Clinical Impact of New Data From Boston 2016*

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Disclosures

Ira M. Jacobson, MD, has disclosed that that he has served as a consultant or on advisory boards for AbbVie, Achillion, Bristol-Myers Squibb, Gilead Sciences, Intercept, Janssen, Merck, and Trek; has served on speaker bureaus for AbbVie, Bristol-Myers Squibb, Gilead Sciences, and Janssen; and has received funds for research support from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Intercept, Janssen, and Merck.

Stefan Zeuzem, MD, has disclosed that he has served as a consultant or on advisory boards for Abbott, AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Idenix, Janssen, Merck, Novartis, Roche, Santaris, and Vertex and has served on speaker bureaus for Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Merck, and Roche.

HCV Treatment: Investigational Regimens

Summary of Approved Direct-Acting Antivirals Discussed in This Slideset

Drug	Abbreviation	Class
Grazoprevir	GZR	NS3/4A protease inhibitor
Paritaprevir	PTV	NS3/4A protease inhibitor
Simeprevir	SMV	NS3/4A protease inhibitor
Daclatasvir	DCV	NS5A inhibitor
Elbasvir	EBR	NS5A inhibitor
Ledipasvir	LDV	NS5A inhibitor
Ombitasvir	OBV	NS5A inhibitor
Velpatasvir	VEL	NS5A inhibitor
Sofosbuvir	SOF	NS5B nucleotide polymerase inhibitor
Dasabuvir	DSV	NS5B nonnucleoside polymerase inhibitor

Summary of Investigational Direct-Acting Antivirals Discussed in This Slideset

Drug	Abbreviation	Class
Glecaprevir (formerly ABT-493)	GLE	NS3/4A protease inhibitor
Voxilaprevir	VOX	NS3/4A protease inhibitor
Pibrentasvir (formerly ABT-530)	PIB	NS5A inhibitor
Ruzasvir (formerly MK-8408)	RZR	NS5A inhibitor
MK-3682	--	NS5B polymerase nucleotide inhibitor

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Overview of Investigational DAA Studies Discussed in This Slideset

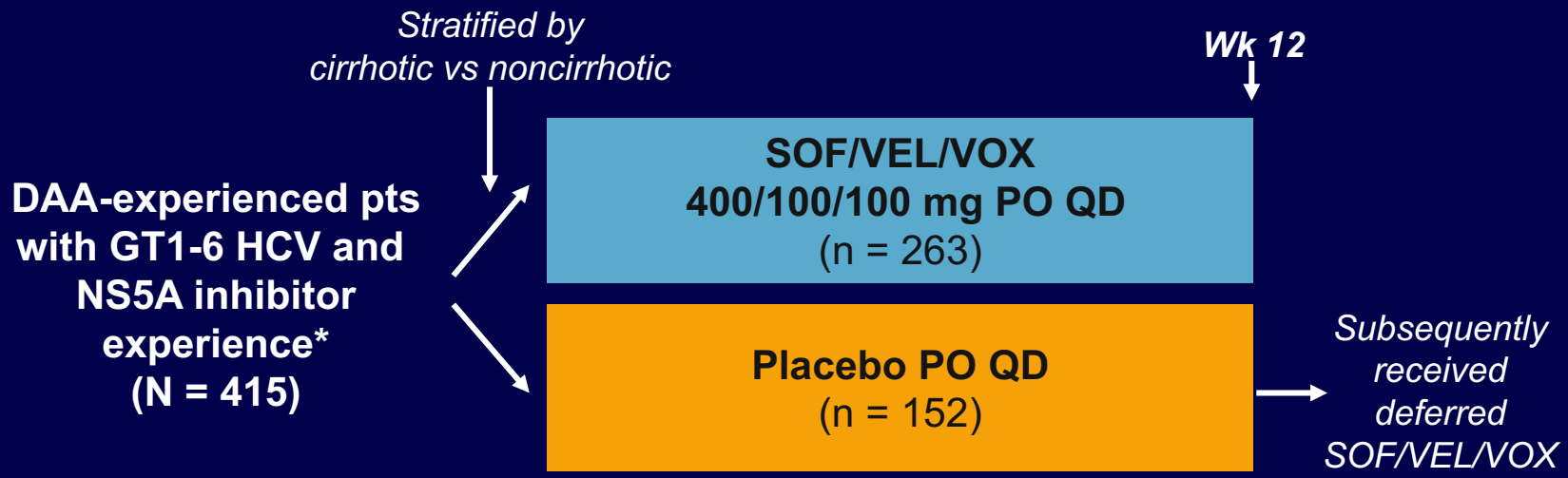
SOF/VEL/VOX	Study Population	Comparator
POLARIS-1[1]	12 wks for NS5A inhibitor experienced GT1-6 HCV	PBO
POLARIS-2[2]	8 wks for DAA-naive GT1-6 HCV	SOF/VEL
POLARIS-3[3]	8 wks for cirrhotic GT3 HCV	SOF/VEL
POLARIS-4[4]	12 wks for DAA-experienced (no NS5A inhibitors) GT1-6 HCV	SOF/VEL
GLE/PIB		
ENDURANCE-1[5]	8 or 12 wks for noncirrhotic pts with GT1 HCV	GLE/PIB
ENDURANCE-2[6]	12 wks for noncirrhotic pts with GT2 HCV	PBO
ENDURANCE-4[7]	12 wks for noncirrhotic pts with GT4-6 HCV	None
SURVEYOR-II/3[8]	12 or 16 wks for pts with GT3 HCV ± tx exp ± cirrhosis	GLE/PIB
EXPEDITION-IV[9]	12 wks for pts with GT1-6 HCV and stage 4/5 CKD	None
MK-3682/GZR/RZR		
C-CREST Part B[10]	8/12/16 wks ± RBV for GT1-3 HCV ± tx exp ± cirrhosis	MK-3682/GZR/RZR
C-CREST Part C[11]	16 wks + RBV for 8-wk MK-3682/GZR/(RZR or EBR) failures	None
C-SURGE[12]	16 or 24 wks ± RBV for GT1 HCV pts relapsing on DAAs	MK-3682/GZR/RZR

References in slidenotes.

Slide credit: clinicaloptions.com

POLARIS-1: SOF/VEL/VOX for 12 Wks After NS5A Failure in GT1-6 HCV

- Randomized, double-blind, placebo-controlled phase III trial



*Pts with GT1 HCV at screening equally randomized between arms; pts with GT2-6 HCV assigned to active treatment arm.

- Previous NS5A treatment in SOF/VEL/VOX group (n = 263)
  - LDV, 51%; DCV, 27%; OBV, 11%; other, 13%
- Cirrhosis definition for POLARIS studies: METAVIR F4 or Ishak 5-6 on biopsy, *or FibroTest* > 0.75 + APRI > 2, *or FibroScan* > 12.5 kPa

Bourlière M, et al. AASLD 2016. Abstract 194.

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POLARIS-1: SVR12 Rates With 12-Wk SOF/VEL/VOX in Previous NS5A Failure

SVR12, % (n/N)	SOF/VEL/VOX
Overall	96 (253/263)
Cirrhosis status	
▪ No cirrhosis	99 (140/142)
▪ Cirrhosis	93 (113/121)
Baseline RAVs	
▪ None	98 (42/43)
▪ Any	96 (199/208)

SVR12, % (n/N)	SOF/VEL/VOX
Genotype	
▪ 1a	96 (97/101)
▪ 1b	100 (45/45)
▪ 2	100 (5/5)
▪ 3	95 (74/78)
▪ 4	91 (20/22)
▪ 5	100 (1/1)
▪ 6	100 (6/6)

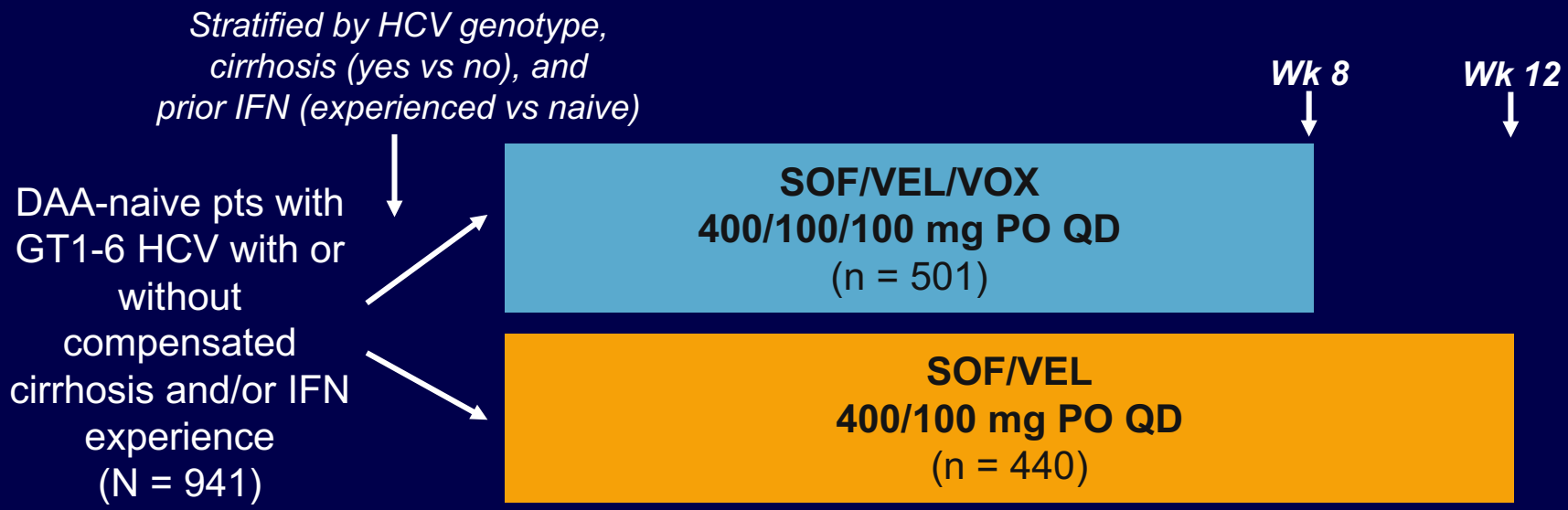
- 7 virologic failures; all cirrhotic pts (GT1a, n = 2; GT3, n = 4; GT4, n = 1)

Bourlière M, et al. AASLD 2016. Abstract 194.

Slide credit: clinicaloptions.com

POLARIS-2: 8-Wk SOF/VEL/VOX vs 12-Wk SOF/VEL for DAA-Naive GT1-6 Pts

- Randomized, open-label, active-controlled phase III trial



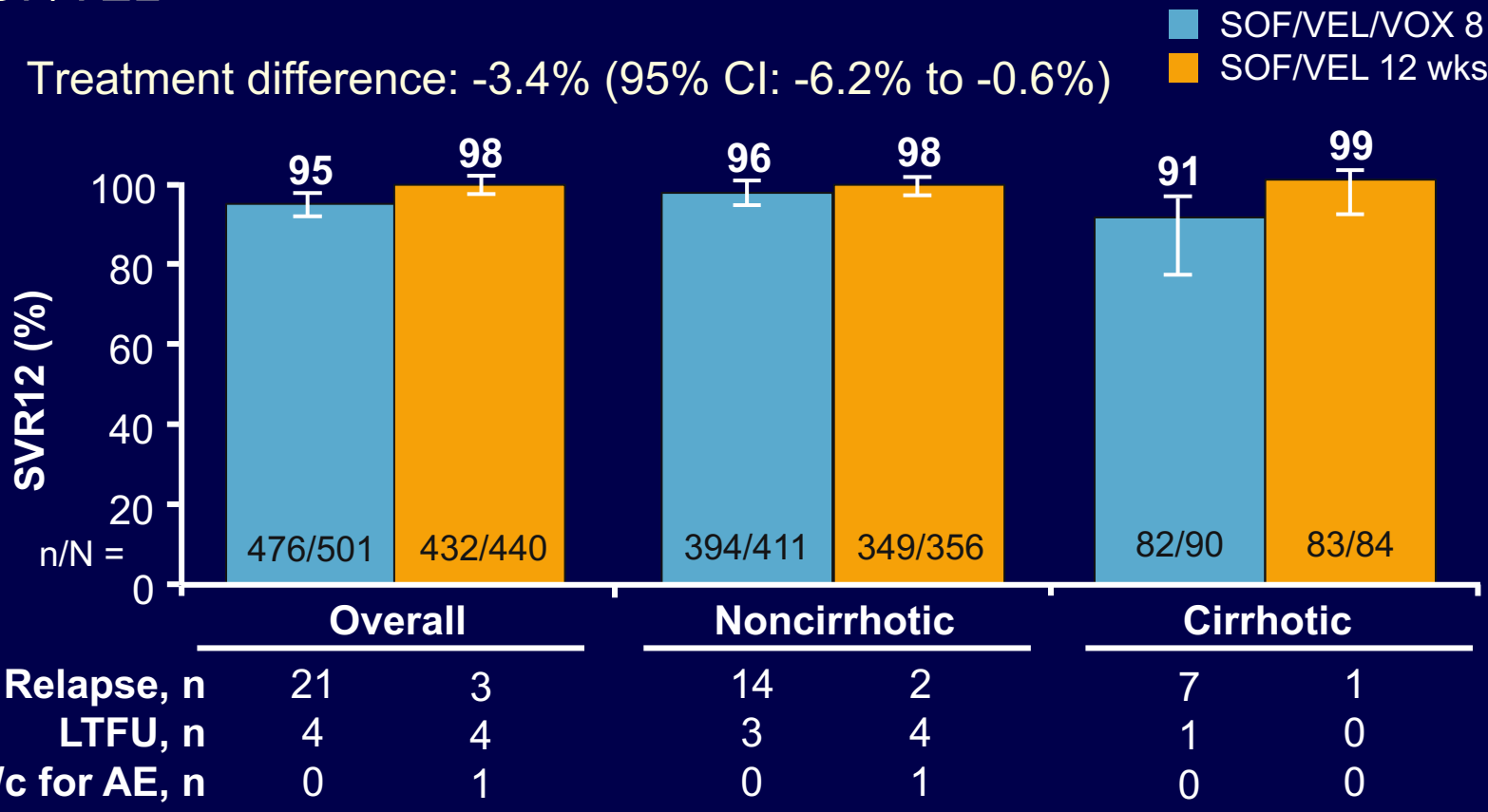
*Treatment allocation randomized in pts with GT1-4 HCV; pts with GT5-6 HCV allocated to SOF/VEL/VOX arm; cirrhotic pts with GT3 HCV infection enrolled in POLARIS-3.

Jacobson IM, et al. AASLD 2016. Abstract LB12.

Slide credit: clinicaloptions.com

POLARIS-2: SVR12 Rates With 8-Wk SOF/VEL/VOX vs 12-Wk SOF/VEL

- 8 wks SOF/VEL/VOX did not meet criteria for noninferiority vs 12 wks SOF/VEL
  - Treatment difference: -3.4% (95% CI: -6.2% to -0.6%)



	Overall		Noncirrhotic		Cirrhotic	
Relapse, n	21	3	14	2	7	1
LTFU, n	4	4	3	4	1	0
D/c for AE, n	0	1	0	1	0	0

Jacobson IM, et al. AASLD 2016. Abstract LB12.
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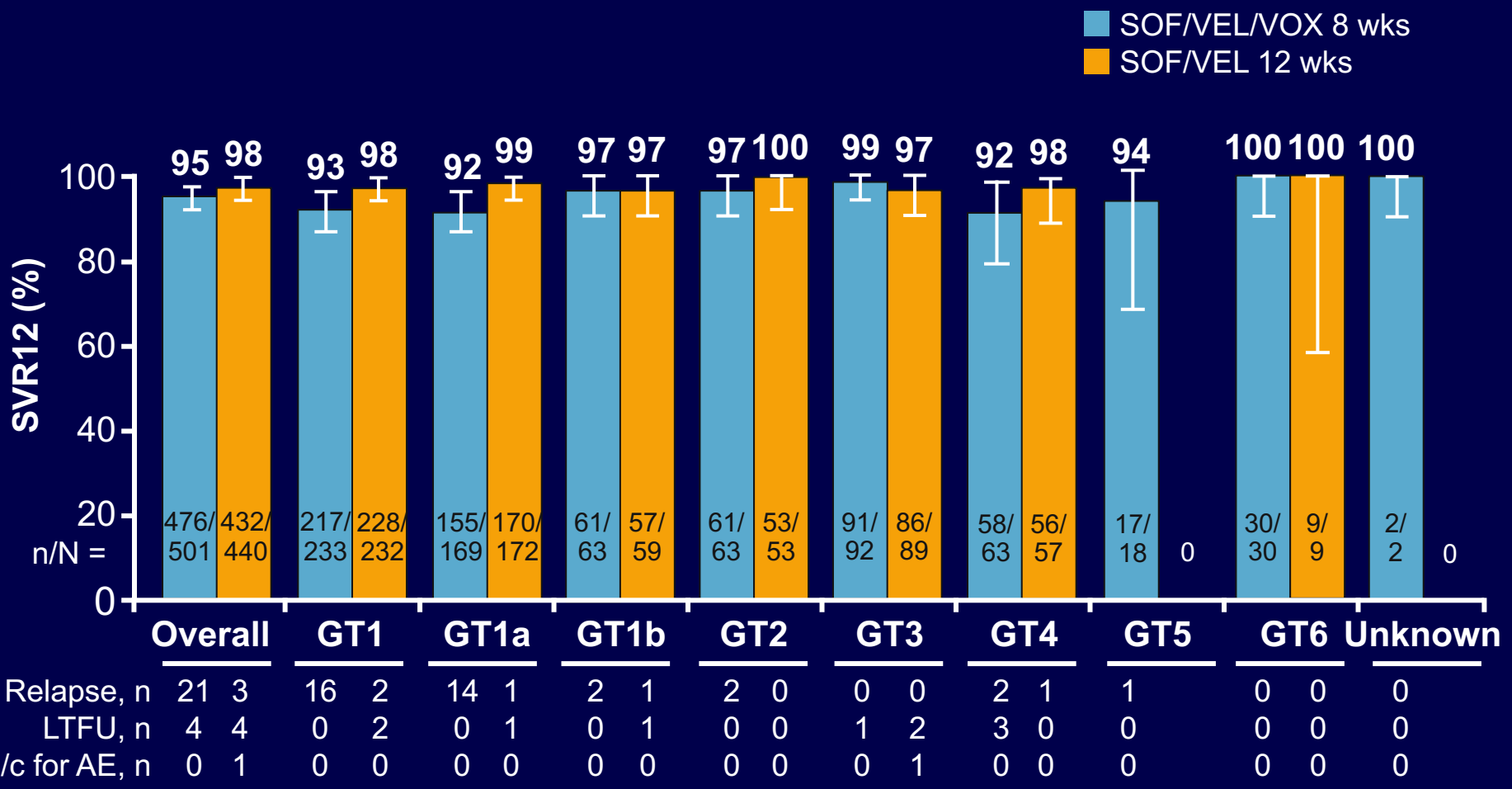
POLARIS-2: Efficacy by HCV GT With 8-Wk SOF/VEL/VOX vs 12-Wk SOF/VEL



Jacobson I, et al. AASLD 2016. Abstract LB12.
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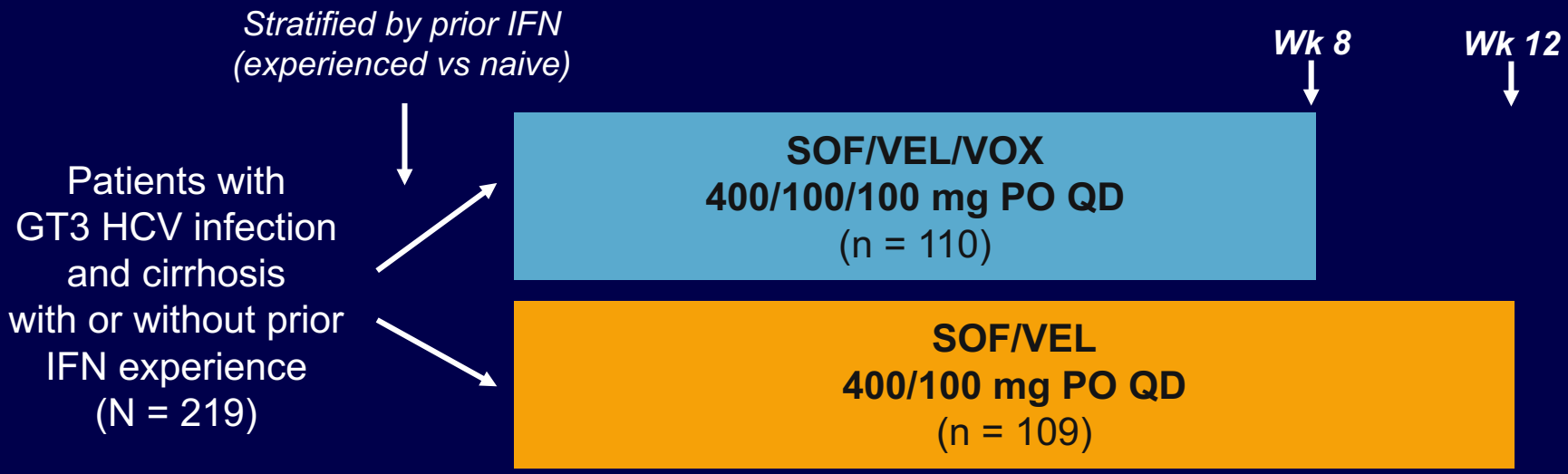
POLARIS-3: 8-Wk SOF/VEL/VOX vs 12-Wk SOF/VEL for Cirrhotic, DAA Naive GT3

- Randomized, open-label, active-controlled phase III trial



- IFN experience in 29% to 32% of pts

Foster GR, et al. AASLD 2016. Abstract 258.

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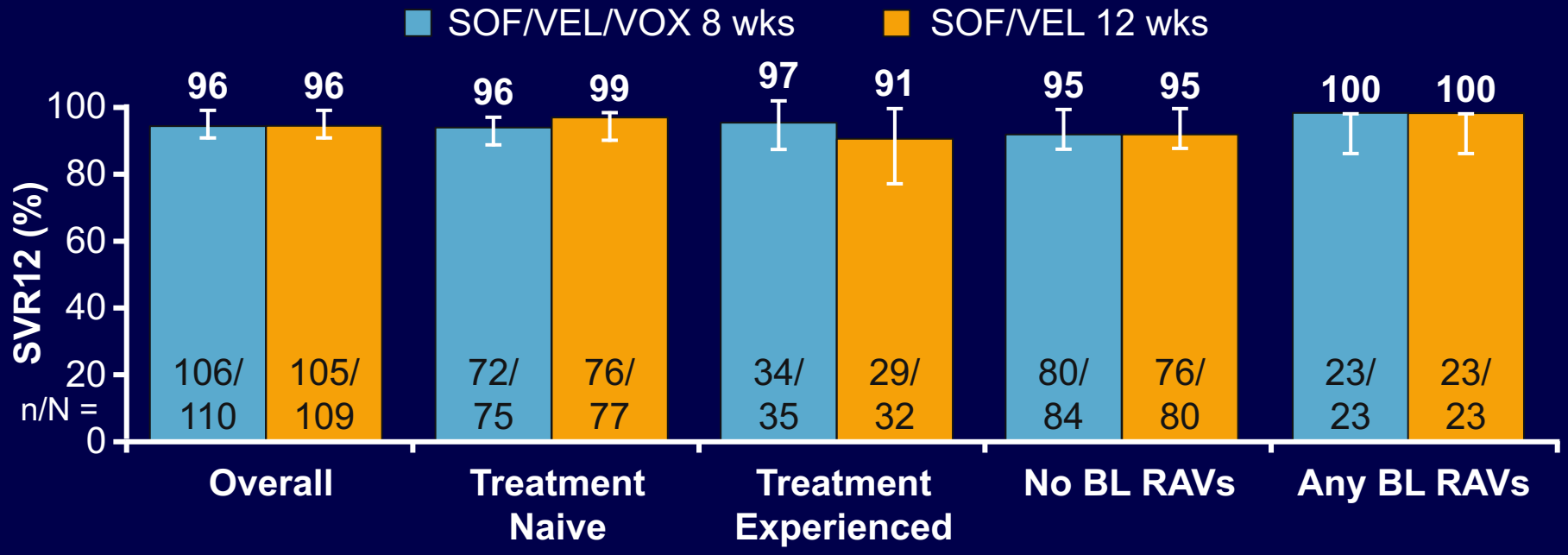
POLARIS-3: SVR12 Rates With 8-Wk SOF/VEL/VOX for Cirrhotic GT3 Pts

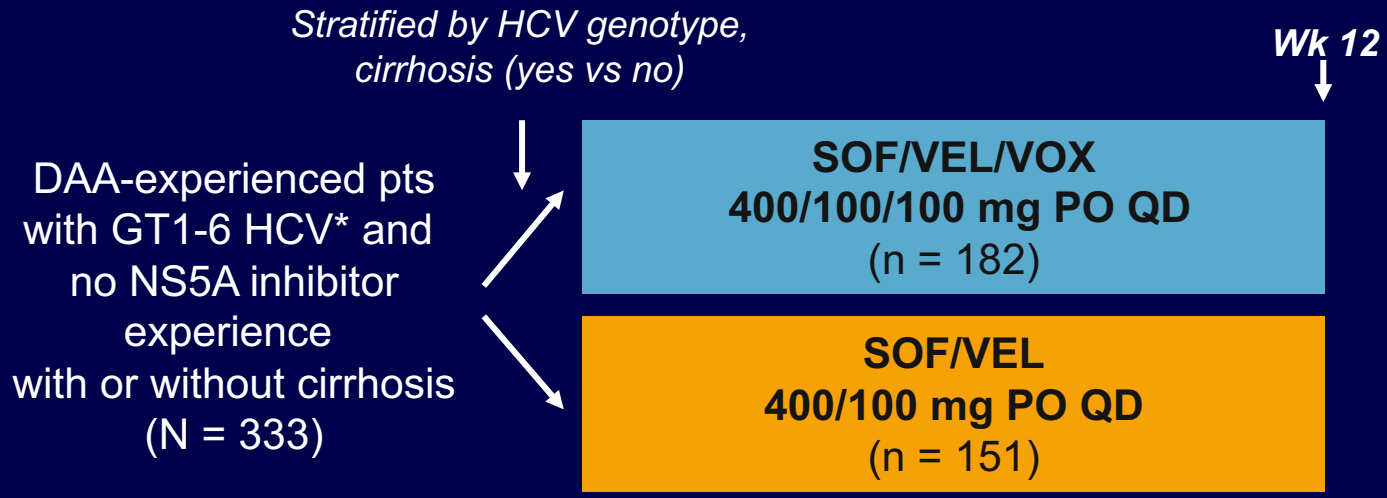


- Both regimens: *P* < .001 for superiority vs prespecified 83% goal
- Overall VF: SOF/VEL/VOX, n = 2 relapses; SOF/VEL, n = 1 each for relapse and on-treatment failure
- No treatment-emergent RAVs in SOF/VEL/VOX arm; Y93H in both virologic failures in SOF/VEL arm

Foster GR, et al. AASLD 2016. Abstract 258. Reproduced with permission. Slide credit: clinicaloptions.com

POLARIS-4: SOF/VEL/VOX for DAA-Exp'd, NS5A Inhibitor-Naive GT1-6 HCV

- Randomized, open-label, active-controlled phase III trial



*Pts with GT1-3 HCV randomized 1:1 between arms. Pts with GT4-6 HCV assigned to SOF/VEL/VOX.

- Prior HCV treatment
  - SOF, 69%; other NS5B inhibitor, 4%
  - SOF + SMV, 11%; other NS5B/NS3 inhibitor combinations, 14%
  - Other, 2%

Zeuzem S, et al. AASLD 2016. Abstract 109.

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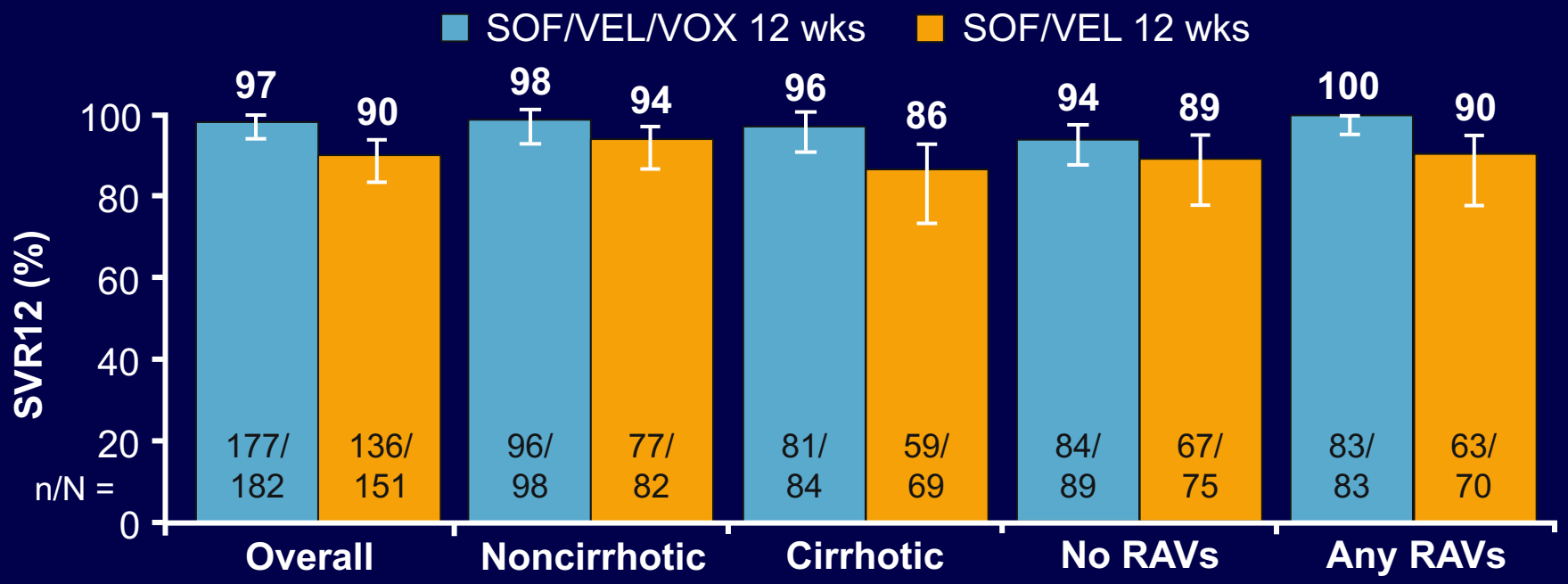
POLARIS-4: Efficacy of SOF/VEL/VOX for DAA-Exp'd, NS5A Inhibitor Naive HCV Pts



- SOF/VEL/VOX: *P* < .001 for superiority vs prespecified 85% goal; SOF/VEL: *P* = .092
- Overall, reduced SVR12 rate for SOF/VEL driven by increased number of relapses
  - SOF/VEL/VOX (n = 182): 1 relapse, 1 death, 3 LTFU
  - SOF/VEL (n = 151): 14 relapses, 1 breakthrough

Zeuzem S, et al. AASLD 2016. Abstract 109. Reproduced with permission. Slide credit: clinicaloptions.com

POLARIS Studies: Safety

Outcome, %	POLARIS-1[1]		POLARIS-2[2]	
	SOF/VEL/VOX (n = 263)	PBO (n = 152)	SOF/VEL/VOX (n = 501)	SOF/VEL (n = 440)
Any AE	78	70	72	69
Grade 3/4 AE	2	3	2	1
Serious AE	2	5	3	2
Serious TRAE	0	0	0	0
D/c for AE	< 1	2	0	< 1
Death	0	0	0	0
AE in > 10% of pts				
▪ Headache	25	17	27	23
▪ Fatigue	21	20	21	20
▪ Diarrhea	18	13	18	7
▪ Nausea	14	8	16	9
Grade 3/4 lab abnormality	7	14	5	4

References in slidenotes.

Slide credit: clinicaloptions.com

POLARIS Studies: Safety

Outcome, %	POLARIS-3[1]		POLARIS-4[2]	
	SOF/VEL/VOX (n = 110)	SOF/VEL (n = 109)	SOF/VEL/VOX (n = 182)	SOF/VEL (n = 151)
Any AE	75	74	77	74
Grade 3/4 AE	3	4	1	1
Serious AE	2	3	2	3
Serious TRAE	0	0	0	0
D/c for AE	0	< 1	0	< 1
Death	< 1*	0	< 1†	0
AE in > 10% of pts				
▪ Headache	25	29	27	28
▪ Fatigue	25	28	24	28
▪ Diarrhea	15	5	20	5
▪ Nausea	21	9	12	8
Grade 3/4 lab abnormality	13	8	6	7

*Death from hypertension deemed unrelated to treatment. †Death from illicit drug overdose.

References in slidenotes.

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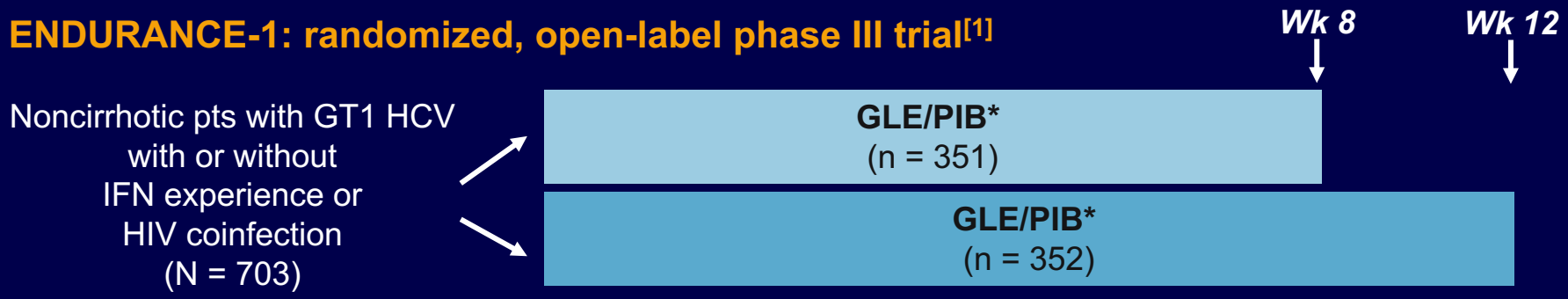
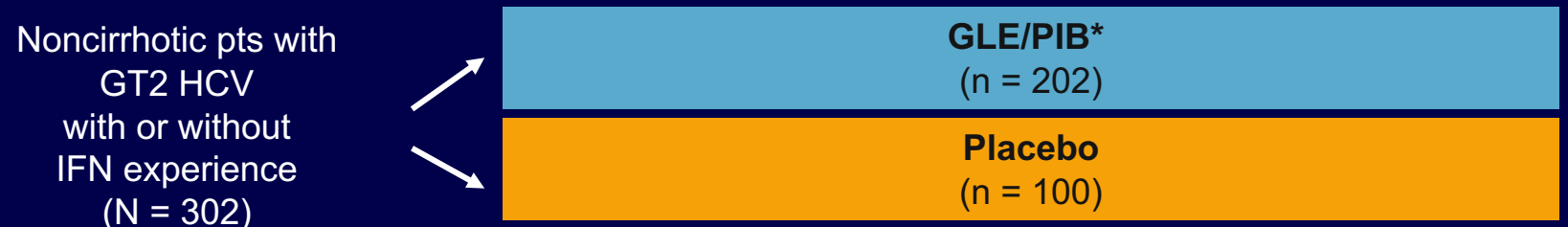
ENDURANCE-1, 2, 4: GLE/PIB for Treatment of GT1, 2, 4, 5, 6 HCV

ENDURANCE-1: randomized, open-label phase III trial[1]



ENDURANCE-2: randomized, double-blind, placebo-controlled phase III trial[2]



ENDURANCE-4: open-label, single-arm phase III trial[3]

*Dosing: GLE/PIB given as 3 coformulated 100/40 mg tablets QD for a total dose of 300/120 mg.

References in slidenotes.

Slide credit: clinicaloptions.com

ENDURANCE Studies: Key Baseline Demographics

Characteristic, %	ENDURANCE-1[1]		ENDURANCE-2[2]		ENDURANCE-4[3]
	GLE/PIB 8 Wks (n = 351)	GLE/PIB 12 Wks (n = 352)	GLE/PIB 12 Wks (n = 202)	PBO 12 Wks (n = 100)	GLE/PIB 12 Wks (N = 121)
Fibrosis stage					
▪ F0-F1	85	85	76	85	86
▪ F2	6	7	9	9	7
▪ F3	9	8	15	6	7
Treatment experienced*	38	38	30	29	32
HIV coinfected	4	5	NA	NA	NA

*Pts could have treatment experience with IFN or pegIFN ± RBV or SOF + RBV ± pegIFN.

1. Zeuzem S, et al. AASLD 2016. Abstract 253.
2. Kowdley KV, et al. AASLD 2016. Abstract 73.
3. Asselah T, et al. AASLD 2016. Abstract 114.

ENDURANCE Studies: Efficacy of GLE/PIB for Treating GT1, 2, 4, 5, 6 HCV

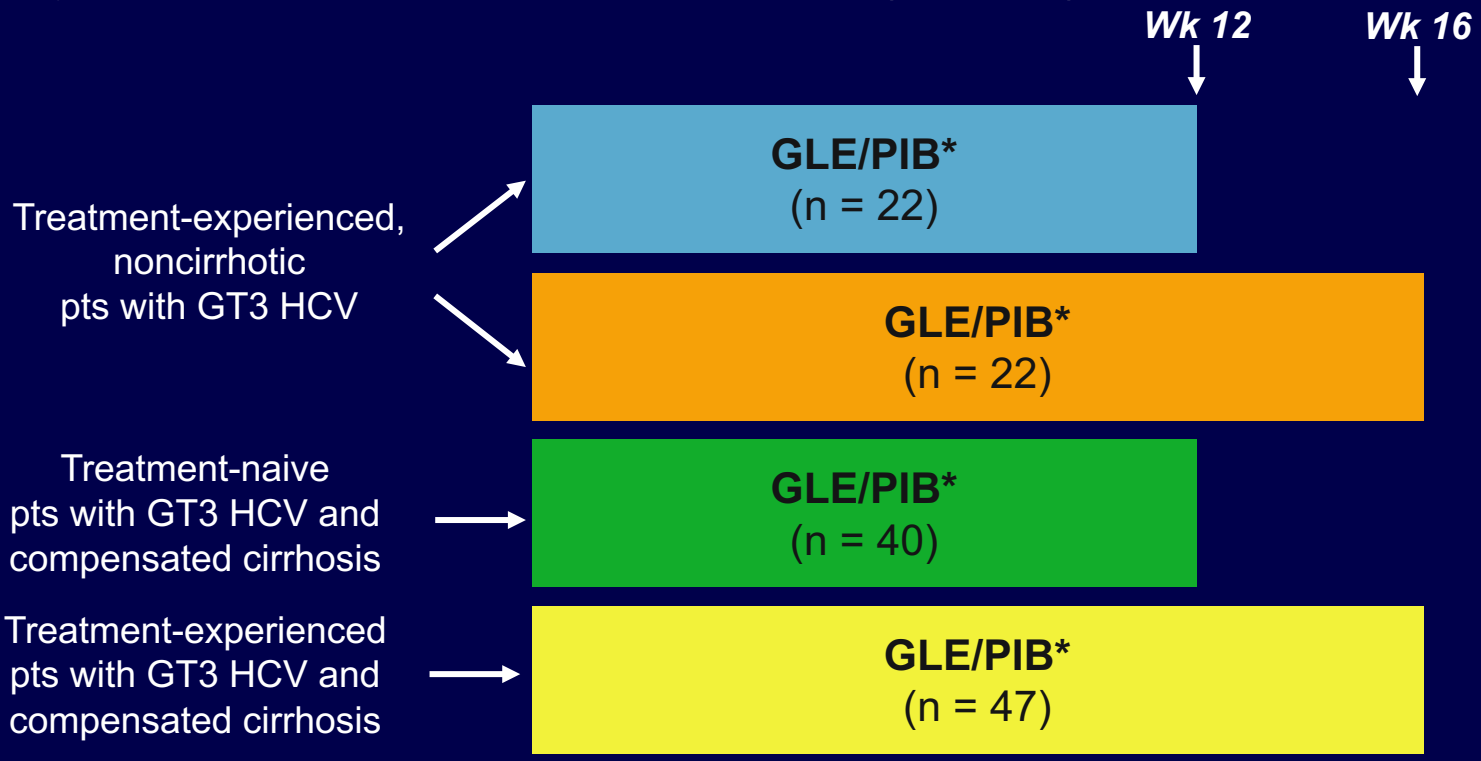
Outcome	ENDURANCE-1[1] (GT1)		ENDURANCE-2[2] (GT2)	ENDURANCE-4[3] (GT4-6)
	GLE/PIB 8 Wks	GLE/PIB 12 Wks	GLE/PIB 12 Wks	GLE/PIB 12 Wks
SVR12, % (n/N)	99.1* (332/335)	99.7* (331/332)	99† (195/196)	99‡ (120/121)
Relapse/ on-treatment failure, n	1§	0	0	0

*ITT-PS analysis: included all pts receiving ≥ 1 dose of study drug; excluded pts with HIV coinfection or SOF experience. †ITT analysis: excluded pts with SOF experience. ‡ITT analysis. §On-treatment virologic failure at Day 29 in pt with GT1a HCV.

1. Zeuzem S, et al. AASLD 2016. Abstract 253.
2. Kowdley KV, et al. AASLD 2016. Abstract 73.
3. Asselah T, et al. AASLD 2016. Abstract 114.

SURVEYOR-II, Part 3: GLE/PIB for Pts With GT3 HCV ± Cirrhosis

- Partially randomized, open-label phase II trial (N = 131)



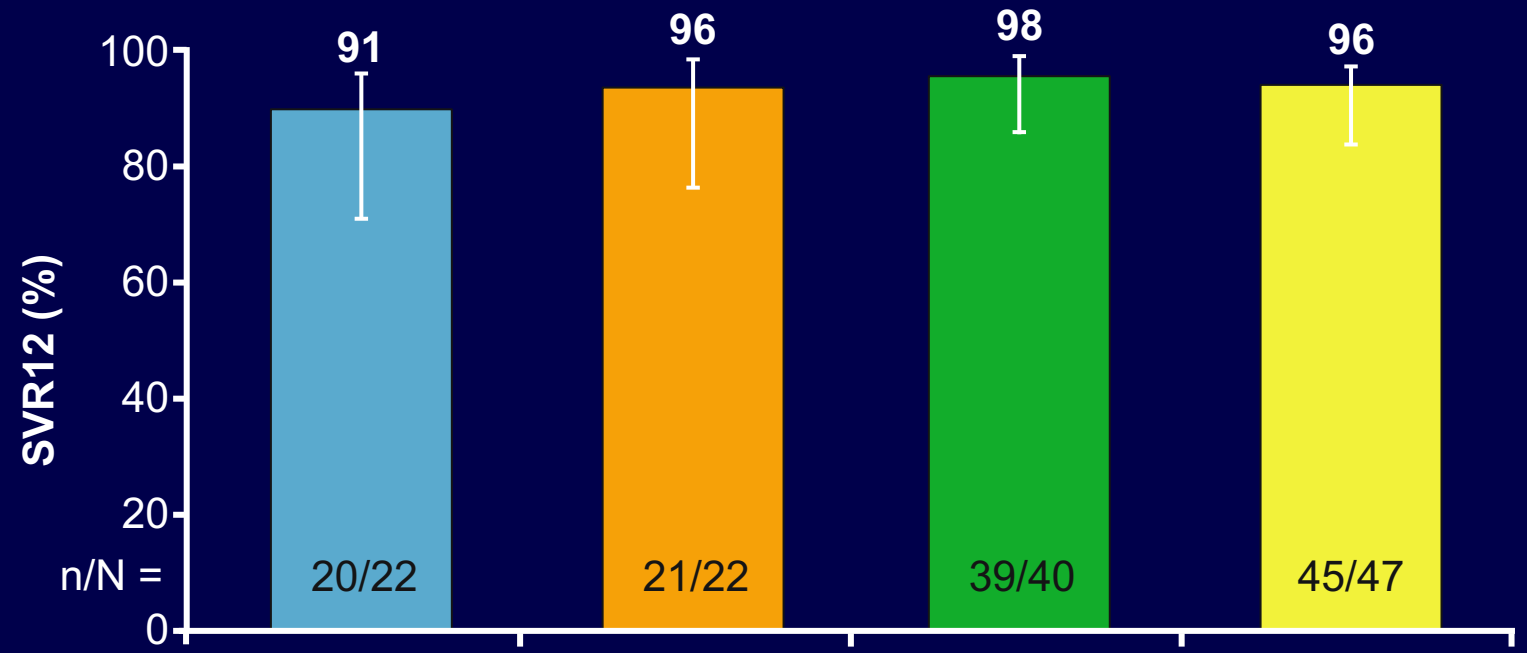
- Prior treatment experience consisted of IFN or pegIFN ± RBV or SOF + RBV ± pegIFN

*Dosing: GLE/PIB given as 3 coformulated 100/40 mg tablets QD for a total dose of 300/120 mg.

Wyles DL, et al. AASLD 2016. Abstract 113.

Slide credit: clinicaloptions.com

SURVEYOR-II, Part 3: SVR12 Rates With GLE/PIB for Pts With GT3 HCV ± Cirrhosis

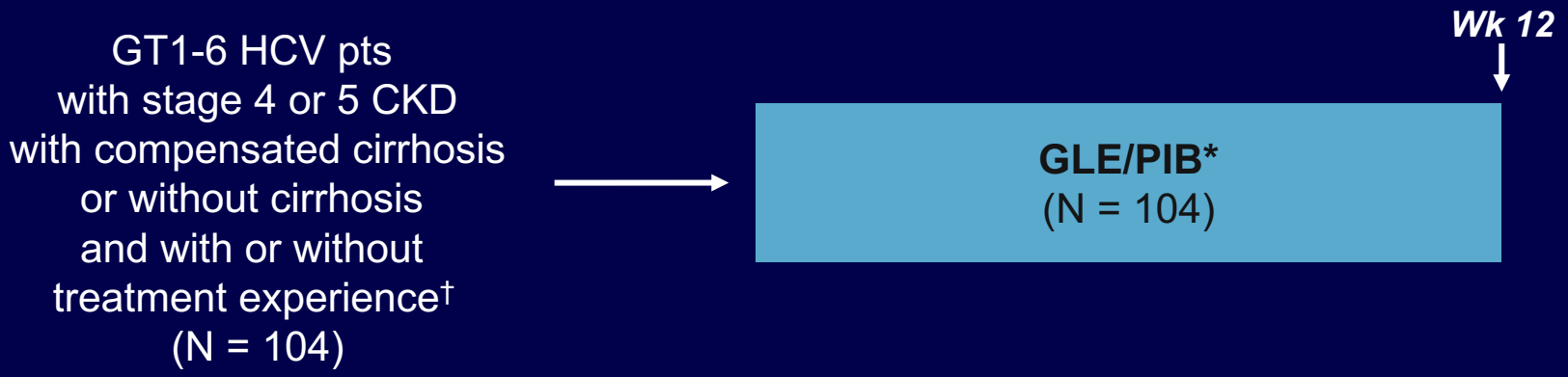


Tx Wks	12	16	12	16
Cirrhosis	-	-	+	+
Tx Experienced	+	+	-	+
Breakthrough	0	0	0	1
Relapse	2	1	0	1
LTFU	0	0	1	0

Wyles DL, et al. AASLD 2016. Abstract 113. Reproduced with permission.

EXPEDITION-IV: GLE/PIB for Pts With GT1-6 HCV and Renal Impairment

- Open-label, single-arm phase III trial



- At baseline, 82% on hemodialysis; 19% cirrhotic; 42% treatment experienced
- SVR12 rate of 98% (ITT; n/N = 102‡/104)

*Dosing: GLE/PIB given as 3 coformulated 100/40-mg tablets QD for a total dose of 300/120 mg.
†Prior treatment experience consisted of IFN or pegIFN ± RBV or SOF + RBV ± pegIFN.
‡1 pt d/c, 1 pt LTFU in ITT analysis of SVR12.

Gane EJ, et al. AASLD 2016. Abstract LB11.

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GLE/PIB Studies: Safety

Outcome, %	ENDURANCE-1[1]		ENDURANCE-2[2]		ENDURANCE-4[3]
	GLE/PIB 8 Wks (n = 351)	GLE/PIB 12 Wks (n = 352)	GLE/PIB 12 Wks (n = 202)	PBO 12 Wks (n = 100)	GLE/PIB 12 Wks (n = 121)
Any AE	62	66	65	58	69
D/c for AE	0	< 1	0	0	2
Serious AE	1	1	1	1	< 1
Death	0	< 1	0	0	0
AE in ≥ 10% of pts					
▪ Fatigue	9	12	11	10	17
▪ Headache	19	18	12	12	21
AST grade ≥ 3*	0	< 1	1	1	0
ALT grade ≥ 3*	0	0	< 1	2	0
Total bilirubin grade 3†	< 1	< 1	< 1	0	0

*> 5 times ULN. †3-10 times ULN.

1. Zeuzem S, et al. AASLD 2016. Abstract 253.
2. Kowdley KV, et al. AASLD 2016. Abstract 73.
3. Asselah T, et al. AASLD 2016. Abstract 114.

GLE/PIB Studies: Safety

Outcome, %	SURVEYOR-II, Part 3[1]				EXPEDITION-IV[2]
	Tx-Exp Noncirr G/P 12 Wks (n = 22)	Tx-Exp Noncirr G/P 16 Wks (n = 22)	Tx-Naive Cirrhotic G/P 12 Wks (n = 40)	Tx-Exp Cirrhotic G/P 16 Wks (n = 47)	Pts With Renal Impairment G/P 12 Wks (n = 104)
Any AE	55	77	80	72	71
D/c for AE	0	0	0	0	4
Serious AE‡	5	5	3	7	24
Death	NR	NR	NR	NR	1
AE in ≥ 10% of pts					
▪ Fatigue	18	18	13	34	14
▪ Headache	23	18	25	13	12
▪ Pruritus	NA	NA	NA	NA	20
AST grade ≥ 3*	5	0	0	0	0
ALT grade ≥ 3*	9	0	0	0	0
Total bilirubin grade ≥ 3†	0	0	0	2	1

*> 5-20 times ULN. †> 3-10 times ULN. ‡No serious drug-related AEs.

1. Wyles DL, et al. AASLD 2016. Abstract 113.
2. Gane EJ, et al. AASLD 2016. Abstract LB11.

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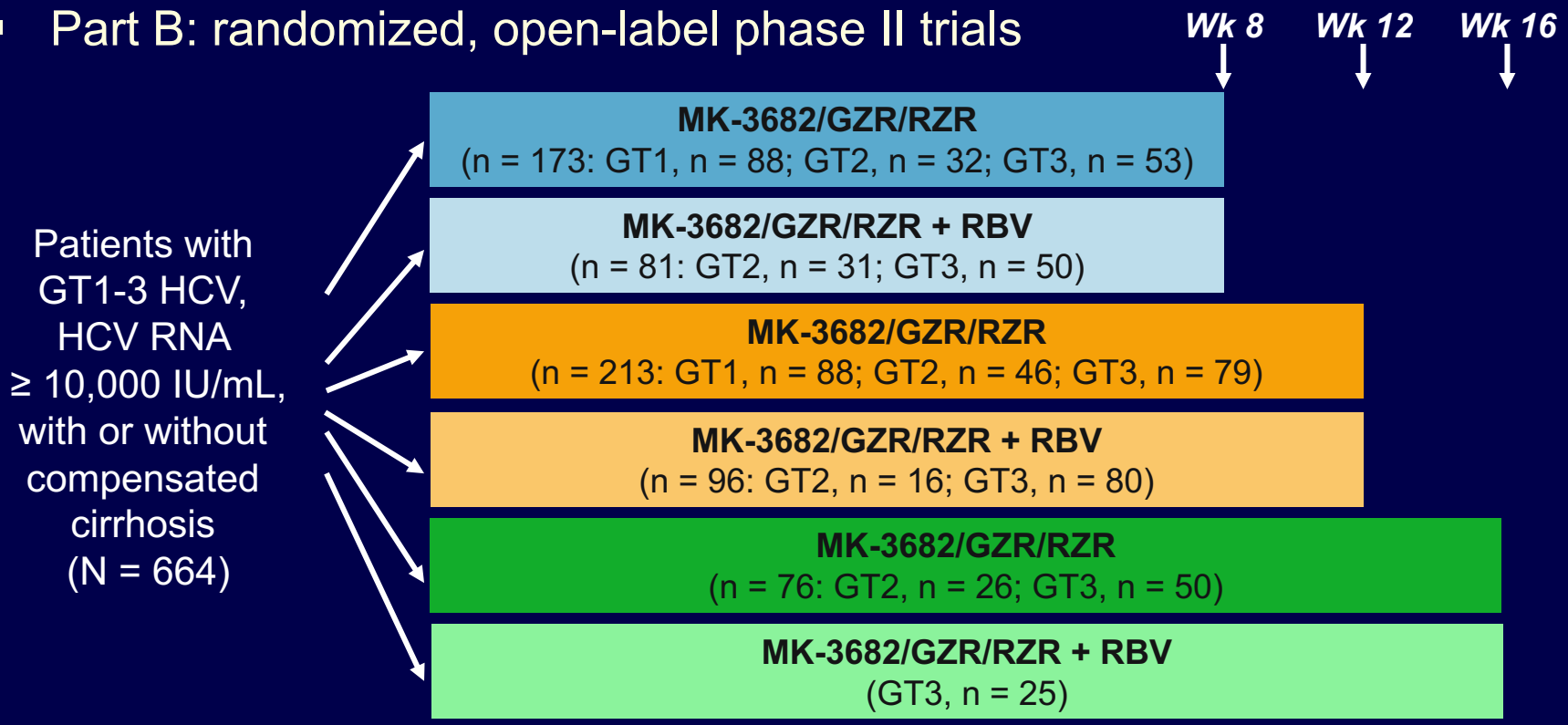
C-CREST 1 & 2: MK-3682/GZR/RZR ± RBV for Treating Pts With GT1-3 HCV

- Part B: randomized, open-label phase II trials



Dosing: MK-3682/GZR/RZR dosed as two 225/50/30-mg tablets QD. Pts with GT3 HCV could be treatment naive or have failed on pegIFN/RBV; all others treatment naive. Cirrhosis definition in notes.

- Baseline: 35% to 43% cirrhotic; 44% of GT3 pts had prior pegIFN/RBV

Lawitz E, et al. AASLD 2016. Abstract 110.

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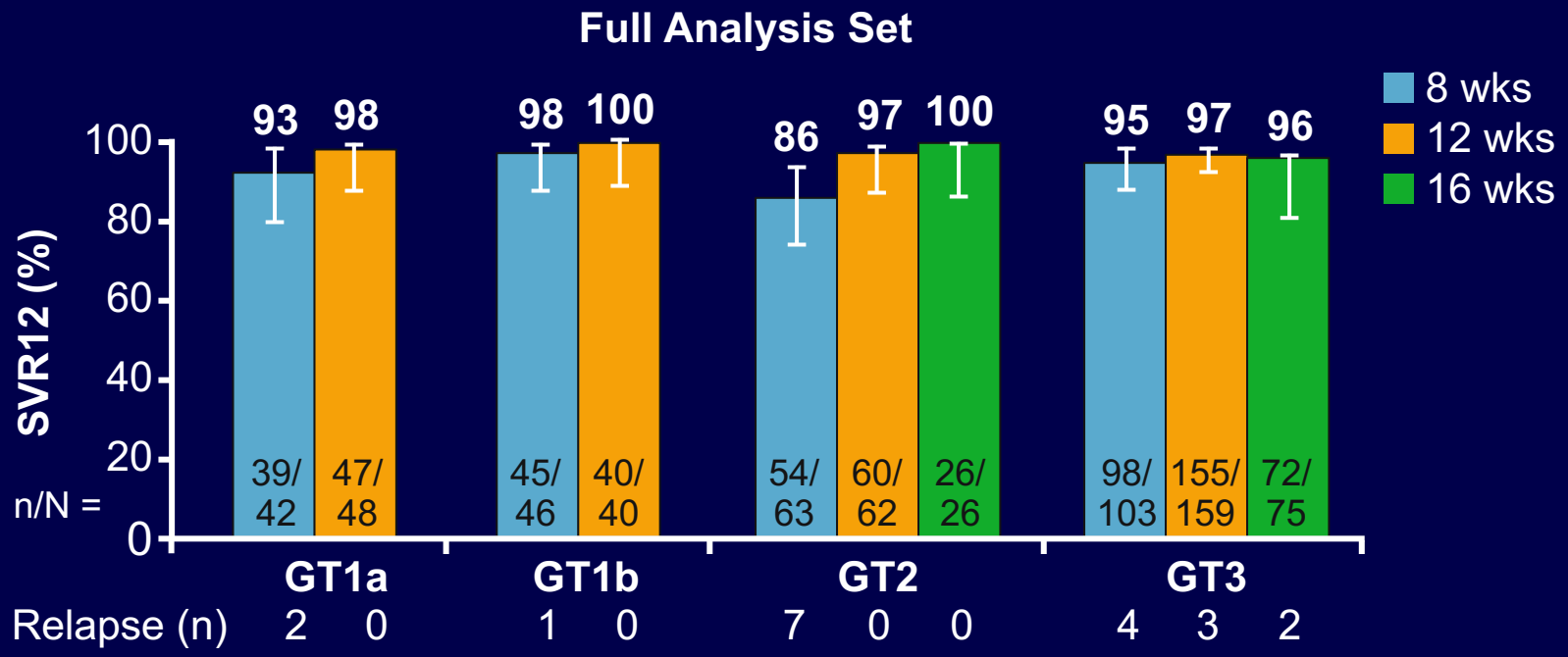
C-CREST 1 & 2: Efficacy of MK-3682/ GZR/RZR ± RBV for Pts With GT1-3 HCV



- Presence of cirrhosis, use of ribavirin, prior tx experience did not impact SVR12 rates

SVR12 by Baseline RAV Presence, % (n/N)	GT2 HCV		GT3 HCV	
	No L31M	L31M	No Y93H	Y93H
8 wks	94 (31/33)	80 (20/25)	98 (95/97)	50 (2/4)
12 wks	100 (23/23)	100 (28/28)	99 (147/148)	71 (5/7)

Lawitz E, et al. AASLD 2016. Abstract 110. Reproduced with permission.

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C-CREST 1 & 2: Retreatment With MK-3682/GZR/RZR for 8-Wk Failures

- Part C: open-label phase II trial retreating pts with GT1-3 HCV who failed 8 wks of treatment with MK-3682/GZR/RZR *or* MK-3682/GZR/EBR during Part A of C-CREST 1 & 2 (n = 24)
  - Pts retreated with MK-3682/GZR/RZR + RBV for 16 wks

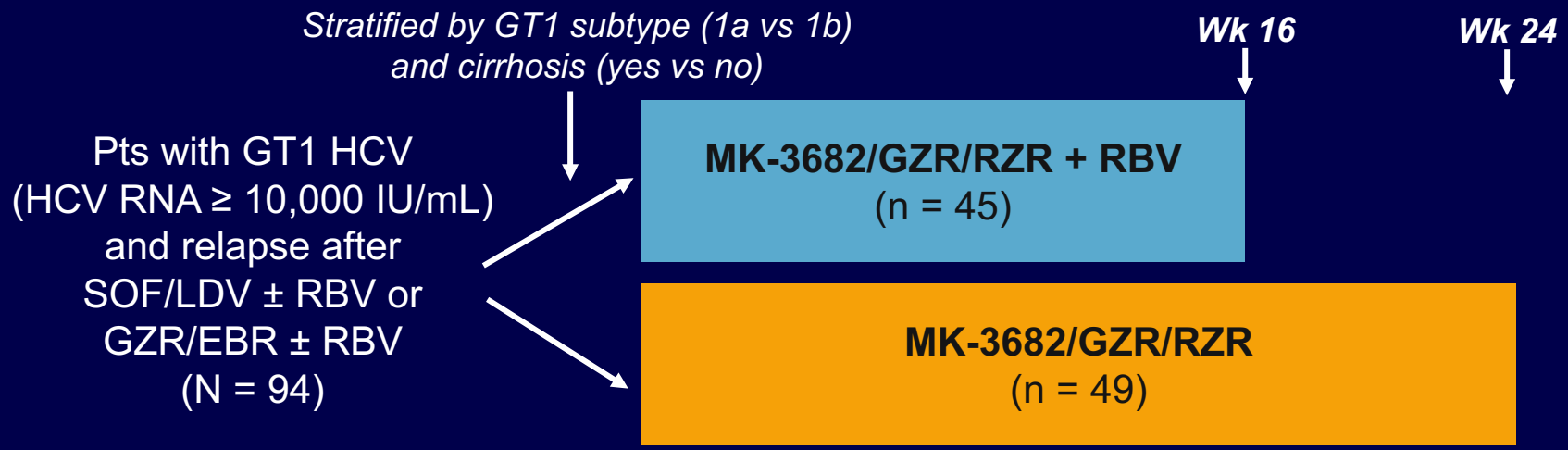
Outcome	GT1 HCV	GT2 HCV	GT3 HCV
SVR12, % (n/N)	100 (2/2)	93 (13/14)	100 (8/8)
Relapsed, n	0	0	0
Discontinued, n	0	1	0

Serfaty L, et al. AASLD 2016. Abstract 112.

Slide credit: clinicaloptions.com

C-SURGE: MK-3682/GZR/RZR for GT1 HCV Pts Who Relapsed on DAA Therapy

- Randomized, open-label phase II trial (interim analysis)



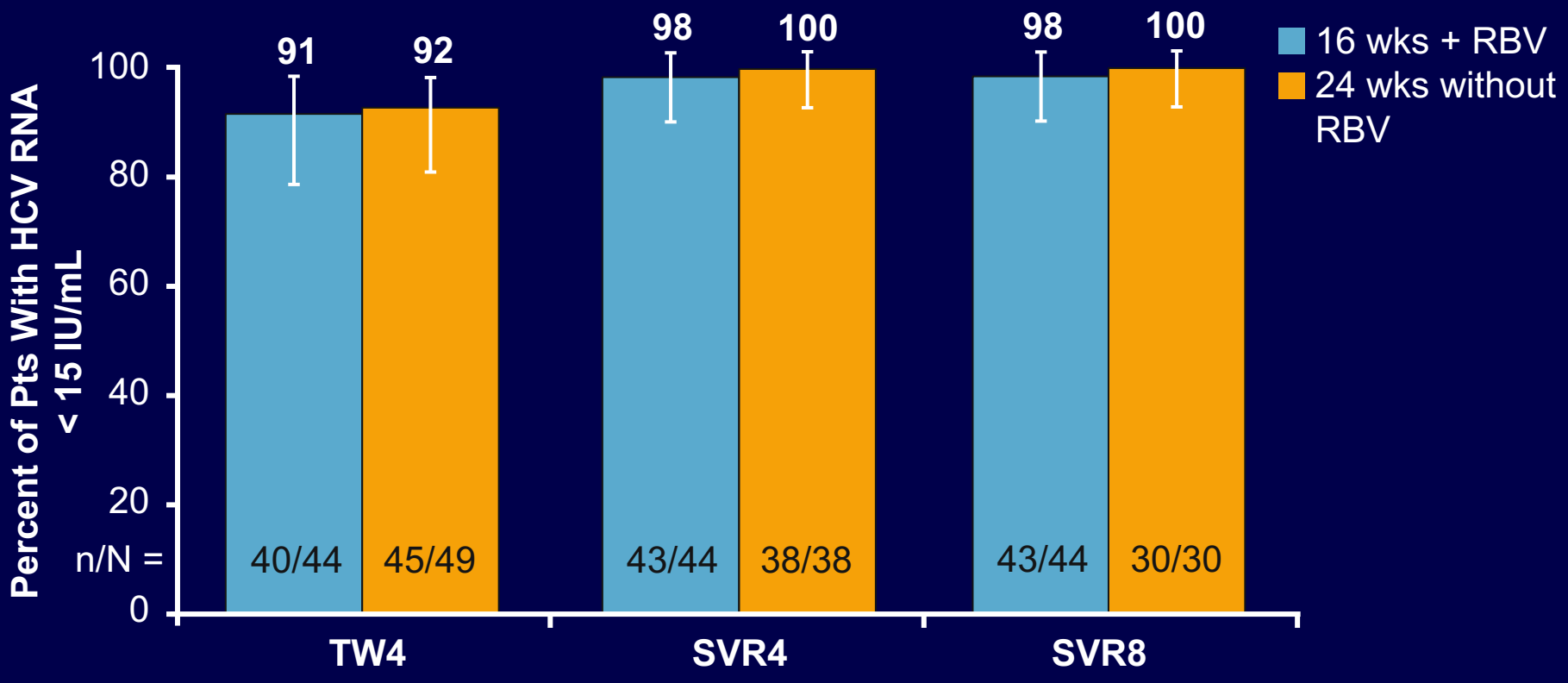
- Baseline characteristics:
  - Previous failing regimen: LDV/SOF 12-24 wks, 61%; LDV/SOF 8 wks, 15%; GZR/EBR 12 wks, 24%
  - NS5A RAVs, 84%; NS3 RAVs, 65%

Dosing: MK-3682/GZR/RZR two 225/50/30-mg tablets once daily; weight-based RBV (800-1400 mg/day). Trial included compensated cirrhotic and noncirrhotic pts; cirrhosis definition in slidenotes.

Wyles DL, et al. AASLD 2016. Abstract 193.

Slide credit: clinicaloptions.com

C-SURGE: SVR8 Rates With MK-3682/GZR/RZR for DAA Relapses



- No impact of NS5A or NS3 RAVs on SVR4, including Y93 RAVs
  - 4% of pts had ≥ 3 NS5A RAVs; 55% had dual NS5A and NS3 RAVs

Wyles DL, et al. AASLD 2016. Abstract 193. Reproduced with permission. Slide credit: clinicaloptions.com

MK-3682/GZR/RZR Studies: Safety

Outcome, %	C-CREST 1 & 2 Part B[1] MK-3682/GZR/RZR		C-SURGE[2] MK-3682/GZR/RZR	
	No RBV (n = 462)	+ RBV (n = 202)	+ RBV, 16 Wks (n = 44)	24 Wks (n = 49)
Any AE	69	86	91	80
Drug-related AE	36	67	75	47
D/c for AE	< 1	3	0	0
Serious AE	2	2	2	8
Death	< 1*	0	0	0
AE in > 10% of pts				
▪ Fatigue	15	29	48	24
▪ Headache	19	27	14	12
▪ Nausea	11	15	NA	NA
▪ Diarrhea	NA	NA	7	10
▪ Pruritus	NA	NA	11	0
▪ Rash	NA	NA	14	4

*Deemed unrelated to study drug.

1. Lawitz E, et al. AASLD 2016. Abstract 110.
2. Wyles DL, et al. AASLD 2016. Abstract 193.

MK-3682/GZR/RZR Studies: Safety

Outcome, %	C-CREST 1 & 2 Part B[1] MK-3682/GZR/RZR		C-SURGE[2] MK-3682/GZR/RZR	
	No RBV (n = 462)	+ RBV (n = 202)	+ RBV, 16 Wks (n = 44)	24 Wks (n = 49)
Hemoglobin < 10 g/dL	< 1	3	9	0
Total bilirubin > 5 x baseline	< 1*	3*	0†	0†
Late ALT/AST > 5 x ULN	1	0	0	0
Creatinine grade 1 (1.1-1.3 x ULN)	< 1	0	NR	NR
Creatinine grade 2 (1.4-1.8 x ULN)	< 1	0	0	2

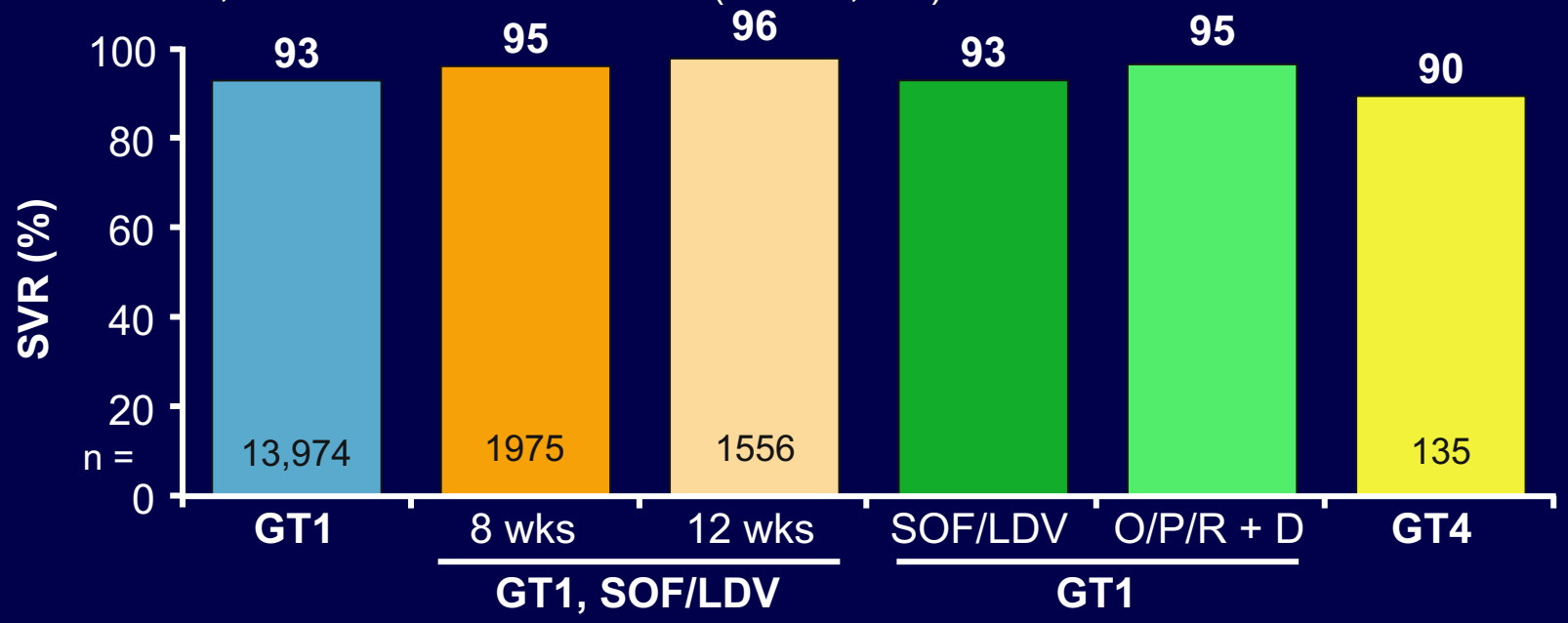
*Total bilirubin. †Direct bilirubin.

1. Lawitz E, et al. AASLD 2016. Abstract 110.
2. Wyles DL, et al. AASLD 2016. Abstract 193.

HCV Treatment: Real-World Studies With Approved Therapies

Real-World HCV Treatment in the US VA Healthcare System

- Analysis of real-world SVR for pts with GT1-4 HCV treated with SOF + RBV ± pegIFN, SOF/LDV, or OBV/PTV/RTV + DSV (N = 17,487)[1]



- Analysis of HCV treatment in VA healthcare system (N = 107,079)[2]
  - Dramatic increases in HCV treatment in 2014-2015 vs 1999-2013 (1999-2011, **1989 to 7196 treatments/yr**; 2014, **9180 treatments**; 2015, **31,028 treatments**)
  - Related to improved antiviral efficacy and availability of funding

1. Ioannou GN, et al. AASLD 2016. Abstract 21. Reproduced with permission.
2. Moon AM, et al. AASLD 2016. Abstract 227.

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Real-World HCV Retreatment Efficacy for DAA Failures

- Analysis of retreatment data in German database

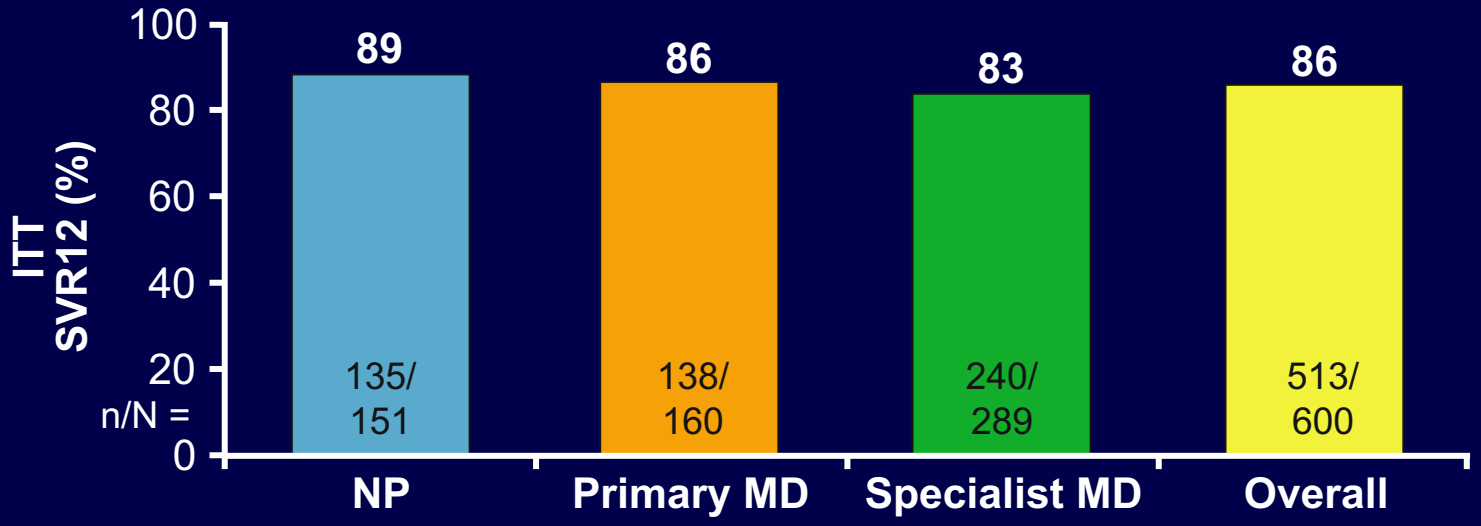
Previous DAA Regimen Failure	Retreatment Regimens	SVR12, % (n/N)
GT1: SMV + SOF ± RBV	**Overall**	**93 (28/30)**
	▪ LDV/SOF ± RBV 12/24 wks	92 (24/26)
	▪ OBV/PTV/RTV + DSV ± RBV 12/24 wks	100 (4/4)
GT1: DCV or LDV + SOF ± RBV	**Overall**	**84 (26/31)**
	▪ SMV + SOF ± RBV 12/24 wks	90 (19/21)
	▪ OBV/PTV/RTV + DSV ± RBV 12 wks	83 (5/6)
	▪ LDV/SOF ± RBV 12/24 wks	50 (2/4)
GT1: OBV/PTV/RTV + DSV ± RBV	**Overall**	**100 (7/7)**
	▪ LDV/SOF ± RBV 12/24 wks	100 (5/5)
	▪ SMV ± LDV + SOF + RBV 24 wks	100 (2/2)
GT3: SOF + RBV	**Overall**	**78 (18/23)**
	▪ DCV + SOF ± RBV 12/24 wks	77 (17/22)
	▪ LDV/SOF + RBV 24 wks	100 (1/1)

Vermehren J, et al. AASLD 2016. Abstract 894.

Slide credit: clinicaloptions.com

ASCEND: HCV Treatment Efficacy and Adherence by Provider Type

- Nonrandomized phase IV trial of HCV-infected pts in Washington, DC (N = 600)
- Pts mostly male (69%), black (96%), GT1a (72%), and treatment naive (82%)
  - 20% of pts had compensated cirrhosis, 23% had HCV/HIV coinfection
- All providers received uniform 3-hr training
- No difference in SVR12 by provider type, cirrhosis status
- Adherence to all treatment visits by cirrhotic pts lower for specialists (61%) vs PCPs (56%) and NPs (75%) (*P* = .04)



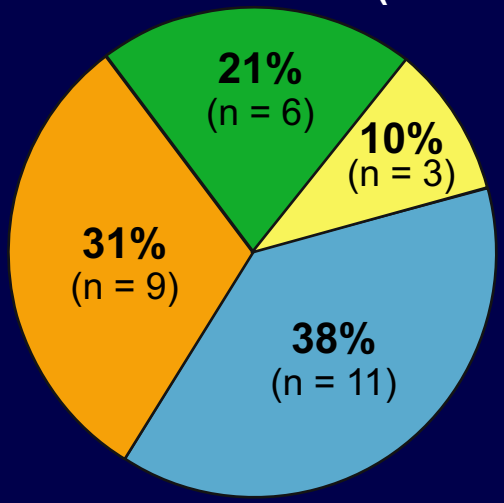
Emmanuel B, et al. AASLD 2016. Abstract 22. Reproduced with permission. Slide credit: clinicaloptions.com

HBV Studies

HBV Reactivation in Pts Receiving DAAs: Postmarketing Cases Reported to FDA

- Case reports of HBV reactivation in pts receiving DAAs
  - Reactivation: increase in HBV DNA or seroconversion to HBsAg positive
- 29 confirmed cases in ~ 3 yrs (November 2013 to October 2016)
  - Pts from Japan (n = 19), US (n = 5), other (n = 5)
  - Most cases occurred within 4-8 wks of initiation
  - 2 deaths, 1 transplant, 6 hospitalizations, 10 DAA discontinuations

HBV Reactivation (N = 29)



HBV at Baseline

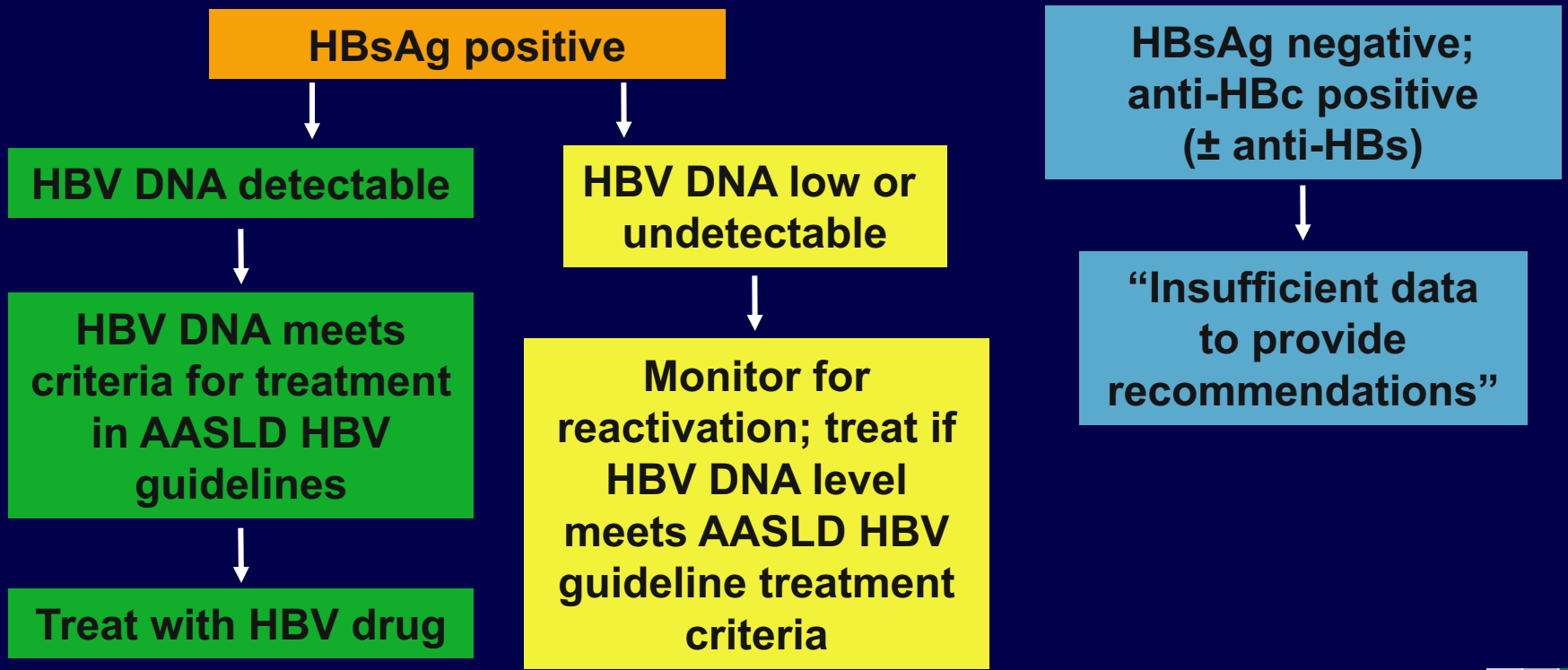
- Not reported, uninterpretable, or undetectable HBV DNA w/o HBsAg status
- Detectable HBV DNA
- HBsAg+, undetectable HBV DNA
- HBsAg-, undetectable HBV DNA

Bersoff-Matcha SJ, et al. AASLD 2016. Abstract LB17.

Slide credit: clinicaloptions.com

HBV Testing and Monitoring During HCV DAA Therapy: AASLD/IDSA Guidance

- Test all pts initiating HCV therapy for HBsAg, anti-HBc, and anti-HBs
  - No HBV markers: VACCINATE (this is not new)
  - HBV markers present:



AASLD/IDSA. HCV guidance. September 2016.
Graphic created by Ira M. Jacobson, MD.

Slide credit: clinicaloptions.com

GS-108/110: Changes in BMD With TAF vs TDF in HBV Pts

- Randomized, double-blind, active-controlled phase III studies in which pts with chronic HBV infection* treated with TAF 25 mg QD (n = 866) or TDF 300 mg QD (n = 432)[1]
  - Noninferior efficacy between groups previously shown[2,3]

Mean Change in BMD at Wk 72, %	TAF	TDF	*P* Value
Hip	-0.29	-2.43	< .001
Spine	-0.60	-2.52	< .001

- TDF also associated with significantly decreased hip and spine BMD at Wks 24 and 48 vs TAF (*P* < .001 for all comparisons)

*HBV DNA ≥ 20,000 IU/mL, ALT > 60/38 U/L (male/female).

1. Seto WK, et al. AASLD 2016. Abstract 67.
2. Buti M, et al. Lancet Gastroenterol Hepatol. 2016;1:196-206.
3. Chan HLY, et al. Lancet Gastroenterol Hepatol. 2016;1:185-195.

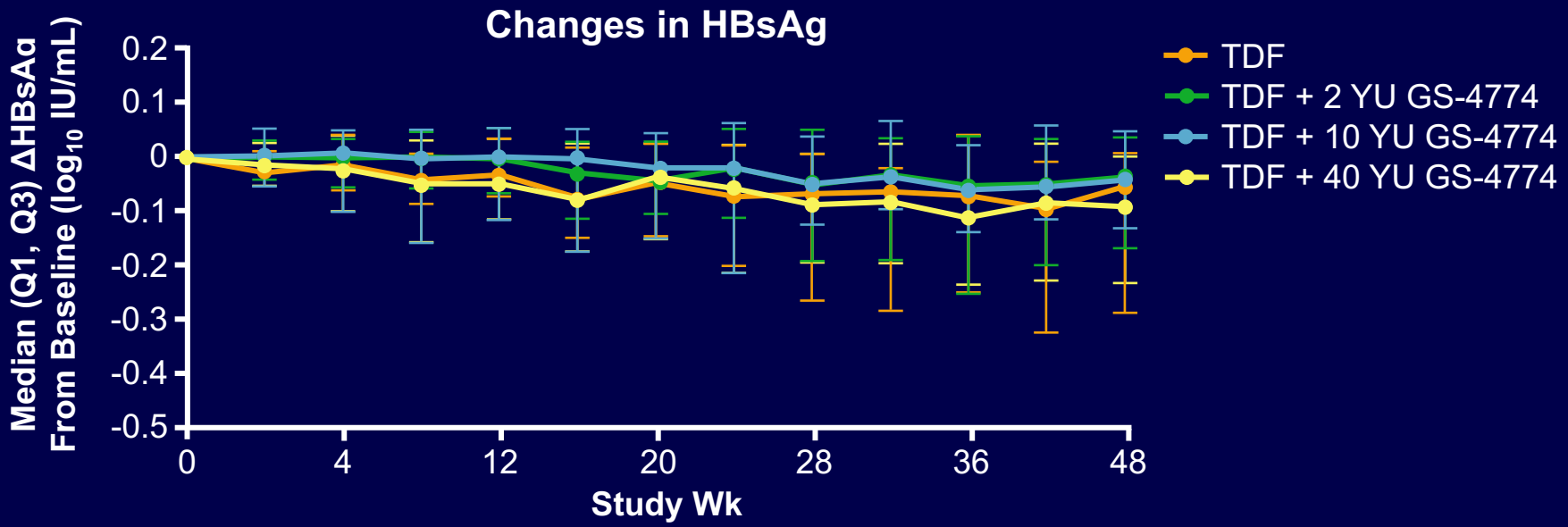
GS-1059: TLR-7 Agonist GS-9620 for Pts With Suppressed Chronic HBV Infection

- Randomized, double-blind, placebo-controlled phase II trial analyzing the immunomodulatory effects of GS-9620
  - Pts with chronic HBeAg-negative GTD HBV infection suppressed with nucleos(t)ide analogue for ≥ 3 yrs were randomized to 12 wks GS-9620 1, 2, or 4 mg PO QW (N = 26) or placebo; all pts continued nucleos(t)ide analogue
- Key results:
  - At Wk 24, no pts treated with GS-9620 had HBsAg change > 0.5 log10; no pts lost HBsAg
  - Improvements in specific T-cell responses observed with GS-9620 (eg, IFN-γ and IL-2 production)

Boni C, et al. AASLD 2016. Abstract 13.
ClinicalTrials.gov. NCT02166047.

GS-4774, a Heat-Inactivated, Yeast-Based T-Cell Vaccine for Pts With Chronic HBV

- Randomized phase II study assessing the GS-4774 vaccine* + TDF in pts with chronic HBV who were not on antivirals (HBV DNA ≥ 2000 IU/mL) (N = 195)
- Through Wk 48, HBsAg changes similar between GS-4774 + TDF and TDF alone groups; no pts lost HBsAg



- At Wks 24 and 48, similar rates of pts in GS-4774 + TDF and TDF alone groups with HBV DNA < 20 IU/mL

*Includes HBV core, surface, and X proteins.

Janssen HL, et al. AASLD 2016. Abstract 231. Reproduced with permission.

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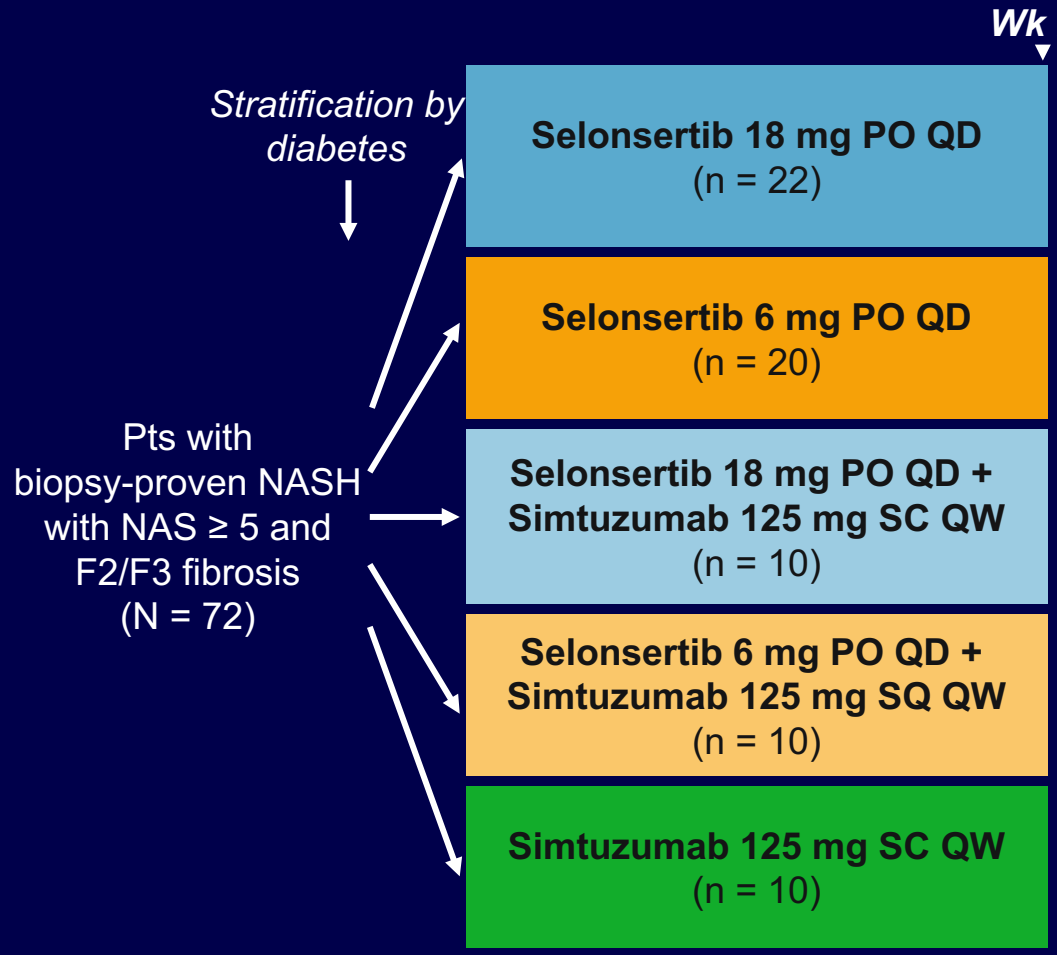
NASH:
Investigational Therapeutics

Selonsertib ± Simtuzumab for Pts With NASH and F2/F3 Fibrosis

- Randomized, open-label, active-controlled phase II trial[1]



- Selonsertib (formerly GS-4997): ASK1 inhibitor
  - ASK1:Ser/Thr kinase that activates p38 and JUN kinases, stimulating apoptotic, fibrinogenic, and inflammatory pathways[2]
- Simtuzumab: monocolonal Ab to LOXL2, an enzyme in the ECM that promotes collagen crosslinking[3]
  - Also studied in other fibrotic diseases, including myelofibrosis

References in slidenotes.

Slide credit: clinicaloptions.com

Selonsertib ± Simtuzumab for Pts With NASH: Key Findings

Wk 24 Outcome, n/N (%)	SEL 18 mg ± SIM†	SEL 6 mg ± SIM†	SIM
Fibrosis improvement*	13/30 (43)	8/27 (30)	2/10 (20)
Fibrosis improvement without NASH worsening*	11/30 (37)	8/27 (30)	2/10 (20)
Progression to cirrhosis*	1/30 (3)	2/27 (7)	2/10 (20)
≥ 2-point reduction in NAS*	7/31 (23)	5/27 (19)	2/10 (20)
NASH resolution*‡	0/31 (0)	1/27 (4)	0/10 (0)
Grade 3/4 AE	3/32 (9)	1/30 (3)	1/10 (10)
Serious AE	3/32 (9)	2/30 (7)	0/10 (0)
Discontinuation for AE	2/32 (6)	1/30 (3)	0/10 (0)
Death	0	0	0

- SEL may have potential role as antifibrotic

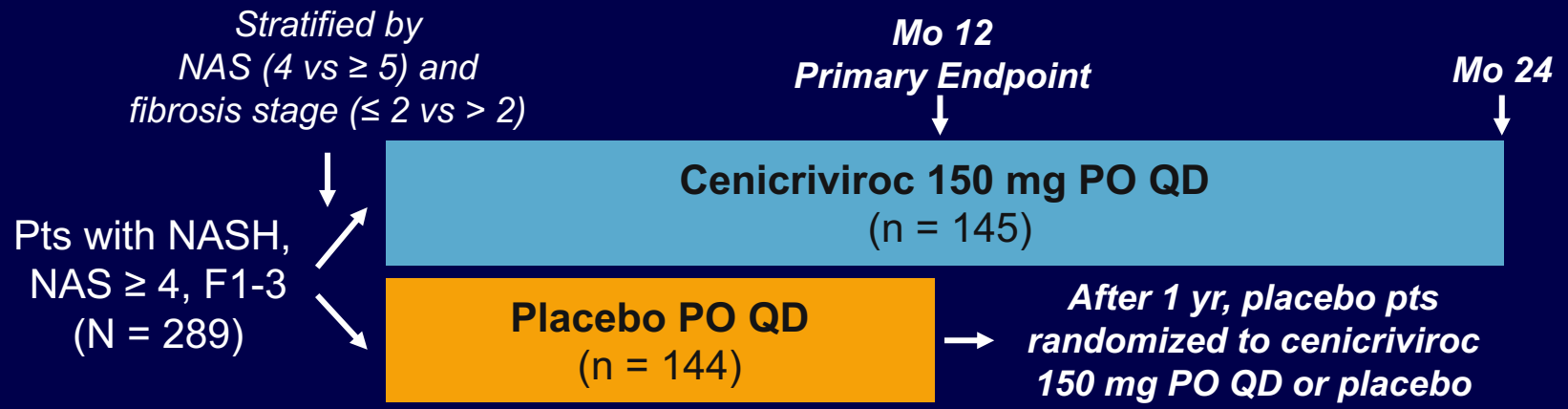
*For pts with evaluable liver biopsies at BL and Wk 24. †Results grouped by SEL dose based on combination tx and monotherapy achieving similar outcomes. ‡Defined as reduction in grade of ballooning to 0 and inflammation to 0 or 1.

Loomba R, et al. AASLD 2016. Abstract LB3.

Slide credit: clinicaloptions.com

CENTAUR: Cenicriviroc for Pts With NASH and F1-3 Fibrosis

- Randomized, double-blind, placebo-controlled phase II trial
- Cenicriviroc: dual C-C chemokine receptor (CCR) type 2/5 antagonist
  - CCR2/5 expressed on Kupfer and other proinflammatory cells; promote inflammation, hepatic stellate cell activation, and liver fibrosis in response to liver fat accumulation[2]
  - CCR5 antagonists have been explored for HIV therapy; CCR5 a coreceptor necessary for cellular entry of certain HIV strains[3]



References in slidenotes.

Slide credit: clinicaloptions.com

CENTAUR: Key Efficacy and Safety Findings

Outcome at Yr 1, n (%)	Cenicriviroc (n = 145)	Placebo (n = 144)	*P* Value
Improvement in NAS by ≥ 2 points* and no fibrosis worsening†	23 (16)	27 (19)	.519
Complete NASH resolution and no fibrosis worsening	11 (8)	8 (6)	.494
Improvement in fibrosis stage of ≥ 1 and no NASH worsening	29 (20)	15 (10)	.023
Grade 3/4 AE	38 (26)‡	37 (26)	NR
Serious AE	16 (11)‡	10 (7)	NR
▪ Causing d/c	1 (< 1)‡	2 (1)	NR
Death	0	0	--

*With ≥ 1 point reduction in lobular inflammation or hepatocellular ballooning. †Primary endpoint. ‡Cenicriviroc safety population, n = 144.

- Cenicriviroc may have potential role as antifibrotic

Sanyal AJ, et al. AASLD 2016. Abstract LB1.

Slide credit: clinicaloptions.com

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