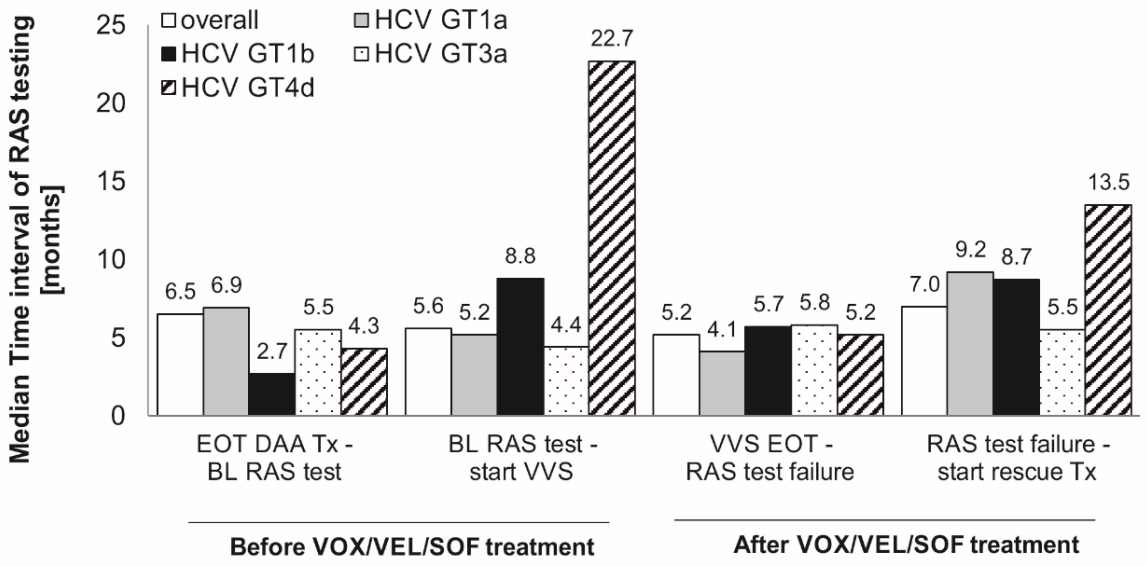
Failure to voxilaprevir, velpatasvir, sofosbuvir and efficacy of rescue therapy

Julia Dietz, Velia Chiara Di Maio, Adolfo de Salazar, Dolores Merino, Johannes Vermehren, Stefania Paolucci, Andreas E. Kremer, Magdalena Lara, Maria Rodriguez Pardo, Heinz Zoller, Elisabetta Degasperi, Kai-Henrik Peiffer, Laura Sighinolfi, Francisco Téllez, Christiana Graf, Valeria Ghisetti, Jonas Schreiber, Elisa Fernández-Fuertes, Lucio Boglione, Leopoldo Muñoz-Medina, Rudolf Stauber, William Gennari Blanca Figueruela, Jesús Santos, Pietro Lampertico, Stefan Zeuzem, Francesca Ceccherini-Silberstein, Federico García, Christoph Sarrazin

Table of contents:

Supplementary Figure……2
Table S1……3
Table S2……4
Table S3……5
Table S4……6-7
Table S5……8
Table S6……9
Table S7……..10
Table S8……..11



In n=22 patients who initiated rescue treatment

BL, baseline; DAA, direct acting antiviral; EOT, end of treatment; RAS, resistance-associated substitution; Tx, treatemnt; VVS, VOX/VEL/SOF

Supplementary Fig. 1: Time intervals of RAS testing and DAA treatments.

Table S1. HCV RASs with >2-fold EC50 analysed within NS3, NS5A and NS5B

Gene	*GT*	
NS3	1a	Q41R, F43L, Y56H, Q80K/R, R155G/K/T/W, A156G/L/T, D168A/E/F/G/H/I/K/L/N/T/R/V/Y
NS3	1b	F43I/S/V, Y56H, Q80K/R, S122D/R, R155K/G/T/W, A156G/S/T/V, D168A/E/F/G/H/I/K/L/T/V/Y
NS3	3	Q41K/R, Y56H, Q80K, R155K, A156G/L/T/V, A166T/H, Q168L/R
NS3	4	Q41R, R155C, A156L//T/V, D168A/E/H/K/T/V
NS5A	1a	K24G/N/R, M28A/G/T/V, Q30E/G/H/K/L/R/T, L31I/M/V, P32L, S38F, H58D, A92T, Y93C/F/H/L/N/R/S/T/W
NS5A	1b	L28T, R30H, L31I/F/M/V, A92K, Y93H/N/T
NS5A	3	A30E/H/K, L31F/M/V, P58G, Y93H/S
NS5A	4	L28M/V, L30C/H/R/S/Q, M31I/L/V, P32L, Y93C/H/S/W
NS5B	1, 3,4	A150V, L159F, K206E, S282T, L320F, C316H/N, V321A

Table S2: Resistance levels of NS3 RASs detected in this study according to the literature.

	HCV GT	EC50 fold change level compared to wildtype replicon*				
		Glecaprevir	Voxilaprevir	Grazoprevir	Paritaprevir	Reference
Q80K	1a	0.9	0.8	1.8	3	[1-3]
D168A	1a	4.0	3.4	154	50	[1-3]
D168E	1a	1.4	0.7	1.8	14	[1-3]
Q80K, D168E	1a	n.d.	3.4	n.d.	n.d.	[3]
Y56F	1b	n.d.	2.5	n.d.	n.d.	[3]
Y56H	1b	n.d.	n.d.	n.d.	n.d.	
Q80R	1b	n.d.	1.9	n.d.	n.d.	[3]
D168E	1b	0.9	1.2	4.1	4	[1-3]
D168V	1b	3.2	2.6	22	159	[1-3]
Y56H, D168V	1b	n.d.	n.d.	n.d.	2472	[4]
Q80R, D168E	1b	n.d.	2.1	n.d.	n.d.	[3]
Y56H	3a	n.d.	n.d.	n.a.	n.a.	
Q168K	3a	n.d.	0.7			[3]
Q168R	3a	54	1.3			[2, 3]
Y56H, Q168R	3a	1387	286			[2, 3]
A156S	4d	n.d.	0.4 (4a)	n.d.	n.d.	[3]
D168V	4d	1.9	3.1 (4a)	14	313	[2, 3, 5]
A156S, D168V	4d	n.d.	n.d.	n.d.	n.d.	

n.d., not determined

*Fold change resistance levels are an indication but are dependent on the type of the assay used and are not directly comparable between different studies.

Table S3: Resistance levels of NS5A RASs detected in this study according to the literature.

	HCV GT	EC50 fold change level compared to wildtype replicon*						
		Pibrentasvir	Velpatasvir	Elbasvir	Daclatasvir	Ledipasvir	Ombitasvir	Reference
M28V	1a	1.8	n.d.	1	1.3	n.d.	58	[6-9]
Q30H	1a	1.0	2.3	6	309	183	3	[6, 7, 9, 10]
Q30R	1a	1.7	2.2	16	252	632	800	[6-9]
L31M	1a	1.1	16	10	197	554	2	[6-9]
L31V	1a	1.3	68	61	594	683	n.d.	[6, 8, 9, 11]
Y93C	1a	1.7	3.8	11	1864	1602	540	[7, 9, 11, 12]
Y93H	1a	6.7	609	220	208	1677	41,383	[8, 9, 11, 12]
Y93N	1a	7.1	2758	929	>16,155	6677	66,740	[6, 8, 9, 11]
Y93S	1a	n.d.	64	n.d.	2734	1626	1013	[7, 11, 12]
Q30H, L31V	1a	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	
Q30R,L31M	1a	2.4	198	n.d.	>4452	23,400	n.d.	[11]
L31V,Y93N	1a	n.d.	>89,660	n.d.	n.d.	n.d.	n.d.	[6]
Q30H, L31V, Y93H	1a	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	
L31I	1b	n.d.	9.7	n.d.	3.4	29.4	n.d.	[11]
L31M	1b	n.d.	1.0	1	3.8	3.4	0.9	[6, 8]
L31V	1b	n.d.	1.7	4	8.9	43	8	[6-8, 13]
Y93H	1b	0.6	3.3	17	38	3310	77	[6-9]
L31M+Y93H	1b	0.7	44	n.d.	4227	20,270	7105	[6, 9, 11, 13]
L31V+Y93H	1b	0.9	510	38,857	8336	75,483	12,328	[6, 7, 9, 14, 15]
A30K	3a	1.1	50	n.a.	44	n.a.	n.a.	[12, 16, 17]
L31F	3a	n.d.	31		255			[6]
L31M	3a	n.d.	71		537			[12, 16]
Y93H	3a	2.3	724		3488			[6, 9]
A30K+L31M	3b	20-100	>10,000		>10,000			[18]
A30K+Y93H	3a	69	>10,000		>10,000			[6, 17, 18]
L31F+Y93H	3a	n.d.	n.d.		n.d.			
A30K, L31F, Y93H	3a	n.d.	n.d.		n.d.			
M31V	4a	n.d.	n.d.	2-20	>10-100	>10-100	n.d.	[19, 20]
Y93H	4d	n.d.	2.9 (4a)	2-20	169 (4a)	135 (4a)	n.d.	[6, 20, 21]
M31V+Y93H	4d	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	

RASs tested in different cell culture systems, no head-to-head comparisons.
GT, genotype; n.a., not applicable as NS5A inhibitor not approved for this HCV genotype; n.d., not determined, as variant was not selected in cell culture experiments.
*Fold change resistance levels are an indication but are dependent on the type of the assay used and are not directly comparable between different studies.

Table S4: Detailed pre-treatment histories and RAS profiles in VOX/VEL/SOF failure patients.

Patient	HCV GT	1st DAA Tx	2nd DAA Tx	3rd DAA Tx	RAS profile at baseline			RAS profile at VOX/VEL/SOF failure		
					NS3	NS5A	NS5B	NS3	NS5A	NS5B
1	1a	PrOD/RBV 12 wks.	-	-	No RASs	No RASs	No RASs	Q80K	No RASs	No RASs
2	1a	G/P 12 wks.	-	-	No RASs	Q30H, L31V, Y93H	No RASs	No RASs	Q30H, L31V, Y93H	No RASs
3	1a	LDV/SOF 24 wks.	-	-	Q80K	No RASs	No RASs	Q80K	No RASs	No RASs
4	1a	LDV/SOF 12 wks.	-	-	No RASs	Q30R, L31M	No RASs	No RASs	Q30R, L31M	No RASs
5	1a	LDV/SOF 12 wks.	-	-	Q80K	L31M	No RASs	Q80K	L31M	No RASs
6	1a	LDV/SOF 12 wks.	-	-	No RASs	Q30H, L31V	No RASs	No RASs	L31V	No RASs
7	1a	LDV/SOF/RBV 12 wks.	GLE/PIB 12 wks.	-	No RASs	Y93S	No RASs	n.d.	n.d.	n.d.
8	1a	VEL/SOF 12 wks.	-	-	Q80K	No RASs	No RASs	Q80K	No RASs	No RASs
9	1a	VEL/SOF 12 wks.	-	-	No RASs	M28V	No RASs	No RASs	M28V	No RASs
10	1a	SMV/SOF	LDV/SOF/RBV	-	n.d.	n.d.	n.d.	D168A	Y93C	No RASs
11	1a	SOF/SMV 12 wks.	LDV/SOF 12 wks.	VEL/SOF/RBV 12 wks.	Q80K, D168E	L31V, Y93N	No RASs	Q80K	L31V, Y93N	No RASs
12	1b	PrOD/RBV 4 wks.	-	-	No RASs	No RASs	No RASs	No RASs	No RASs	No RASs
13	1b	LDV/SOF 12 wks.	-	-	No RASs	L31I	No RASs	No RASs	L31I	No RASs
14	1b	LDV/SOF 24 wks.	-	-	Y56F	No RASs	No RASs	Y56F	No RASs	No RASs
15	1b	LDV/SOF 12 wks.	-	-	n.d.	n.d.	No RASs	No RASs	Y93H	No RASs
16	1b	VEL/SOF 12 wks.	-	-	n.d.	n.d.	n.d.	No RASs	No RASs	No RASs
17	1b	VEL/SOF 12 wks.			No RASs	Y93H	No RASs	No RASs	No RASs	No RASs
18	1b	LDV/SOF 12 wks.	VEL/SOF/RBV 16 wks.	-	No RASs	Y93H	No RASs	No RASs	L31M, Y93H	No RASs
19	1b	SOF/RBV 12 wks.	LDV/SOF/RBV 24 wks.	VEL/SOF/RBV 24 wks.	Q80R, D168E	L31M, Y93H	No RASs	Q80R	L31M, Y93H	No RASs
20	1b	LDV/SOF 8 wks.	PrOD 12 wks	GZR/EBR/SOF/RBV 12 wks	Y56H, D168V	L31V, Y93H	L159F, C316N	Y56H, D168V	L31V, Y93H	L159F, C316N
21	3a	G/P 12 wks.	-	-	Y56H, Q168R	A30K, Y93H	No RASs	Y56H, Q168R	A30K, Y93H	No RASs

22	3a	DCV/SOF 12 wks.	-	-	n.d.	Y93H	No RASs	No RASs	Y93H	No RASs
23	3a	DCV/SOF 12 wks.	-	-	Q168R	Y93H	No RASs	Q168R	A30K, Y93H	No RASs
24	3a	DCV/SOF 12 wks.	-	-	n.d.	Y93H	n.d.	No RASs	Y93H	No RASs
25	3a	DCV/SOF 12 wks.	-	-	No RASs	A30K	No RASs	No RASs	A30K, Y93H	No RASs
26	3a	DCV/SOF/RBV 12 wks.	-	-	n.d.	Y93H	No RASs	No RASs	No RASs	No RASs
27	3a	DCV/SOF/RBV 12 wks.	-	-	No RASs	Y93H	No RASs	No RASs	Y93H	No RASs
28	3a	DCV/SOF/RBV 24 wks.	-	-	n.d.	n.d.	n.d.	Q168K	Y93H	No RASs
29	3a	DCV/SOF/RBV 8 wks.	-	-	No RASs	No RASs	No RASs	No RASs	No RASs	No RASs
30	3a	VEL/SOF 12 wks.	-	-	No RASs	Y93H	No RASs	No RASs	Y93H	No RASs
31	3a	VEL/SOF 12 wks.	-	-	No RASs	n.d.	No RASs	No RASs	No RASs	No RASs
32	3a	VEL/SOF 12 wks.	-	-	n.d.	n.d.	n.d.	No RASs	Y93H	No RASs
33	3a	VEL/SOF 12 wks.	-	-	n.d.	n.d.	n.d.	No RASs	Y93H	No RASs
34	3a	VEL/SOF 12 wks.	-	-	n.d.	n.d.	n.d.	Q168R	Y93H	No RASs
35	3a	VEL/SOF 12 wks.	-	-	Q168K	Y93H	A150V, V321A	Q168K	Y93H	A150V, V321A
36	3a	DCV/SOF/RBV 24 wks.	LDV/SOF 24 wks.	-	No RASs	Y93H	No RASs	No RASs	Y93H	No RASs
37	3a	SOF/RBV	DCV/SOF/RBV	VEL/SOF/RBV	No RASs	Y93H	No RASs	No RASs	Y93H	No RASs
38	3a	G/P 12 wks.	-	-	n.d.	A30K, Y93H	n.d.	No RASs	A30K, Y93H	No RASs
39	3b	G/P 8 wks.	-	-	n.d.	n.d.	n.d.	No RASs	A30K, L31M	No RASs
40	4d	SMV/DCV/RBV	LDV/SOF/RBV	-	D168V	M31V,Y93H	No RASs	D168V, A156S	M31V,Y93H	No RASs

DCV, daclatasvir; GLE, glecaprevir; LDV, ledipasvir; n.d., not determined; NS5Ai, NS5A inhibitor; NS5A, non-structural protein 5A; PIB, pibrentasvir; PI, NS3 protease inhibitor; PrOD, ritonavir-boosted paritaprevir, ombitasvir plus dasabuvir; pts., patients; RBV, ribavirin; SOF, sofobuvir; TVR, VEL, velpatasvir; VOX, voxilaprevir, wks., weeks

Table S5: RAS analyses available at baseline and at VOX/VEL/SOF failure.

HCV GT	Total no. of pts.	Baseline				VOX/VEL/SOF failure			
		Serum samples	Sequencing data available			Serum samples	Sequencing data available		
			NS3	NS5A	NS5B		NS3	NS5A	NS5B
1a	11	10	10	10	10	10	10	10	10
1b	9	7	7	7	8	9	9	9	9
3a	18	14	10	13	12	18	18	18	18
3b	1	0	0	0	0	1	1	1	1
4d	1	1	1	1	1	1	1	1	1
Overall, n (%)	40		28 (70)	31 (78)	31 (78)		39 (98)	39 (98)	39 (98)
Median, n (%)				31 (78)				39 (98)	

In HCV GT1a, a serum sample from one patient was not available at baseline and after treatment failure, the sample from another patient was missing.

SOF, sofosbuvir; pts., patients; VEL, velpatasvir; VOX, voxilaprevir

Table S6: Patients with discordant RAS profile between baseline and VOX/VEL/SOF failure.

Patient	HCV GT	RASs at baseline		RASs at VOX/VEL/SOF failure	
		NS3	NS5A	NS3	NS5A
1	1a	No RASs	No RASs	Q80K	No RASs
6	1a	No RASs	Q30H, L31V*	No RASs	L31V
11	1a	Q80K, D168E	L31V, Y93N	Q80K	L31V, Y93N
17	1b	No RASs	Y93H	No RASs	No RASs
18	1b	No RASs	Y93H	No RASs	L31M, Y93H
19	1b	Q80R, D168E	L31M, Y93H	Q80R	L31M, Y93H
23	3a	Q168R	Y93H	Q168R	A30K, Y93H
25	3a	No RASs	A30K	No RASs	A30K, Y93H
40	4d	D168V	M31V, Y93H	D168V, A156S	M31V, Y93H

GT, genotype; NS3, non-structural protein 3; NS5A, non-structural protein 5A; RASs, resistance-associated substitutions; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.
RASs conferring a >2-20 fold increase in Voxilaprevir or Velpatasvir resistance compared to wildtype are marked in purple and RASs conferring a >20 fold resistance are marked in red.
*No testing of resistance level available, double NS5A RASs are supposed to be more NS5Ai resistant compared to single RASs

Table S7: Patients with combined NS3, NS5A or NS5B RASs either at baseline or after VOX/VEL/SOF failure.

Patient	HCV GT	Pretreatment	RASs at baseline			RASs at VOX/VEL/SOF failure		
			NS3	NS5A	NS5B	NS3	NS5A	NS5B
2	1a	G/P 12 wks.	No RASs	Q30H, L31V, Y93H*	No RASs	No RASs	Q30H, L31V, Y93H*	No RASs
4	1a	LDV/SOF	No RASs	Q30R, L31M	No RASs	No RASs	Q30R, L31M	No RASs
6	1a	LDV/SOF 12 wks.	No RASs	Q30H, L31V*	No RASs	No RASs	L31V	No RASs
11	1a	SOF/RBV 12 wks. LDV/SOF 24 wks. VEL/SOF 12 wks.	Q80K, D168E	L31V, Y93N	No RASs	Q80K	L31V, Y93N	No RASs
18	1b	LDV/SOF 12 wks. VEL/SOF/RBV 16 wks.	No RASs	Y93H	No RASs	No RASs	L31M, Y93H	n.d.
19	1b	SMV/SOF 12 wks. LDV/SOF/RBV 24 wks. VEL/SOF/RBV 24 wks.	Q80R, D168E	L31M, Y93H	No RASs	Q80R	L31M, Y93H	No RASs
20	1b	LDV/SOF 8 wks. PrOD 12 wks. GZR/EBR/SOF/RBV 12 wks.	Y56H, D168V	L31V, Y93H	L159F, C316N	Y56H, D168V	L31V, Y93H	L159F, C316N
21	3a	G/P	Y56H, Q168R	A30K, Y93H	No RASs	Y56H, Q168R	A30K, Y93H	No RASs
23	3a	DCV/SOF 12 wks.	Q168R	Y93H	No RASs	Q168R	A30K, Y93H	No RASs
25	3a	DCV/SOF 12 wks.	No RASs	A30K	No RASs	No RASs	A30K, Y93H	No RASs
35	3a	VEL/SOF 12 wks.	Q168K	Y93H	A150V, V321A	Q168K	Y93H	A150V, V321A
38	3a	G/P 12 wks.	n.d.	A30K, Y93H	n.d.	No RASs	A30K, Y93H	No RASs
39	3b	G/P 8 wks.	n.d.	n.d.	n.d.	No RASs	A30K, L31M	No RASs
40	4d	SMV/DCV/RBV LDV/SOF/RBV	D168V	M31V,Y93H	No RASs	A156S, D168V	M31V,Y93H	No RASs

DCV, daclatasvir; EBR, elbasvir; G/P, Glecaprevir/Pibrentasvir; GZR, grazoprevir; NS3, non-structural protein 3; n.d., not determined; NS5A, non-structural protein 5A; NS5B, nonstructural protein 5B; LDV, ledipasvir; PrOD (Paritaprevir/Ritonavir/Ombitasvir with Dasabuvir); RASs, resistance-associated substitutions, SMV, simeprevir; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir
RASs conferring a >2-20 fold increase in voxilaprevir or velpatasvir resistance compared to wildtype are marked in purple and RASs conferring a >20 fold resistance are marked in red.
*No testing of resistance level available, double NS5A RASs are supposed to be more NS5Ai resistant compared to single RASs

Table S8: Characteristics of patients who did not receive rescue treatment (n=18).

Patient	Reasons for not conducting rescue treatment
3	Resumption drug abuse (incompliance)
6	HCC
7	Psychiatric illness, patient lost/cannot be reached.
10	HCC, treatment postponed (wait for compassionate use program)
11	HCC
12	Advanced age, compensated cirrhosis
14	Suspicion of HCC
16	No cirrhosis, no worsening of liver stiffness
17	Treatment postponed (patient wish)
18	Renal deficiency, LTX, no cirrhosis, no worsening of liver stiffness
19	Treatment postponed (patient wish)
21	CCC, Exitus
25	Treatment postponed due to Covid-19 pandemic
30	Treatment postponed (patient wish)
31	Treatment postponed due to Covid-19 pandemic
36	HCC
37	HCC
39	Patient without a permanent residence permit, returned to home country

CCC, cholangiocarcinoma; HCC, hepatocellular carcinoma; LTX, liver transplantation;

REFERENCES:

[1] Pilot-Matias T, Tripathi R, Cohen D, Gaultier I, Dekhtyar T, Lu L, et al. In vitro and in vivo antiviral activity and resistance profile of the hepatitis C virus NS3/4A protease inhibitor ABT-450. Antimicrob Agents Chemother 2015;59:988-997.

[2] Ng TI, Tripathi R, Reisch T, Lu L, Middleton T, Hopkins TA, et al. In Vitro Antiviral Activity and Resistance Profile of the Next-Generation Hepatitis C Virus NS3/4A Protease Inhibitor Glecaprevir. Antimicrob Agents Chemother 2018;62.

[3] Han B, Parhy B, Zhou E, Hsieh D, Camus G, Martin R, et al. In Vitro Susceptibility of Hepatitis C Virus Genotype 1 through 6 Clinical Isolates to the Pangenotypic NS3/4A Inhibitor Voxilaprevir. J Clin Microbiol 2019;57.

[4] Krishnan P, Tripathi R, Schnell G, Reisch T, Beyer J, Irvin M, et al. Pooled Analysis of Resistance in Patients Treated With Ombitasvir/ABT-450/r and Dasabuvir With or Without Ribavirin in Phase 2 and Phase 3 Clinical Trials. Hepatology 2014;60:1134A-1135A.

[5] Schnell G, Tripathi R, Beyer J, Reisch T, Krishnan P, Lu L, et al. Hepatitis C virus genotype 4 resistance and subtype demographic characterization of patients treated with ombitasvir plus paritaprevir/ritonavir. Antimicrob Agents Chemother 2015;59:6807-6815.

[6] Dvory-Sobol H, Han B, Lu J, Yu M, Beran RK, Cheng G, et al. In vitro resistance profile of hepatitis C virus NS5A inhibitor velpatasvir in genotypes 1 to 6. J Viral Hepat 2019;26:991-1001.

[7] Krishnan P, Beyer J, Mistry N, Koev G, Reisch T, DeGoey D, et al. In vitro and in vivo antiviral activity and resistance profile of ombitasvir, an inhibitor of hepatitis C virus NS5A. Antimicrob Agents Chemother 2015;59:979-987.

[8] Liu R, Curry S, McMonagle P, Yeh WW, Ludmerer SW, Jumes PA, et al. Susceptibilities of genotype 1a, 1b, and 3 hepatitis C virus variants to the NS5A inhibitor elbasvir. Antimicrob Agents Chemother 2015;59:6922-6929.

[9] Ng TI, Krishnan P, Pilot-Matias T, Kati W, Schnell G, Beyer J, et al. In Vitro Antiviral Activity and Resistance Profile of the Next-Generation Hepatitis C Virus NS5A Inhibitor Pibrentasvir. Antimicrob Agents Chemother 2017;61.

[10] Hernandez-Conde M, Fernandez I, Perello C, Gallego A, Bonacci M, Pascasio JM, et al. Effectiveness and safety of elbasvir/grazoprevir therapy in patients with chronic HCV infection: Results from the Spanish HEPA-C real-world cohort. J Viral Hepat 2019;26:55-64.

[11] Wyles D, Dvory-Sobol H, Svarovskaia ES, Doehle BP, Martin R, Afdhal NH, et al. Post-treatment resistance analysis of hepatitis C virus from phase II and III clinical trials of ledipasvir/sofosbuvir. J Hepatol 2017;66:703-710.

[12] Lawitz EJ, Dvory-Sobol H, Doehle BP, Worth AS, McNally J, Brainard DM, et al. Clinical Resistance to Velpatasvir (GS-5816), a Novel Pan-Genotypic Inhibitor of the Hepatitis C Virus NS5A Protein. Antimicrob Agents Chemother 2016;60:5368-5378.

[13] Krishnan P, Schnell G, Tripathi R, Beyer J, Reisch T, Zhang X, et al. Analysis of Hepatitis C Virus Genotype 1b Resistance Variants in Japanese Patients Treated with Paritaprevir-Ritonavir and Ombitasvir. Antimicrob Agents Chemother 2016;60:1106-1113.

[14] Fridell RA, Qiu D, Wang C, Valera L, Gao M. Resistance analysis of the hepatitis C virus NS5A inhibitor BMS-790052 in an in vitro replicon system. Antimicrob Agents Chemother 2010;54:3641-3650.

[15] Lahser FC, Bystol K, Curry S, McMonagle P, Xia E, Ingravallo P, et al. The Combination of Grazoprevir, a Hepatitis C Virus (HCV) NS3/4A Protease Inhibitor, and

Elbasvir, an HCV NS5A Inhibitor, Demonstrates a High Genetic Barrier to Resistance in HCV Genotype 1a Replicons. Antimicrob Agents Chemother 2016;60:2954-2964.

[16] Hernandez D, Zhou N, Ueland J, Monikowski A, McPhee F. Natural prevalence of NS5A polymorphisms in subjects infected with hepatitis C virus genotype 3 and their effects on the antiviral activity of NS5A inhibitors. J Clin Virol 2013;57:13-18.

[17] Krishnan P, Pilot-Matias T, Schnell G, Tripathi R, Ng TI, Reisch T, et al. Pooled Resistance Analysis in Patients with Hepatitis C Virus Genotype 1 to 6 Infection Treated with Glecaprevir-Pibrentasvir in Phase 2 and 3 Clinical Trials. Antimicrob Agents Chemother 2018;62.

[18] Smith D, Magri A, Bonsall D, Ip CLC, Trebes A, Brown A, et al. Resistance analysis of genotype 3 hepatitis C virus indicates subtypes inherently resistant to nonstructural protein 5A inhibitors. Hepatology 2019;69:1861-1872.

[19] Zhou N, Hernandez D, Ueland J, Yang X, Yu F, Sims K, et al. NS5A Sequence Heterogeneity and Mechanisms of Daclatasvir Resistance in Hepatitis C Virus Genotype 4 Infection. J Infect Dis 2016;213:206-215.

[20] Zepatier. Fachinformation. Merck/MSD 2016.

[21] Wang C, Jia L, Huang H, Qiu D, Valera L, Huang X, et al. In vitro activity of BMS-790052 on hepatitis C virus genotype 4 NS5A. Antimicrob Agents Chemother 2012;56:1588-1590.