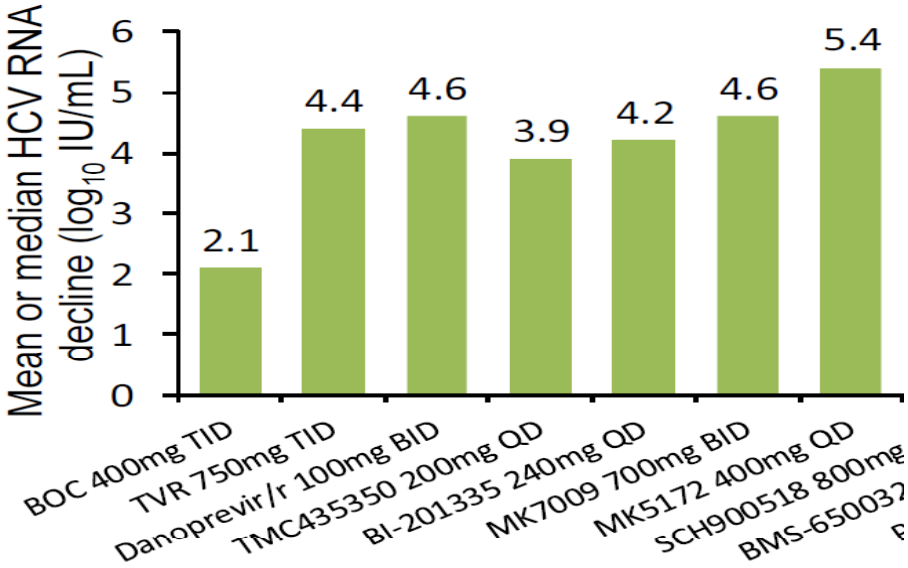
Antivirales de Acción Directa (AAD) en Desarrollo

Clase	Antiviral Acción Directa	Compañía
✧ **Inhibidores de la proteasa (NS3/4A)**	• **Simeprevir** (TMC-435) • **Faldaprevir** (BI-201335) • **Asunaprevir** • **Danoprevir/r** • Vaniprevir (MK-7009) • **ABT-450** • GS-9451	Jansen Boehringer BMS Roche MSD Abbott Gilead
✧ **Inhibidores de la NS5A**	• **Daclatasvir** (BMS790052) • **Ledipasvir** (GS 5885)	BMS Gilead
✧ **Inhibidores de la polimerasa (NS5B)** ✧ Nucleos(t)idos ✧ No-nucleosidos	• **Sofosbuvir** (GS-7977) • Mericitabina (RG-7128) • VX-135 • Tegobuvir (GS-9190) • VX-222 • **ABT-072** • **ABT-333** • BI-207127	Gilead Roche Vertex Gilead Vertex Abbott Abbott Boheringer
✧ **Inhibidor ciclofilina**	• Alisporivir (DEB025)	Novartis

Ventajas Potenciales de los AAD en Desarrollo

- **Elevada potencia antiviral**
- **Fuerte barrera contra resistencias**
- **Efecto pan-genotípico (IP 2ªG)**
- **Administración oral**
- **Fácil dosificación**
- **Mejor tolerancia**
- **Escasos efectos adversos**
- **Pocas interacciones farmacológicas**

Descenso RNA-VHC (3-14 d) monoterapia



Sarrazin C, et al. Gastroenterology 2010

HCV Regimens in Phase II Clinical Trials

1 DAA + PegIFN/ RBV (TRIPLE)

Faldaprevir	*(BI201335), Boheringer
Vaniprevir	^(MK7009), MSD
Simeprevir	*(TMC435), Jansen
Danoprevirr	Roche
Daclatasvir	*(BMS790052), BMS
Sofosbuvir	*(GS7977), Gilead

2 DAAs + PegIFN/ RBV (QUAD)

Danoprevir/r	Mericitabina	Roche
Daclatasvir	Asunaprevir	BMS
Telaprevir	VX-222	Jansen

New IFNs

PegIFN lambda-1a + RBV +	Daclatasvir	BMS
	Asunaprevir	BMS

IFN-Free/ IFN and RBV-Free Regimens

Sofosbuvir	Daclatasvir	± RBV	Gilead/BMS
Faldaprevir	BI-207127	+RBV	Boheringer
Sofosbuvir	Ledipasvir	± RBV	Gilead
ABT-450/r	ABT-267	ABT-333 ± RBV	Abbott
Daclatasvir	Asunaprevir	BMS791325	BMS

ClinicalTrials.gov. November 27, 2012.

HCV Regimens in Phase II Clinical Trials

1 DAA + PegIFN/ RBV (TRIPLE)

Faldaprevir	*(BI201335), Boheringer	
Vaniprevir	^(MK7009), MSD	
Simeprevir	*(TMC435), Jansen	ASPIRE (Tx-Exp)
Danoprevirr	Roche	DAUPHINE (Naïve)
Daclatasvir	*(BMS790052), BMS	COMMAND-1 (Naïve)
Sofosbuvir	*(GS7977), Gilead	ATOMIC (Naïve)

New IFNs

PegIFN lambda-1a + RBV +

Daclatasvir	BMS	D-LITE (Naïve)
Asunaprevir	BMS	

2 DAAs + PegIFN/ RBV (QUAD)

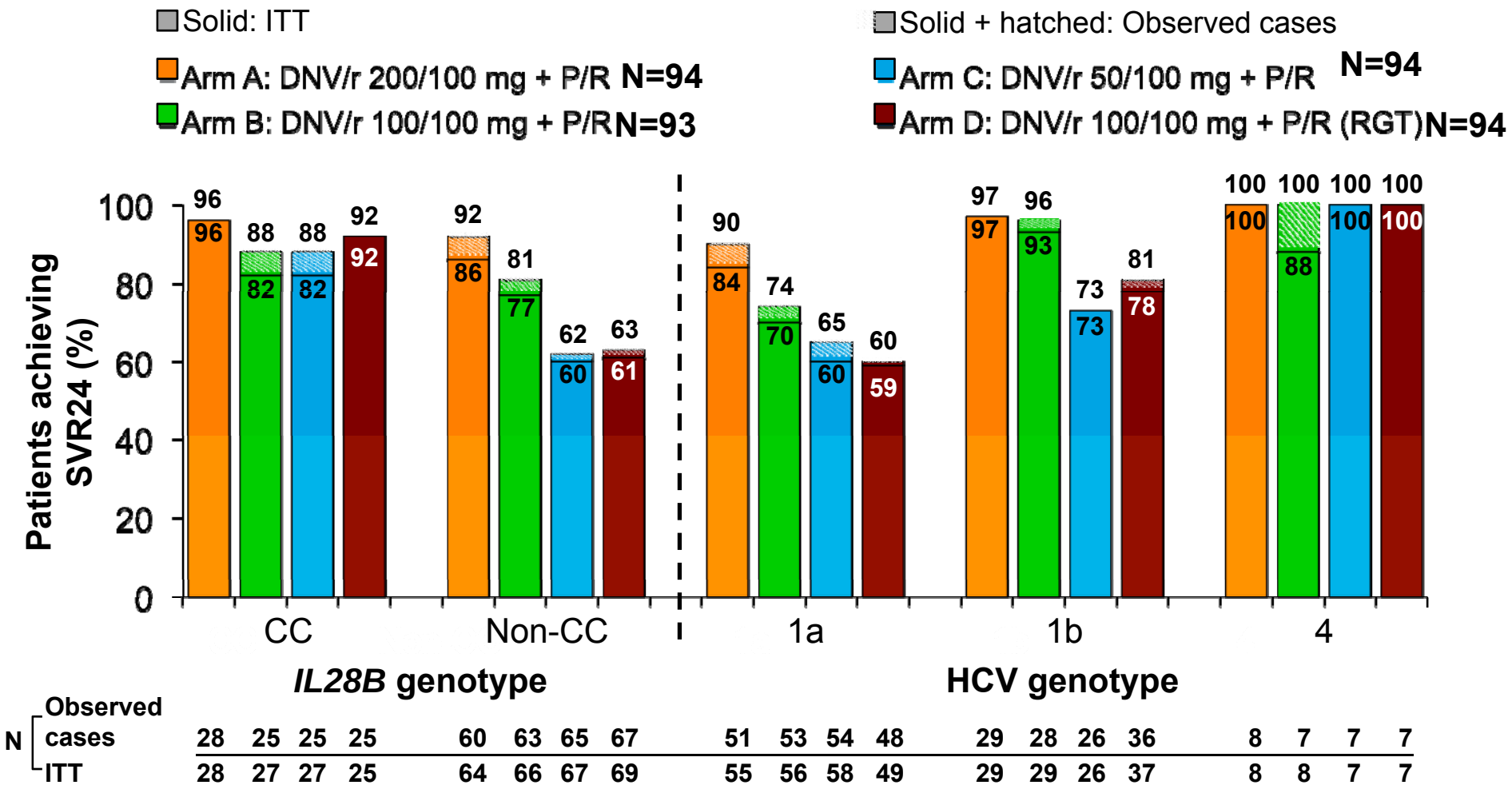
Danoprevir/r	Mericitabina	Roche	MATTERHORN (Tx-Exp)
Daclatasvir	Asunaprevir	BMS	AI447-011 (Nulls)
Telaprevir	VX-222	Jansen	ZENITH (Naive)

ClinicalTrials.gov. November 27, 2012.

DAUPHINE (FIIb): Danoprevir/r + PR in Naive G1/4

Danoprevir 50-100-200 mg/ritonavir + PegIFN + RBV during 24W

Danoprevir/r
2 tomas/d

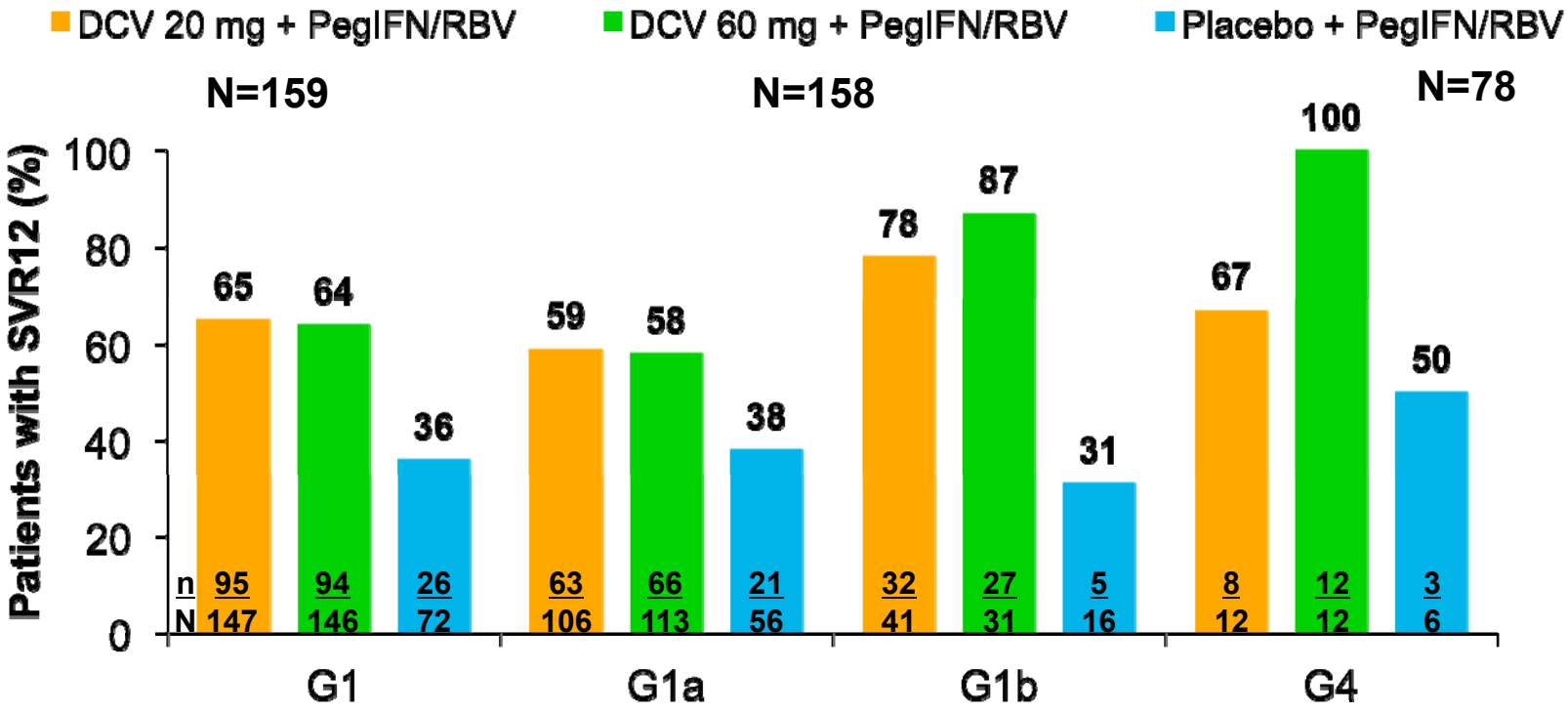


Everson GT, et al. AASLD 2012. Poster 0754.

COMMAND-1 (FIIb): Daclatasvir + PR in Naive G1/4

Daclatasvir 20 or 60 mg/d during 12 W (ILD W4 and W10) or 24 W

Daclatasvir
1 toma/d

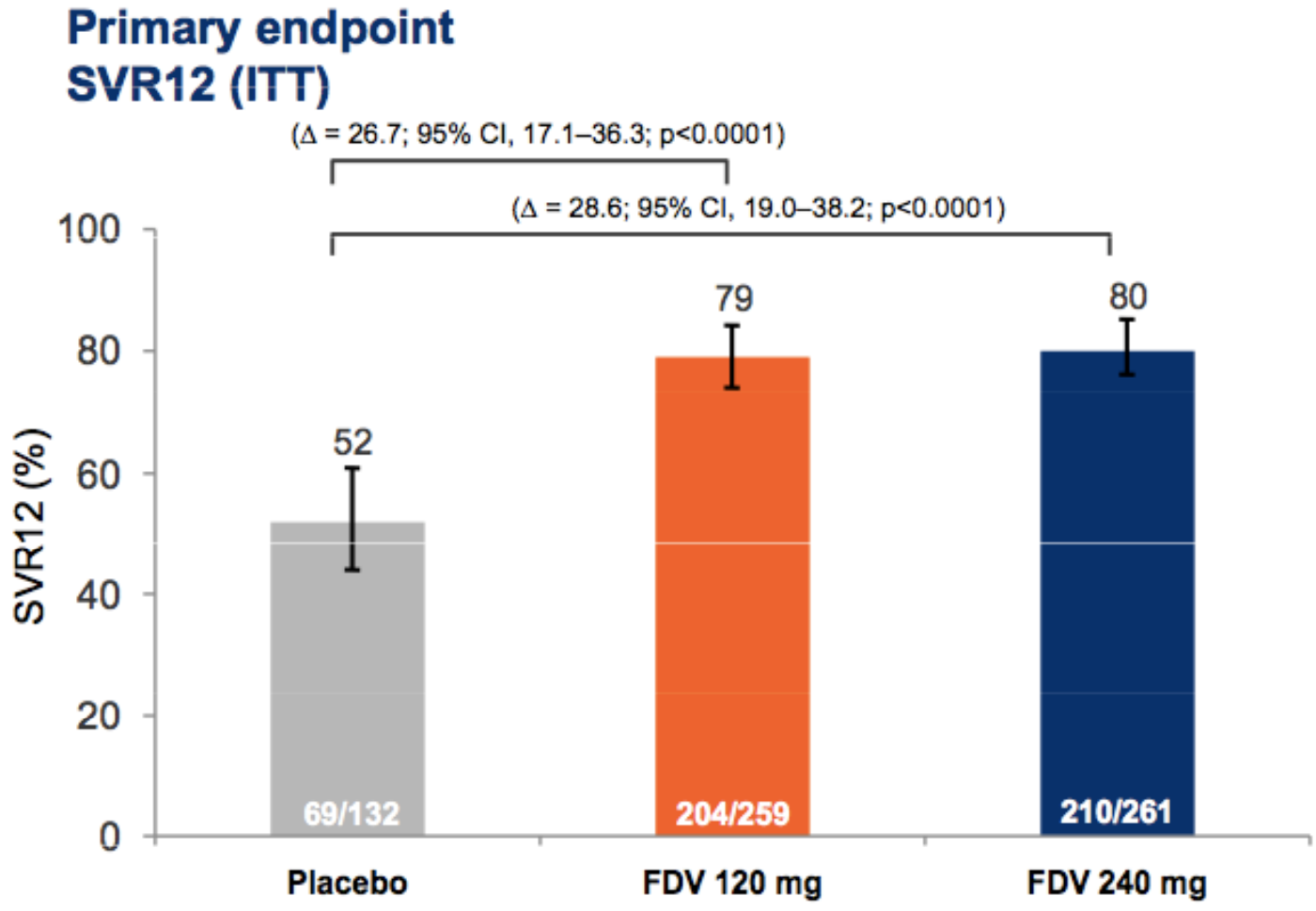


Most Common Adverse Events (30%): Dry skin, Nausea, Influenza-like illness

Hezode C, et al. AASLD 2012. Poster 0755.

N=652

Faldaprevir + PR

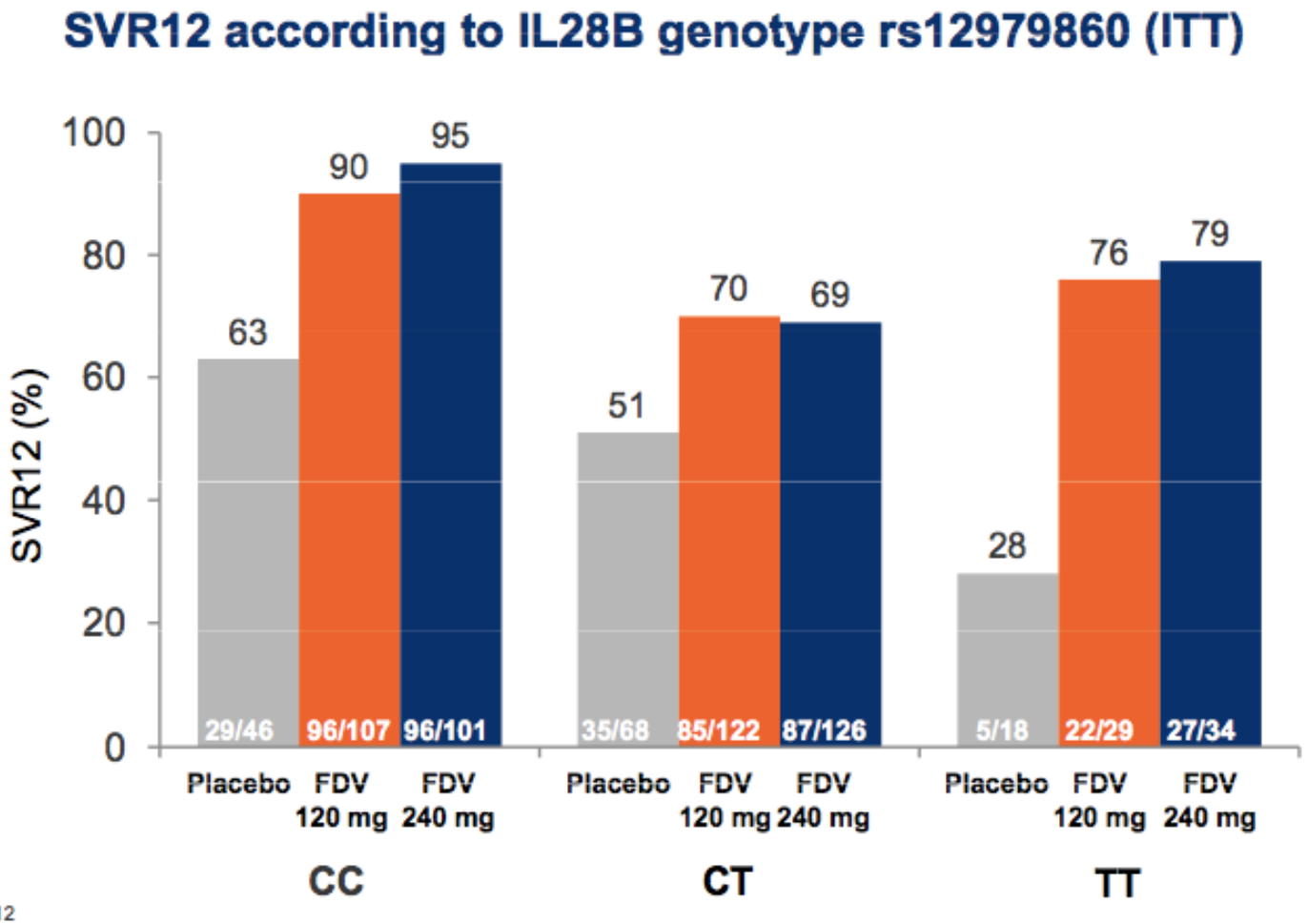


SVR12 rates adjusted for race and genotype
ITT, intention-to treat

Fereneci et al. EASL 2013

N=652

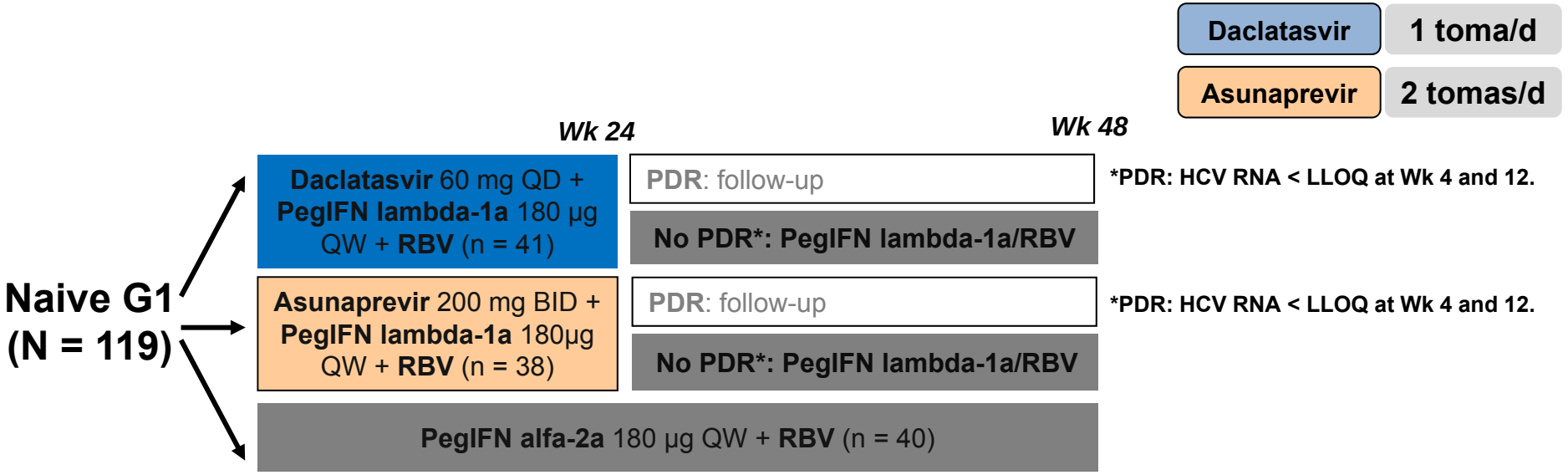
Faldaprevir + PR



12

Fereneci et al. EASL 2013

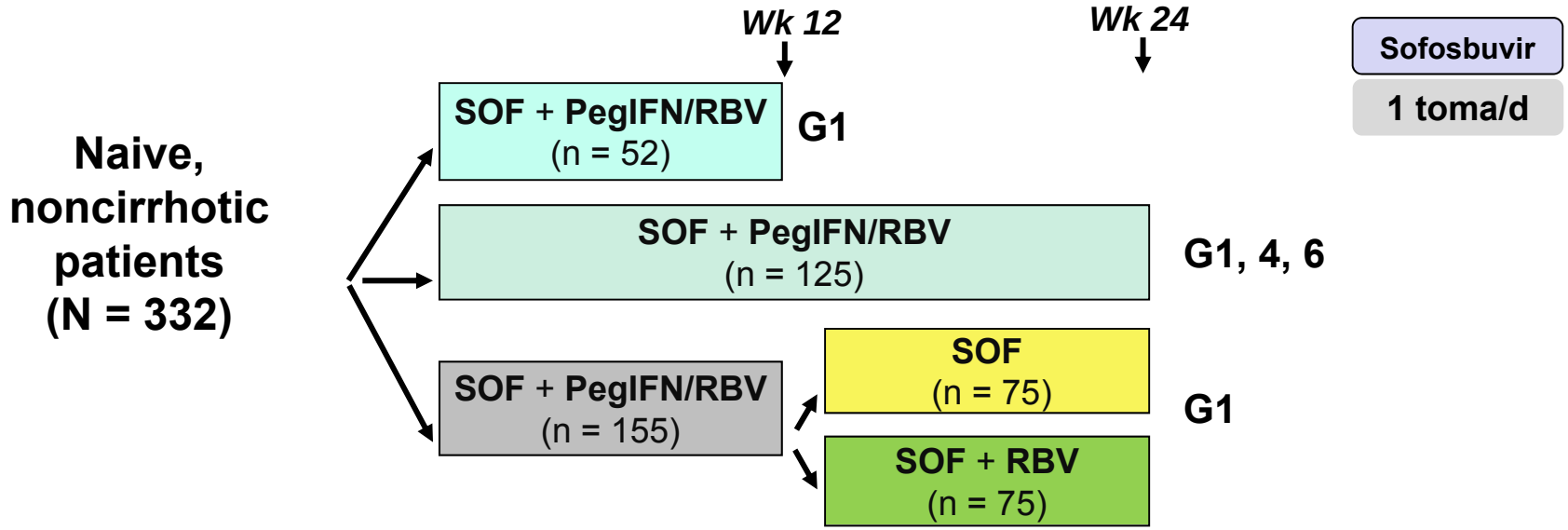
D-LITE (FIIb): PegIFN lambda-1a + RBV + Daclatasvir or Asunaprevir in Naive G1

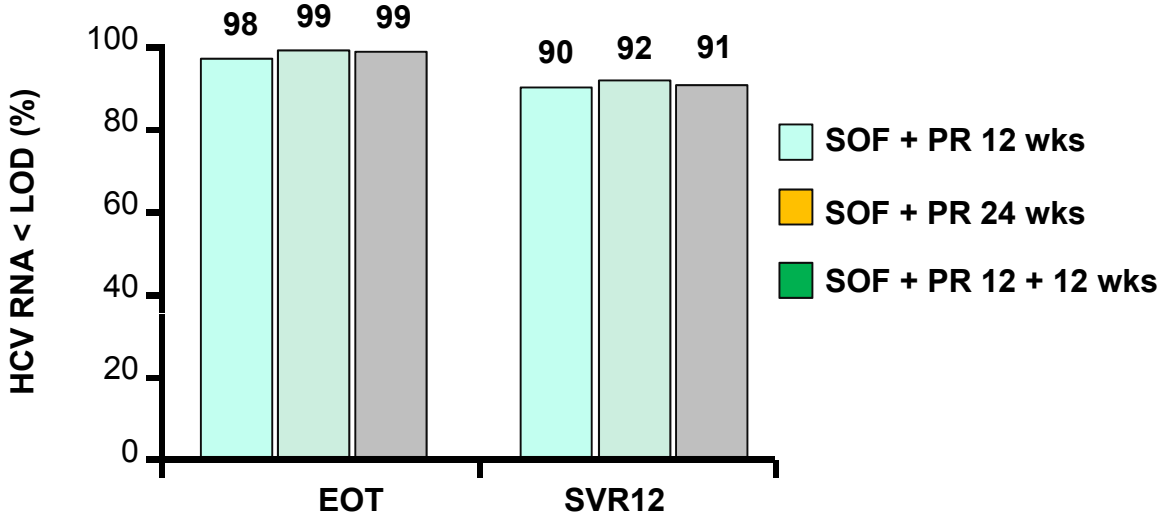


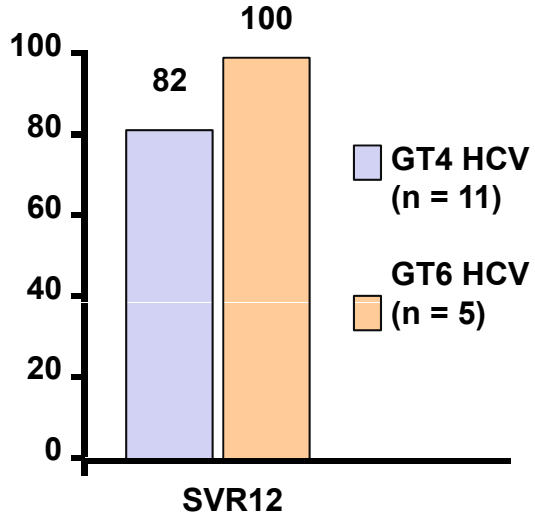
	PegIFN lamba-1a + RBV + Daclatasvir (n = 41)	PegIFN lamba-1a + RBV + Asunaprevir (n = 38)
SVR12	76%	75%
▪ 1b	93 (13*/14)	91 (10*/11)
▪ 1a	65 (15*/23)	67 (14†/21)

Vierling JM, et al. AASLD 2012. Abstract LB-9.

ATOMIC (FIIb): Sofosbuvir + PR in Naive G1/4/6







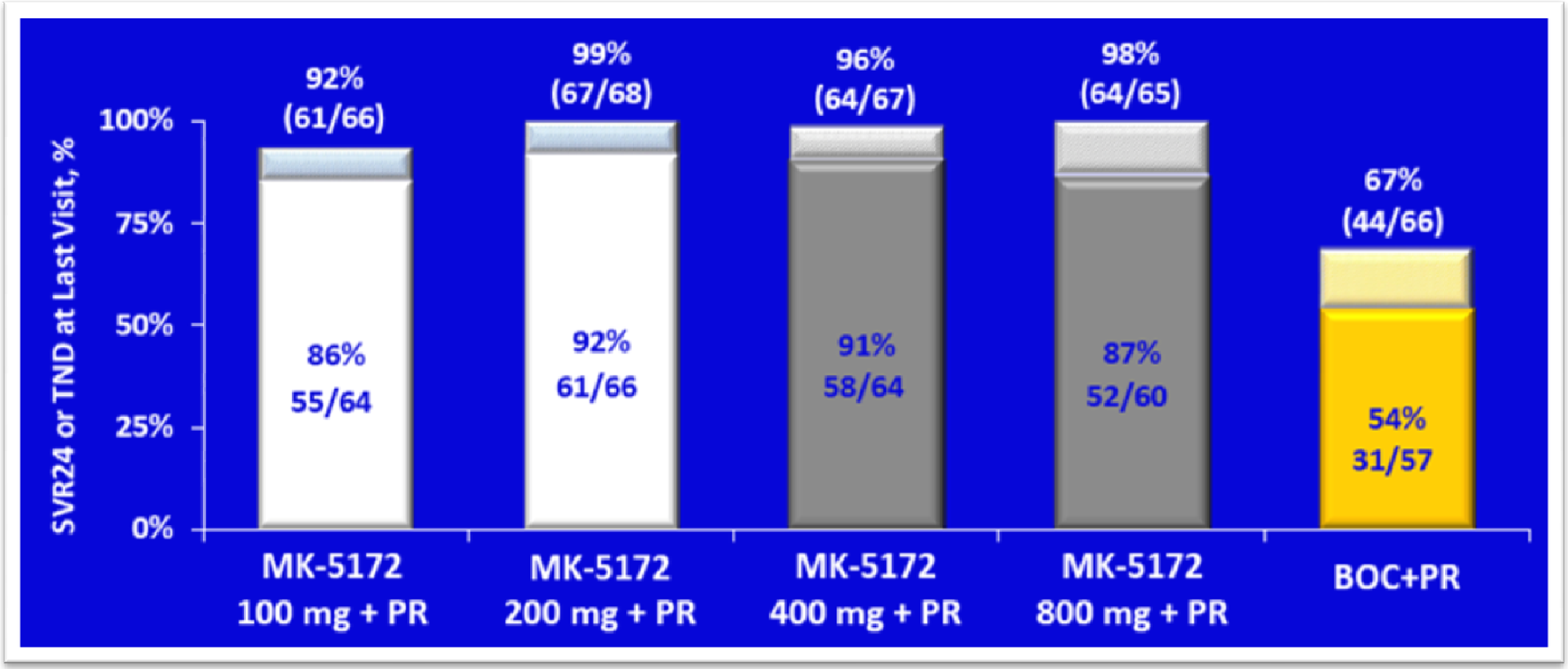
SVR12 in ~ 90% patients with 12 or 24 wks of treatment

Sofosbuvir well tolerated up to 24 wks

Hassanein T, et al. AASLD 2012. Abstract 230.

MK-5172 + PR
SVR 24 and HCV-RNA TND at last visit

- **332 treatment naive non-cirrhotic G1 patients**
- **2 sequentially randomized cohorts**
- **73% IL28B non-CC, 13% African Americans, 60% G1a**
- **MK-5172 dosing 100, 200, 400 or 800 mg QD**
- **Peg-2b + ribavirin**

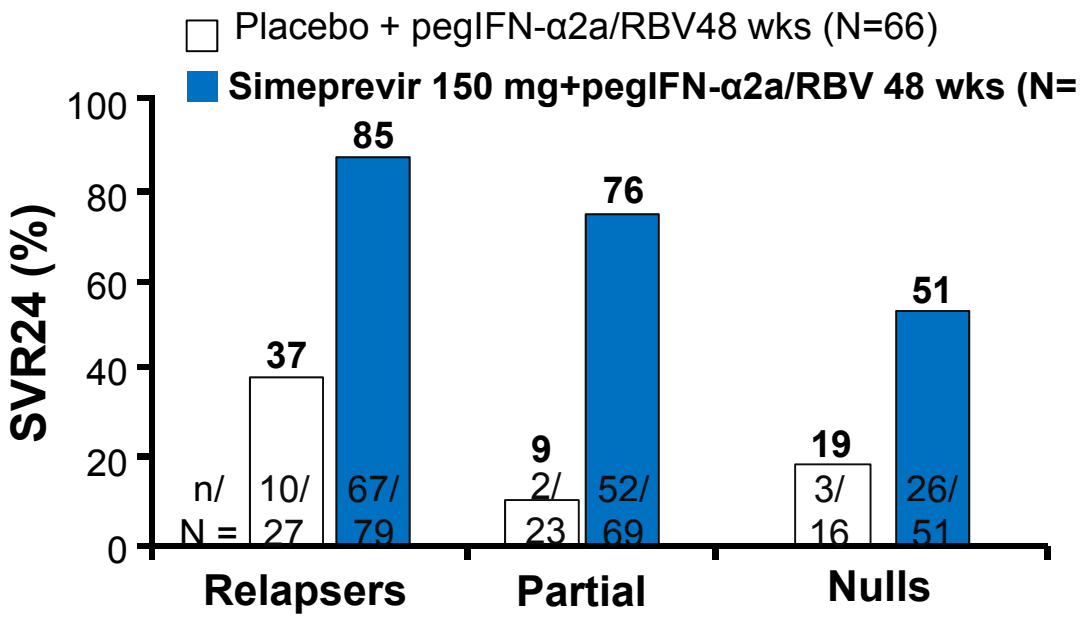


Manns M et al. Abstract. The 48th Annual Meeting of the EASL. April 2013. Amsterdam. The Netherlands

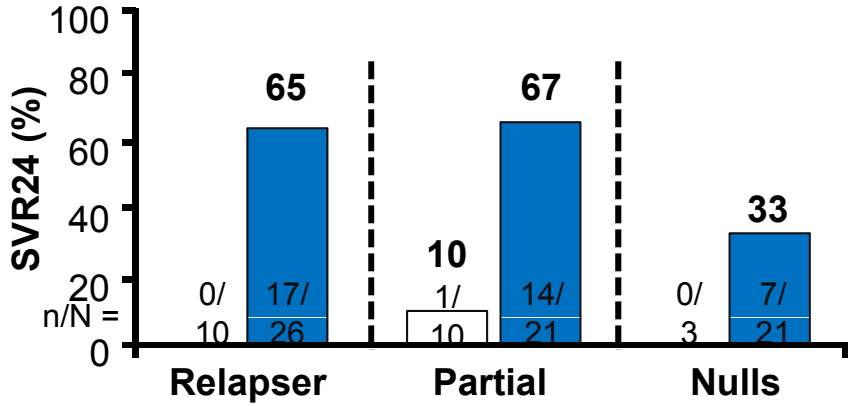
ASPIRE (FIIb): Simeprevir (TMC435) 150 mg for 12, 24, 48 Wks + PR in Relapser, Partial and Null G1

Simeprevir
1 toma/d

ASPIRE (Tx-Exp-G1)

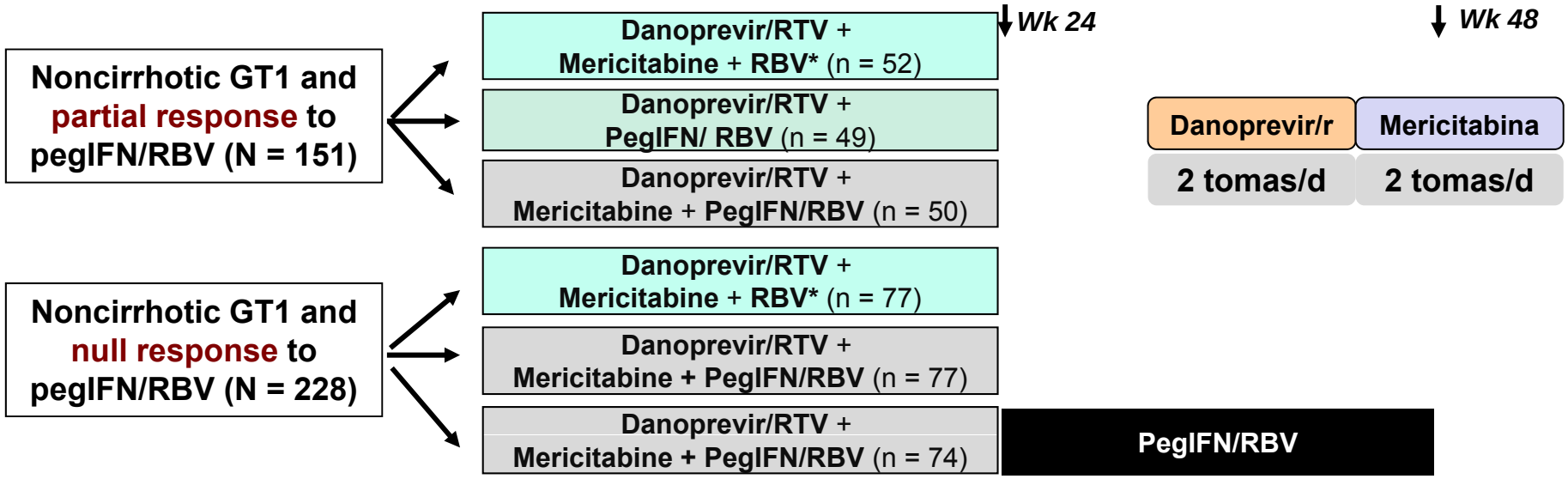


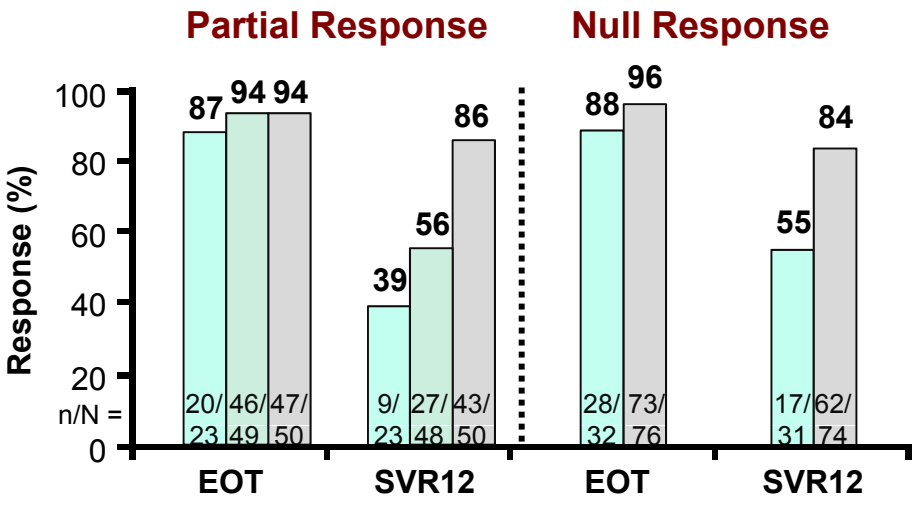
SVR24 by Prior IFN Response in Pts With F3/F4 (N=91)

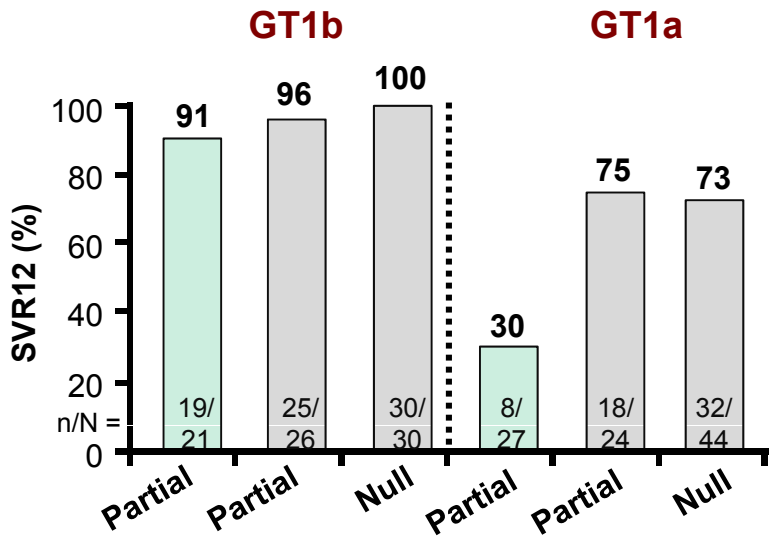


1. Jacobson I, et al. IDSA 2012. Abstract 1287. 2. Poordad F, et al. AASLD 2012. Abstract 83.

MATTERHORN (FII): Danoprevir/r + Mericitabine + PegIFN/RBV in Partial and Null G1







Feld JJ, et al. AASLD 2012. Abstract 81.

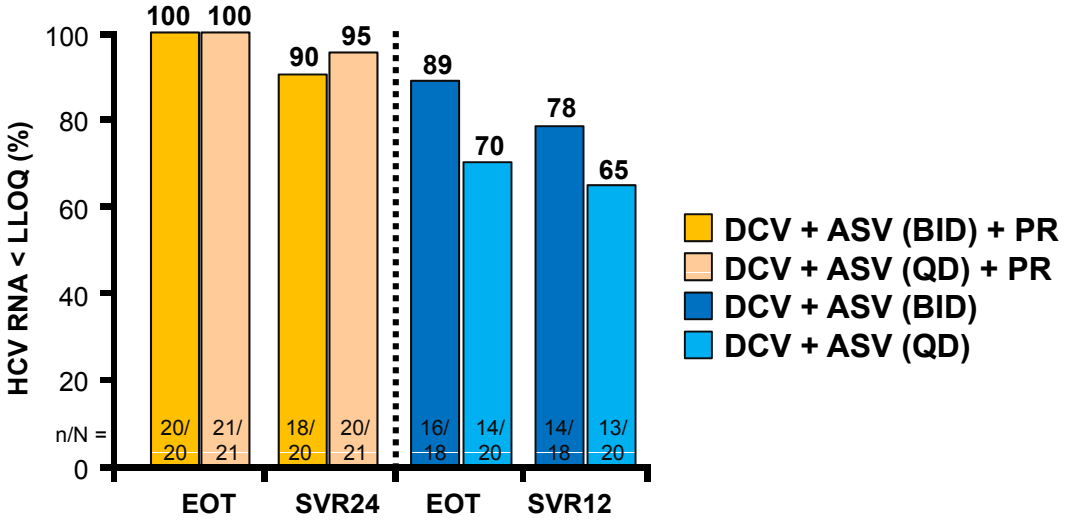
AI447-011 (FIIa): Daclatasvir + Asunaprevir +/- PegIFN or RBV in Previous Null Responders GT1

Noncirrhotic GT1 and null response to pegIFN/RBV (N = 101)

- **Daclatasvir** 60 mg QD + **Asunaprevir** 200 mg BID* (n = 18)
- **Daclatasvir** 60 mg QD + **Asunaprevir** 200 mg QD* (n = 20)
- **Daclatasvir** 60 mg QD + **Asunaprevir** 200 mg BID + **PegIFN/ RBV** (n = 20)
- **Daclatasvir** 60 mg QD + **Asunaprevir** 200 mg QD + **PegIFN/ RBV** (n = 21)
- **Daclatasvir** 60 mg QD + **Asunaprevir** 200 mg BID + **RBV**(n = 22)

Wk 24

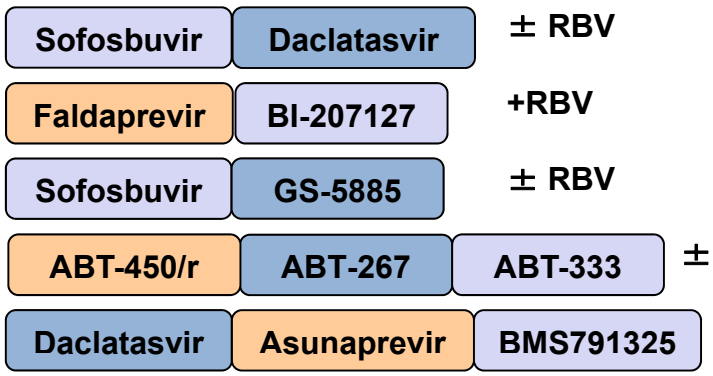
Daclatasvir	Asunaprevir
1 toma/d	1-2 tomas/d



Lok AS, et al. AASLD 2012. Abstract 79.

HCV Regimens in Phase II Clinical Trials

IFN-Free/ IFN and RBV-Free Regimens



SOUND-C2 (Naïve)

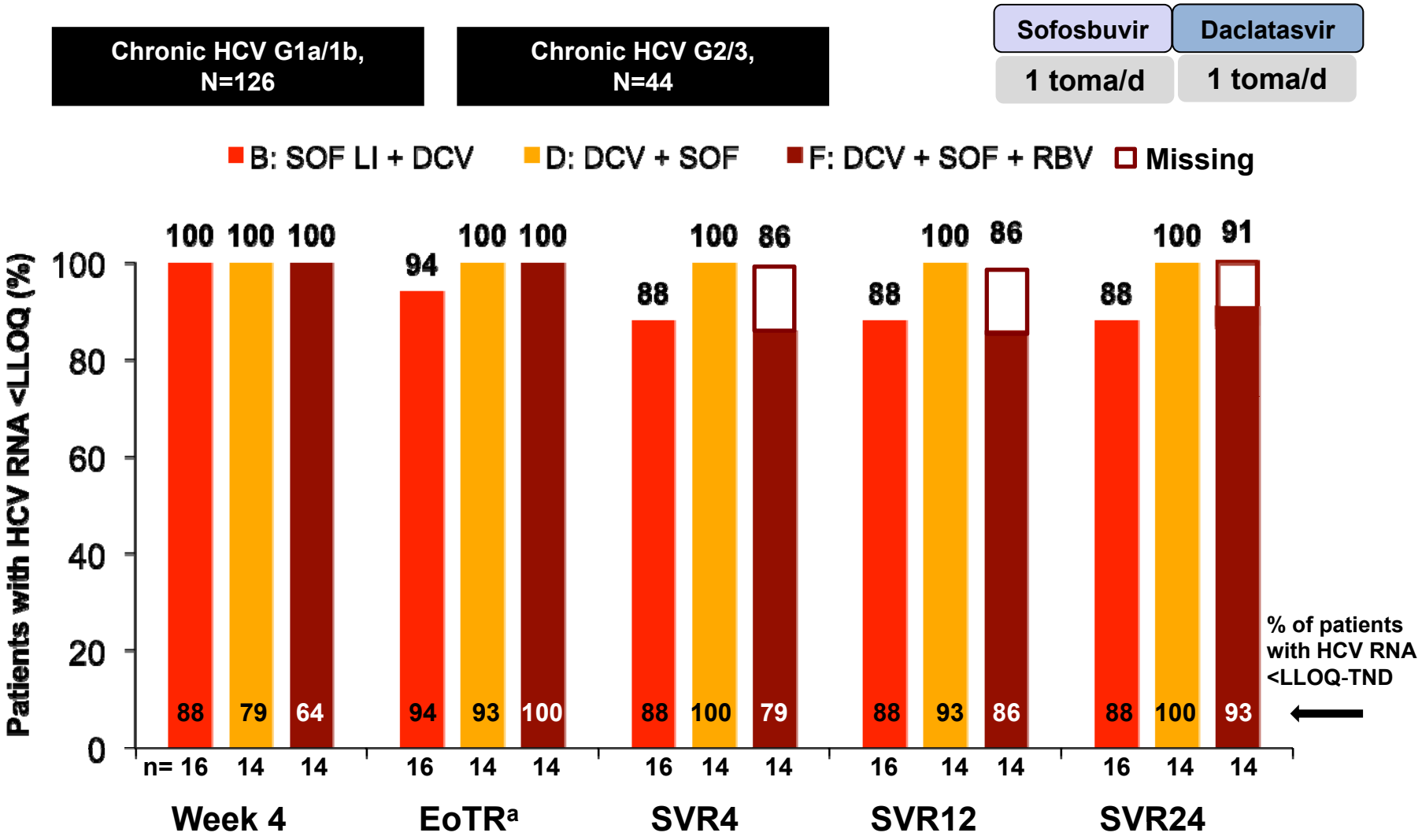
ELECTRON (Naïve/ Nulls G1/2/3)

AVIATOR (Naïve/ Nulls)

AI443-014

ClinicalTrials.gov. November 27, 2012.

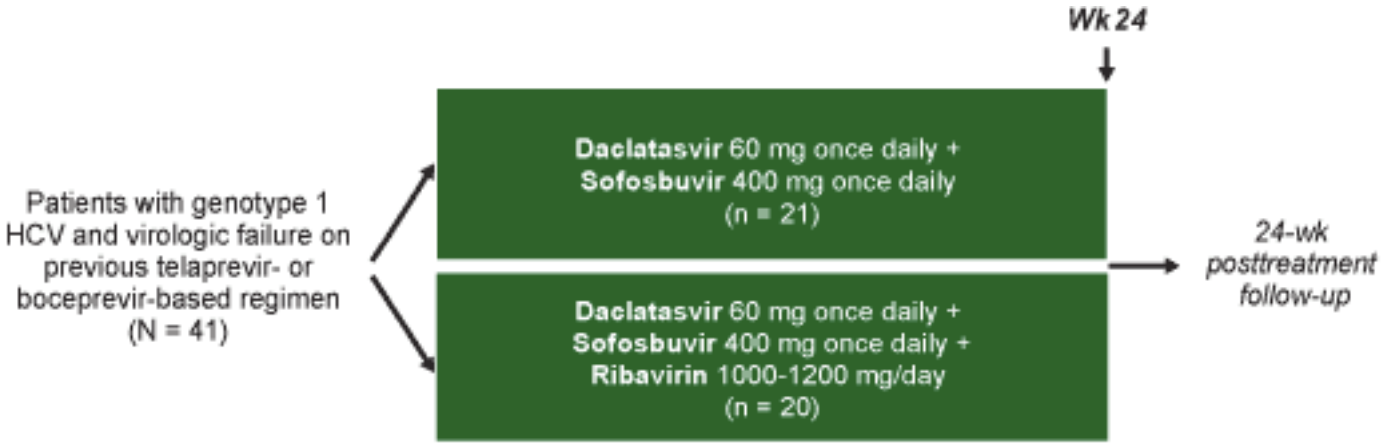
Sofosbuvir + Daclatasvir ± RBV (FIIa) during 24W in Naïve HCV G1 or G2/3



[a] EoTR includes patients who discontinued early, with last visit considered EoTR; TND = target not detected (LLOD <10 IU/mL).

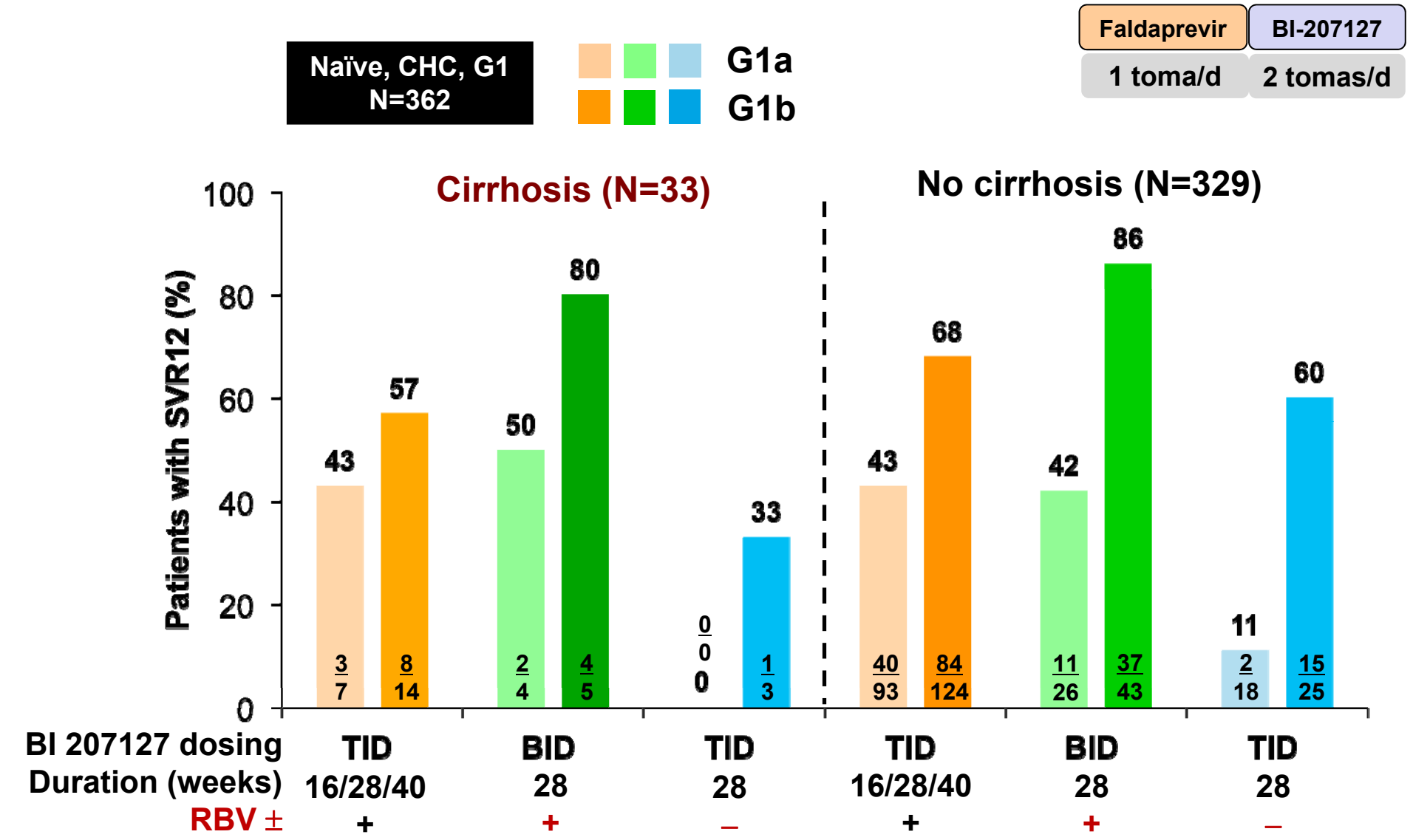
Sulkowski M, et al. AASLD 2012. Oral Presentation LB-02

Sofosbuvir + Daclatasvir ± RBV in PI nonresponders



HCV RNA < LLOQ, % (mITT)	Daclatasvir + Sofosbuvir (n = 21)	Daclatasvir + Sofosbuvir + Ribavirin (n = 20)
Wk 2	91	80
Wk 4	100	95
End of treatment	100	100
SVR4	100	100
SVR12	100	95

SOUND-C2 (FIIb): Faldaprevir + BI 207127 ± RBV



Soriano V, et al. AASLD 2012. Abstract 84.

ELECTRON (Fase II): Sofosbuvir +/- Ledipasvir + RBV in Naïve and Nulls G1, G2 and G3

Noncirrhotic G2,3 and G1 in Naïve and Null responders to pegIFN/RBV

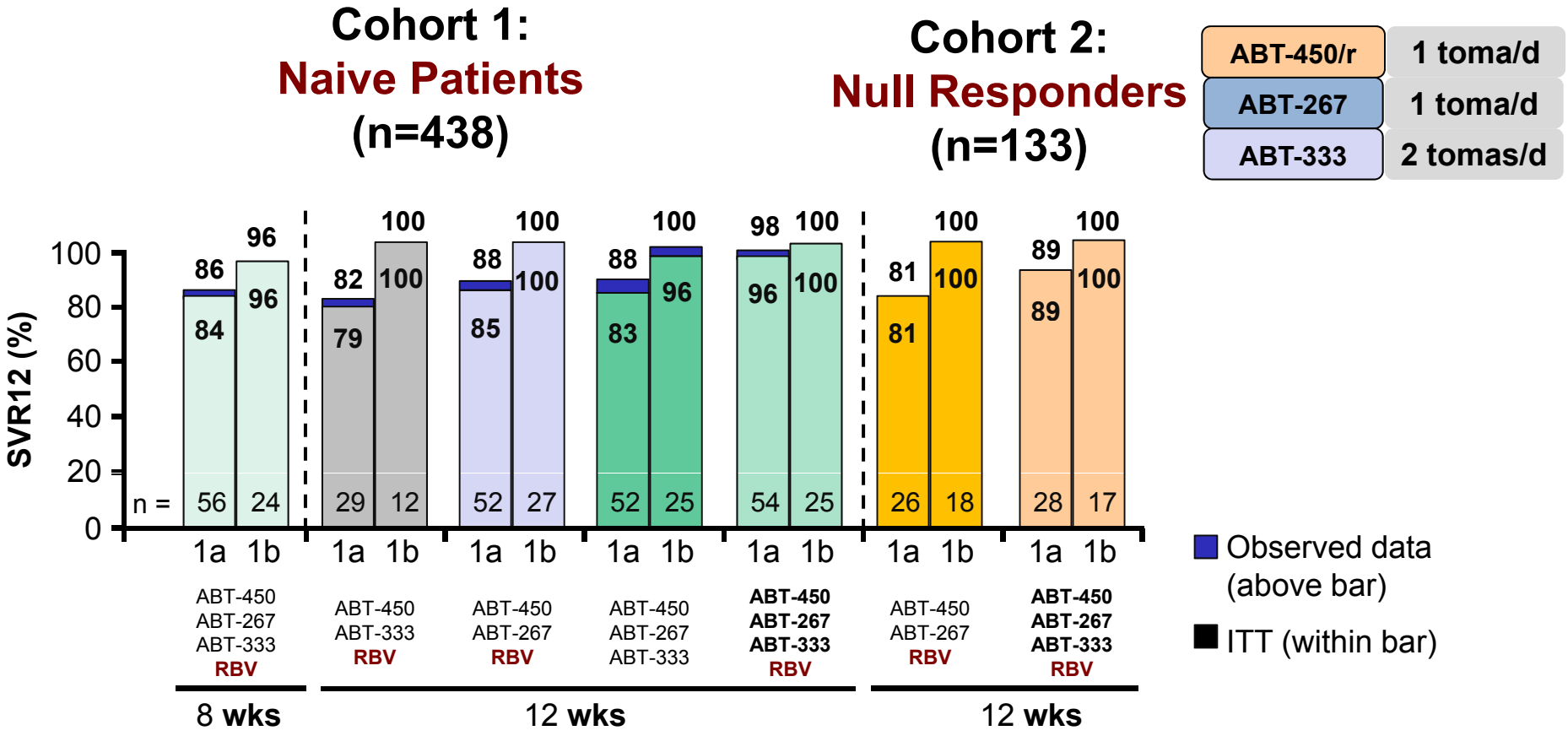
Sofosbuvir	Ledipasvir
1 toma/d	1 toma/d

Naïve and Null responders G1 (n=69)	Wk 12 SVR4	Wk 12 SVR12
Sofosbuvir + RBV 1000/1200 mg (GT1; naive) (n = 25)		84%
Sofosbuvir + RBV 1000/1200 mg (GT1; nulls) (n = 10)		10%
Sofosbuvir + Ledipasvir + RBV 1000/1200 mg (GT1; naive) (n = 25)	100%	
Sofosbuvir + Ledipasvir + RBV 1000/1200 mg (GT1; nulls) (n = 9)	100%*	

*Data reported for 3 pts only. Data collection ongoing.

1. Gane EJ, et al. AASLD 2012. Abstract 229. 2. Sulkowski MS, et al. AASLD 2012. Abstract LB-2

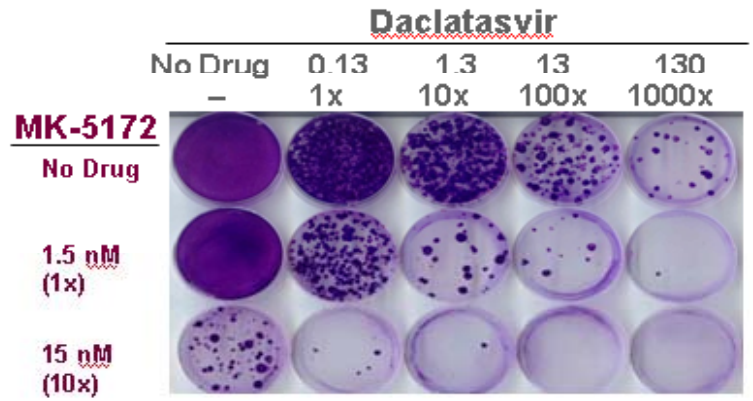
AVIATOR (FII): ABT450/r, ABT267, ABT333 +/- RBV

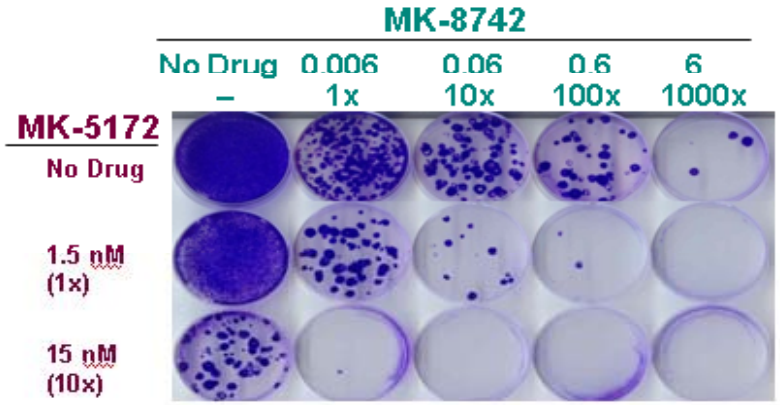


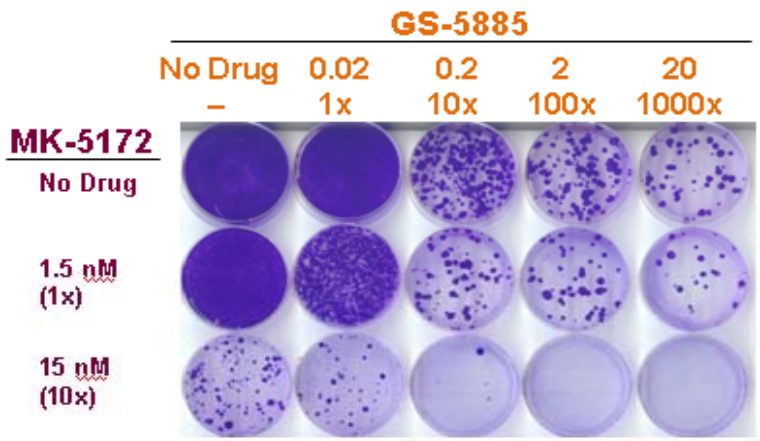
- **SVR12 higher in G1b but also high in G1a**
- **12-wk regimen with all 3 DAAs + RBV produced highest SVR12 rates**
- **No drug-related SAEs reported; 2 pts discontinued tx due to drug-related AEs**

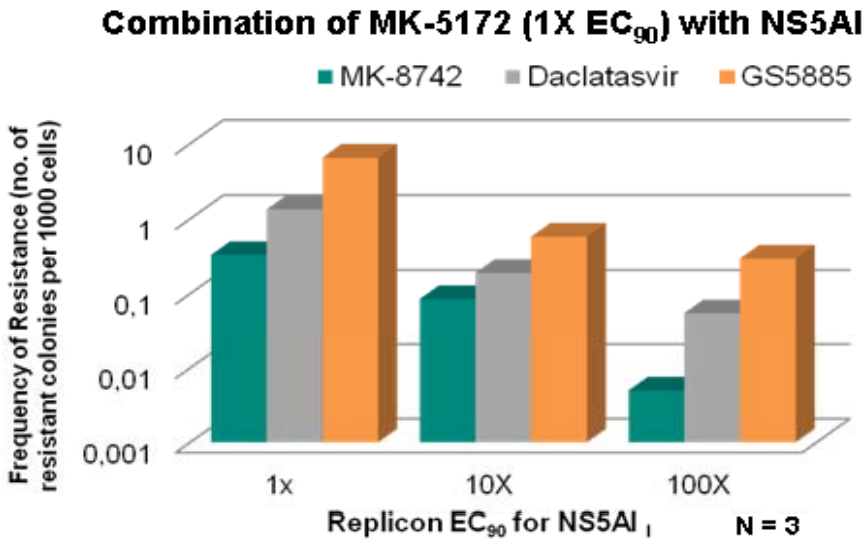
Kowdley KV, et al. AASLD 2012. Abstract LB-1. Reproduced with permission.

The Combination of MK-5172 and MK-8742 Significantly Reduces the Number of Resistant Replicons









Multiples of EC_{90} are shown in parentheses N = 3 for each combination

Lahser et al. Abstract 87. The 63rd Annual Meeting of the AASLD. November 9-13. Boston, MA, USA

Seguridad de Antivirales de Acción Directa (AAD)

AAD	Síntomas más frecuentes	Retirada (SAE)
Danoprevir/r	Cefalea, fatiga, fiebre, náuseas	3-5%
Simeprevir (TMC435)	Aumento BT, Neutropenia	6-8%
MK-5172	Aumento BT, ALT	-
Sofosbuvir (GS-7977)	-	0%
Daclatasvir	Aumento BT, ALT	8%
Daclastavir + Asunaprevir	Cefalea, diarrea, astenia	10%
VX-222	Diarrea, náusea	4%
Faldaprevir (BI 201335)	Prurito, Rash, aumento BT	8%
GS-9451, GS-5885, Tegobuvir	Náuseas, vértigo, aumento BT	8%
ABT-450, ABT-260, ABT-333	Fatiga, cefalea, artralgia	1%

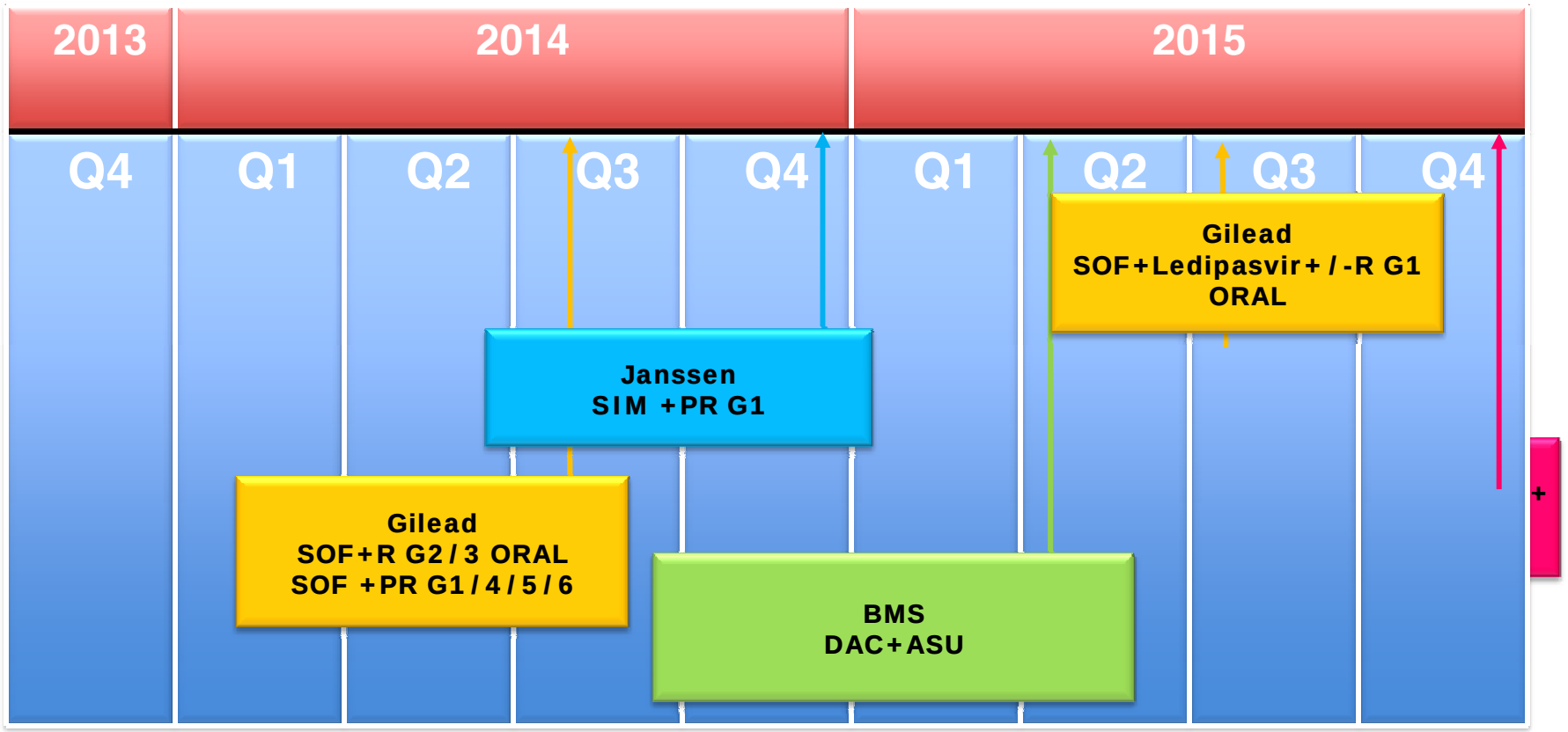
Therapeutic options

	P+R	P+R+PI	P+R+PI+NS5Ai	IFN-free
Naïve RVR	**90%**			**97%**
Naïve non-RVR		**79%**		
Relapsers		**85% - 88%**		
Genotype 2&3 RVR	**95% - 100%**			**100%**
Non-responders Non-cirrhotics			**95%**	**93%**
Non-responders BOC/TVP				**95%-100%**
Cirrhotic			¿?	¿?

Preliminary data:

- **No data on cirrhosis**

TIMELINE



P: Peginterferon
R: Ribavirin