Direct-acting antivirals Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir with or without Ribavirin in HCV genotype 1-infected treatment-naïve or treatment-experienced patients with or without cirrhosis: real-life experience

Ligita Jancoriene[1], Alina Voinic[1], Katazyna Polubenko[2], Edita Kazenaite[3], Arida Buivydiene[3], Jolita Jakutiene[3], Ieva Tolmane[4], Agita Jeruma[4]

1 – Vilnius University Hospital Santariskiu klinikos Centre of Infectious Diseases;
2 – Vilnius University, Faculty of Medicine;
3 – Vilnius University Hospital Santariskiu klinikos Centre of Hepatology, Gastroenterology and Dietetics;
4 – Riga Stradins University Department of Infectology and Dermatology; Infectology Center of Latvia

Conflict of Interest Disclosures

Advisory activities and honoraria for the lectures AbbVie, MSD, Oriola Vilnius

Principal Investigator in MSD, AbbVie clinical trials

Introduction

- Direct-acting antiviral (DAA) regimens improved the efficacy of chronic hepatitis C (CHC) treatment

- Ombitasvir, paritaprevir boosted with ritonavir and dasabuvir and possibly combined with ribavirin (OBV/PTV/r + DSV ± RBV) for use as a combination therapy for HCV infection were licensed in US in Dec 2014 and in European Union in Jan 2015

- Phase 3 clinical trials carried out with OBV/PTV/r + DSV ± RBV have shown SVR rates exceeding 90%, irrespective of genotype, liver fibrosis, previous history of treatment, HIV co-infection or liver transplantation

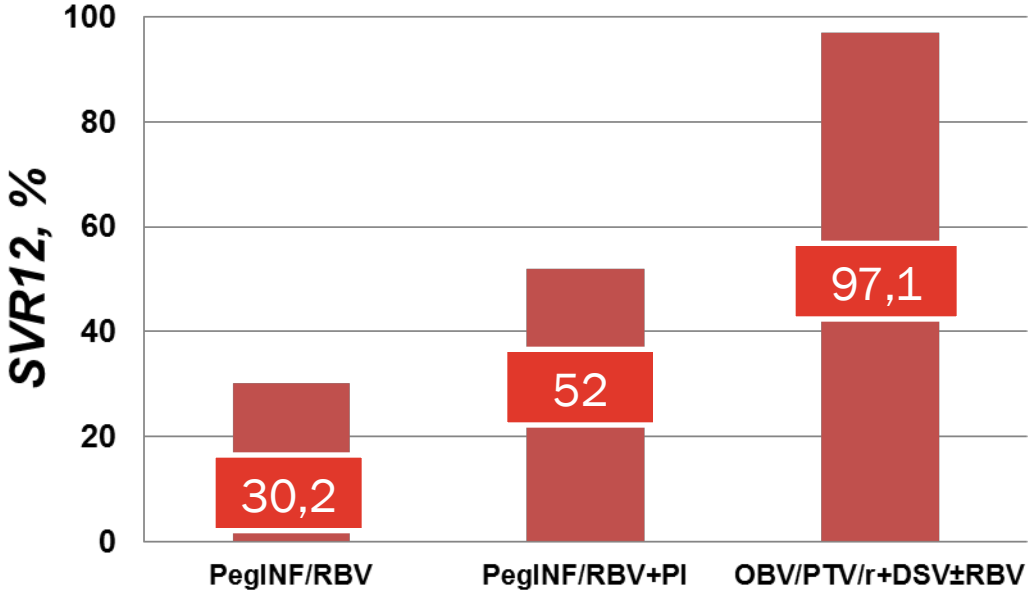
European Association for Study of Liver. EASL recommendations on treatment of hepatitis C 2015. J Hepatol 2015; 63: 199-236.

Summary of Key Phase 3 Studies

Study	Patient Populations	Treatment	SVR12	Relapse	Virologic failure
SAPPHIRE-I[1-2] (n=631)	GT1, without cirrhosis, treatment-naive	viekirax + exviera + RBV 12 weeks (n=473) placebo 12 weeks (n=158)	96%	1.5%	0.2%
SAPPHIRE-II[1,2] (n=394)	GT1, without cirrhosis, treatment-naive	viekirax + exviera + RBV 12 weeks (n=297) placebo 12 weeks (n=97)	96%	2.4%	0%
TURQUOISE-II[1,2] (n=380)	GT1, treatment-naive and treatment-experienced with compensated cirrhosis (Child-Pugh A)	viekirax + exviera + RBV 12 weeks (n=208) viekirax + exviera + RBV 24 weeks (n=172)	92% 97%	5.9% 0.6%	0.5% 1.7%
PEARL-II[1,2] (n=179)	GT1b, without cirrhosis, treatment-naive	viekirax + exviera + RBV 12 weeks (n=88) viekirax + exviera – RBV 12 weeks (n=91)	98% 100%	0%	0%
PEARL-III[1,2] (n=419)	GT1b, without cirrhosis, treatment-naive	viekirax + exviera + RBV for 12 weeks (n=210) viekirax + exviera – RBV for 12 weeks (n=209)	99.5% 100%	0%	0.5% 0%
PEARL-IV[1,2] (n=305)	GT1a, without, treatment-naive	viekirax + exviera + RBV 12 weeks (n=100) viekirax + exviera – RBV 12 weeks (n=205)	97% 90%	1% 5%	1% 2.9%

Viekirax (ombitasvir/paritaprevir/ritonavir), Summary of Product Characteristics , 2016
Exviera (dasabuvir), Summary of Product Characteristics, 2016

Antiviral treatment after liver transplantation



J Hepatol. Systematic review of the treatment of established recurrent hepatitis C with pegylated interferon in combination with ribavirin. 2008 Aug;49(2):274-87. Verna EC et al. High post-transplant virological response in hepatitis C virus infected patients treated with pretransplant protease inhibitor-based triple therapy. Liver Int. 2015 Feb;35(2):510-7. Paul Y. Kwo et al. An Interferon-free Antiviral Regimen for HCV after Liver Transplantation. N Engl J Med 2014;371:2375-82.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An Interferon-free Antiviral Regimen for HCV after Liver Transplantation

Paul Y. Kwo, M.D., Parvez S. Mantry, M.D., Eoin Coakley, M.D., Helen S. Te, M.D., Hugo E. Vargas, M.D., Robert Brown, Jr., M.D., M.P.H., Fredric Gordon, M.D., Josh Levitsky, M.D., Norah A. Terrault, M.D., M.P.H., James R. Burton, Jr., M.D., Wangang Xie, Ph.D., Carolyn Setze, M.S., Prajakta Badri, Ph.D., Tami Pilot-Matias, Ph.D., Regis A. Vilchez, M.D., Ph.D., and Xavier Forns, M.D.

RESULTS

Of the 34 study participants, 33 had a sustained virologic response at post-treatment weeks 12 and 24, for a rate of 97% (95% confidence interval, 85 to 100). The most common adverse events were fatigue, headache, and cough. Five patients (15%) required erythropoietin; no patient required blood transfusion. One patient discontinued the study drugs owing to adverse events after week 18 but had a sustained virologic response. Blood levels of calcineurin inhibitors were monitored, and dosages were modified to maintain therapeutic levels; no episode of graft rejection was observed during the study.

CONCLUSIONS

Treatment with the multitargeted regimen of ombitasvir–ABT-450/r and dasabuvir with ribavirin was associated with a low rate of serious adverse events and a high rate of sustained virologic response among liver-transplant recipients with recurrent HCV genotype 1 infection, a historically difficult-to-treat population. (Funded by AbbVie; CORAL-I ClinicalTrials.gov number, NCT01782495.)

Clinical trials data and real world experience

- Real-world data usually provide efficacy lower compared to clinical trials because they include more divergent and non-adherent populations
- In a number of real world studies OBV/PTV/r ± DSV ± RBV based treatment was effective as it was demonstrated in clinical trials and achieved high rates of SVR12 in the range of 91-100%, irrespective of liver fibrosis, previous history of treatment or genotype
- This regimen was well tolerated in adults and was associated with low rates of treatment discontinuation

Pogorzelska J, Flisiak R. Real-world experience **with ombitasvir/paritaprevir boosted with ritonavir and possibly combined with dasabuvir and ribavirin in HCV infection.** Clinical and Experimental Hepatology, 2016; 2: 34–37

Overview of efficacy in real-world studies with OBV/PTV/r + DSV ± RBV in HCV infection

Clinical and Experimental Hepatology, 2016

Reference	Country	Number of patients *n*	Proportion of known genotypes 1/1a/1b/4 *n*	Cirrhosis *n* (%)	SVR 12 in all patients *n* (%)	SVR 12 in cirrhosis *n* (%)
Aghemo [14]	Italy	42		42 (100)	41 (98)	41 (98)
Calleja [11]	Spain	1422	8/247/1312/0	732 (47)	1376 (97)	710 (97)
Christensen [15]	Germany	87			83 (95)	
Derbala [16]	Qatar	42	0/0/0/42	24 (36)	41 (98)	24 (100)
Flisiak [6]	Poland	209	11/13/176/9	119 (57)	207 (99)	117 (98)
Gomez [17]	Spain	31			31 (100)	
Hinrichsen [18]	Germany	558	0/141/351/53	127 (24)	539 (97)	129 (95)
Hunyady [13]	Hungary	61	61/0/0/0		60 (98)	
Jeruma [19]	Latvia	15	0/0/15/0	15 (100)	15 (100)	15 (100)
Londono [20]	Spain	37			36 (97)	
Lubel [21]	Australia	167	167/0/0/0		167 (92)	(91)
Mateya [22]	Bulgaria	62			61 (98)	
McCombs [12]	USA	1012	773/0/0/0	350 (35)	945 (93)	329 (94)
Ouzan [23]	France	20	15/0/0/5		20 (100)	
Perello [24]	Spain	77			75 (97)	
Petta [25]	Italy	728		728 (100)	712 (98)	712 (98)
Rincon [26]	Spain	547			538 (98)	
Teti [27]	Italy	193	193/0/0/0		188 (97)	
Zuckerman [10]	Israel	416	416/0/0/0	253 (62)	413 (99)	251 (99)
Overall		5726	1644/401/1854/109	2390 (54)	5548 (97)	2328 (97)

Available safety data of OBV/PTV/r + DSV ± RBV treatment in real-world experience

Reference	Patients discontinued due to adverse events *n* (%)	Patients with hepatic decompensation *n* (%)	Serious adverse events *n* (%)
Calleja [11]	24 (1.8)	8 (0.5)	84 (5.4)
Flisiak [5, 6]	5 (2.4)	7 (3.3)	8 (3.8)
Hinrichsen [18]	8 (3)	0	13 (2)
Hunyady [13]	0	0	3 (3.8)
Lubel [21]	3 (1.1)	6 (2.2)	9 (3.4)
Zuckerman [10]	20 (3)	8 (1.2)	25 (3.8)

Pogorzelska J, Flisiak R. Real-world experience **with ombitasvir/paritaprevir boosted with ritonavir and possibly combined with dasabuvir and ribavirin in HCV infection.** Clinical and Experimental Hepatology, 2016; 2: 34–37

Characteristics of the regimen

- The three DAA (3D) – ombitasvir 12.5 mg (OBV), paritaprevir 75 mg (PTV) and dasabuvir 250 mg (DSV) – are formulated into two tablets
- According to the products' characteristics, OBV/PTV/r ± DSV ± RBV are dedicated for the treatment of CHC in adults infected with gen 1 and 4
- Therapy for gen 1a and 1b is based on a fixed-dose regimen that includes OBV/PTV/r taken as 2 tablets once daily, and DSV in the second tablet taken twice a day
- The addition of a weight-adjusted dose of RBV is required in all patients infected with genotype 1a and 4 HCV
- According to the most recent label, RBV is not required in patients infected with genotype 1b, which is predominant in Central Europe

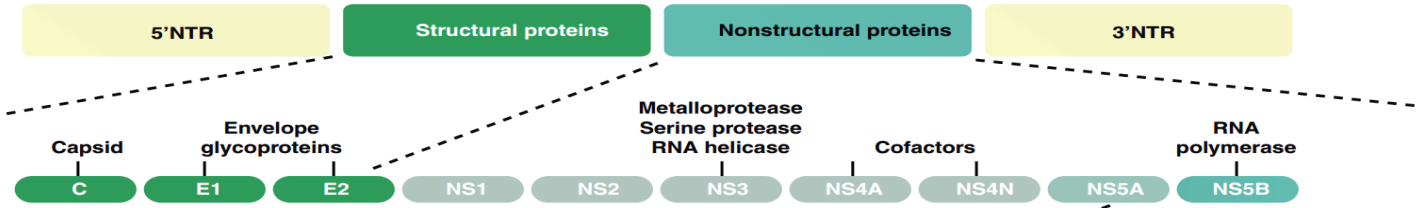
Viekirax (ombitasvir/paritaprevir/ritonavir), Summary of Product Characteristics , 2016
Exviera (dasabuvir), Summary of Product Characteristics, 2016

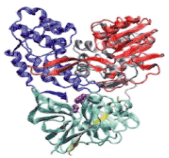
Characteristics of the regimen

- The standard duration of therapy is 12 weeks for gen 1b infection without cirrhosis and with compensated cirrhosis
- Patients infected with gen 1a without cirrhosis should be treated in combination with RBV for 12 weeks, and in the case of those with compensated cirrhosis treatment should be extended to 24 weeks
- OBV/PTV/r ± DSV therapy should not be used in patients with advanced liver failure and a Child-Pugh score of C
- Patients with a history of hepatic decompensation including patients with a Child-Pugh score of B can be considered for treatment under close monitoring in experienced hepatologic centers

Viekirax (ombitasvir/paritaprevir/ritonavir), Summary of Product Characteristics , 2016
Exviera (dasabuvir), Summary of Product Characteristics, 2016

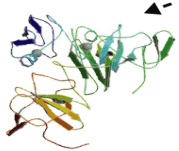
Ombitasvir/Paritaprevir/Ritonavir (25/150/100 mg) + Dasabuvir (250 mg) ± Ribavirin





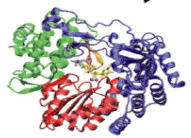
Protease Inhibitors
« ...previr »

Telaprevir
Boceprevir
Simeprevir
Paritaprevir (ABT-450)
ABT 493
Grazoprevir (MK-5172)
GS-9857
Sovaprevir
ACH-2684



NS5A Inhibitors
« ....asvir »

Daclatasvir
Ledipasvir
Velpatasvir (GS-5816)
Ombitasvir
ABT 530
Elbasvir
MK-8408
Samatasvir
Odalasvir (ACH-3102)



Polymerase Inhibitors
« .....buvir »

Nucs
Sofosbuvir
MK 3682
ACH-3422
ALS-335

Non-Nucs
Dasabuvir
GS-9669
MK-8876

Tarik Asselah et al. Direct-acting antivirals for the treatment of hepatitis C virus infection: optimizing current IFN-free treatment and future perspectives. Liver Int. 2016; 36 (Suppl. S1): 47–57

Tarik Asselah

Background and Aims

- The OBV/PTV/r + DSV ± RBV regimen has been approved in Europe for CHC patients with gen 1 infection in January 2015

- OBV/PTV/r + DSV ± RBV became reimbursed (100%) in Lithuania for patients infected with gen 1, irrespectively of previous treatment history with F3 - F4 fibrosis (METAVIR) starting from 29 October 2015 as the first available interferon-free regimen and included in clinical practice guidelines issued by the Lithuanian Group of HCV Experts in 2016

- Since 13 Jul 2016 – OBV/PTV/r + DSV ± RBV (3D) became 100% reimbursed for gen 1 CHC treatment-naïve and treatment-experienced patients with fibrosis stage ≥ F2

Individual Patient Early Access to AbbVie ABT-450/ritonavir/ ABT-267 and ABT-333 Coadministered with Ribavirin (RBV)

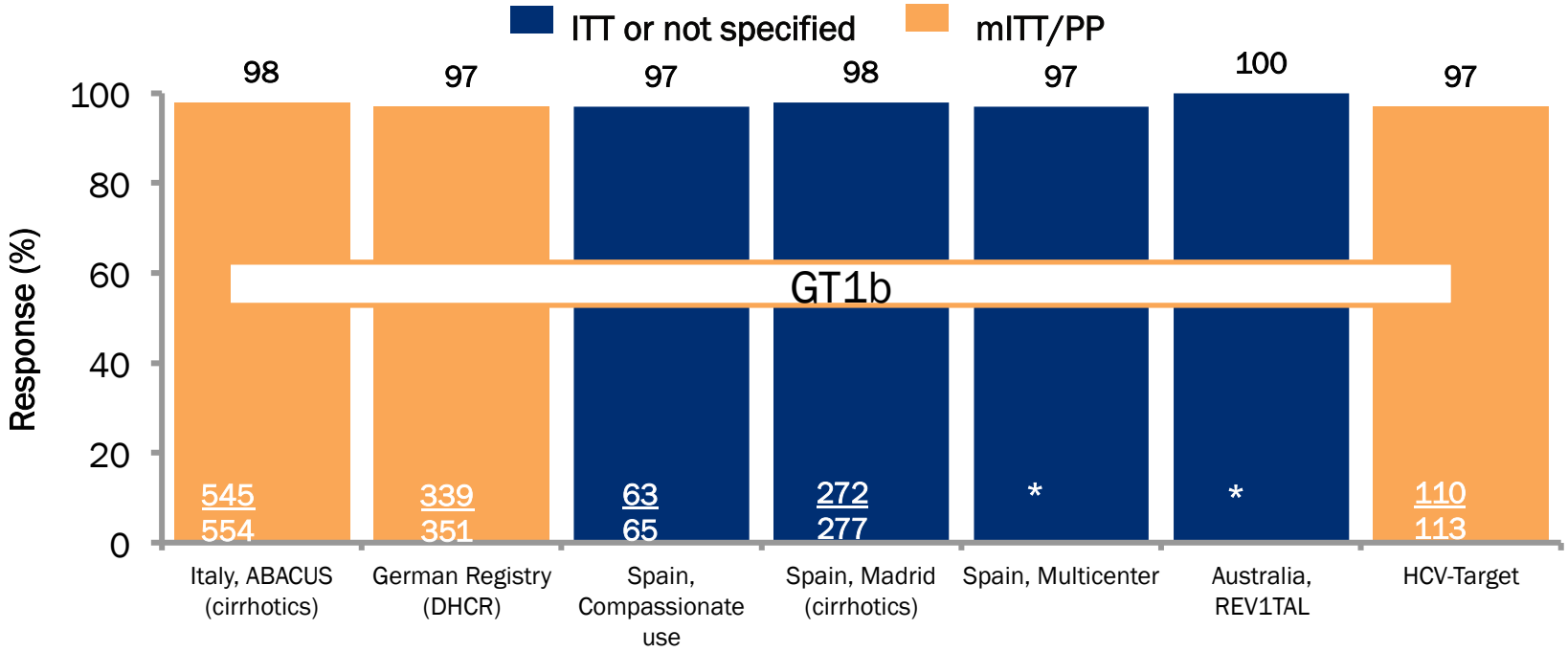
- However, early access to these innovative medications has been provided in Lithuania since December 2014, mostly for patients with advanced liver fibrosis, who were included in this real life experienced study

- Similar real-world studies were carried out in numerous countries and preliminary results became available during the European Association for the Study of the Liver (EASL) International Liver Congress in Barcelona in April 2016 (ILC-EASL 2016)

- In our study we have collected currently available data on the efficacy and safety of OBV/PTV/r ± DSV ± RBV in individual patients early access program in Lithuania and Latvia and in real-life practice in Lithuania from Dec 2014 till Sep 2016

Real-World Evidence in GT1b-infected Patients

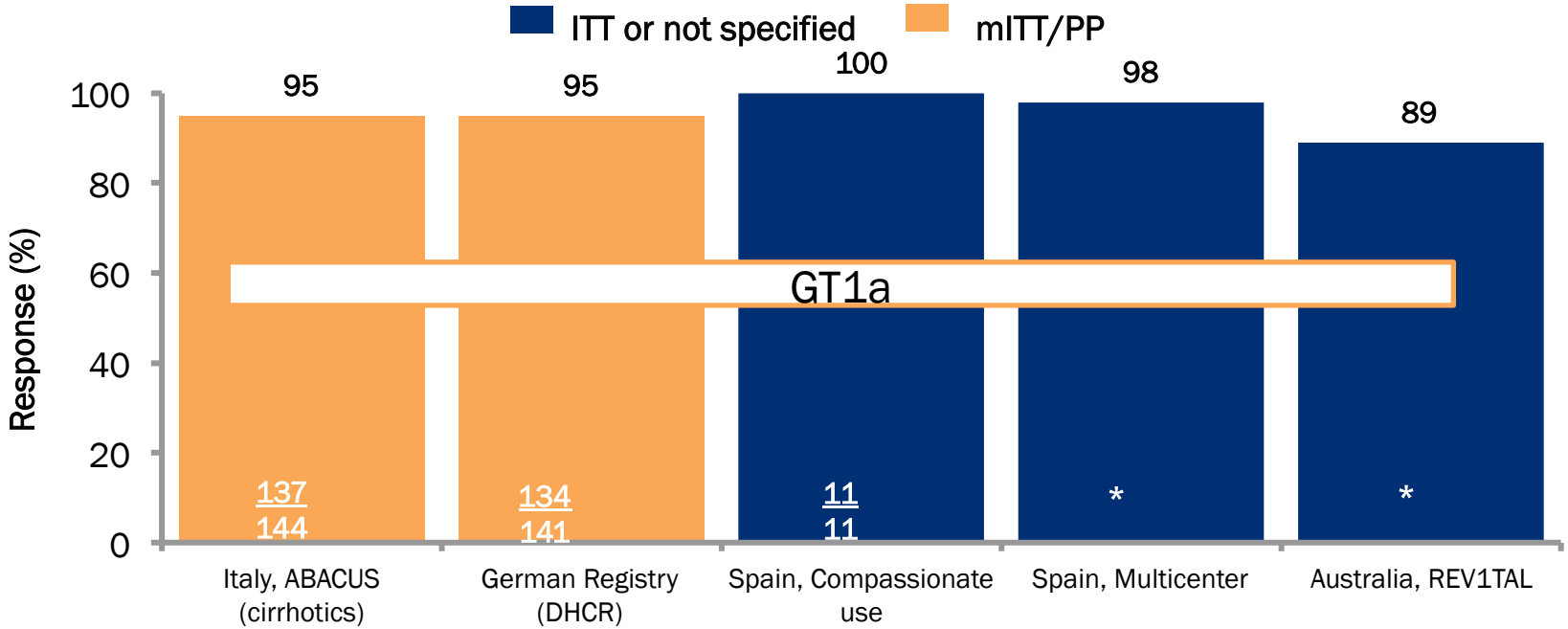
(Up to April 2016)



- Petta S, AISF Annual Meeting, Rome 17-19 February 2016; Hinrichsen H, *et al. EASL* 2016 (oral presentation);
- Perello C, *et al.* 41st Congreso Anual AEEH 2016 P#95;
- Rincon D, *et al.* 41st Congreso Anual AEEH 2016 (Oral presentation); Calleja J L. *et al, EASL 2016;* #LBP512 (poster presentation);
- Lubel JS, *et al. EASL* 2016 ; #SAT-182 (poster presentation); Manns M, *et al. APASL* 2016 (oral presentation).

- *Not reported;
- PP/mITT data presented where available.

Real-World Evidence in GT1a-infected Patients
(Up to April 2016)



- *Not reported;
- PP/mITT data presented where available.

- Petta S, AISF Annual Meeting, Rome 17-19 February 2016; Hinrichsen H, *et al. EASL* 2016 (oral presentation);
- Perello C, *et al.* 41st Congreso Anual AEEH 2016 P#95; Calleja J L. *et al, EASL 2016 ;* #LBP512 (poster presentation);
- Lubel JS, *et al. EASL* 2016 ; #SAT-182 (poster presentation).

The aim of the real-life experience study

The aim of this open-label, non-randomised, multicenter, international, real-life study was to evaluate the **efficacy** and **safety** of **OBV/PTV/r + DSV ± RBV** in **Lithuanian** and **Latvian** patient population:

- ***In HCV gen 1 infected treatment-naïve*** *and* ***treatment with PegIFN/RBV ± PI (boceprevir or telaprevir) experienced*** *patients with or without cirrhosis*

- ***In HCV gen 1 infected treatment-naïve*** *and* ***treatment with PegIFN/RBV ± PI (boceprevir or telaprevir) experienced*** *patients after liver transplantation*

Study Design (1)

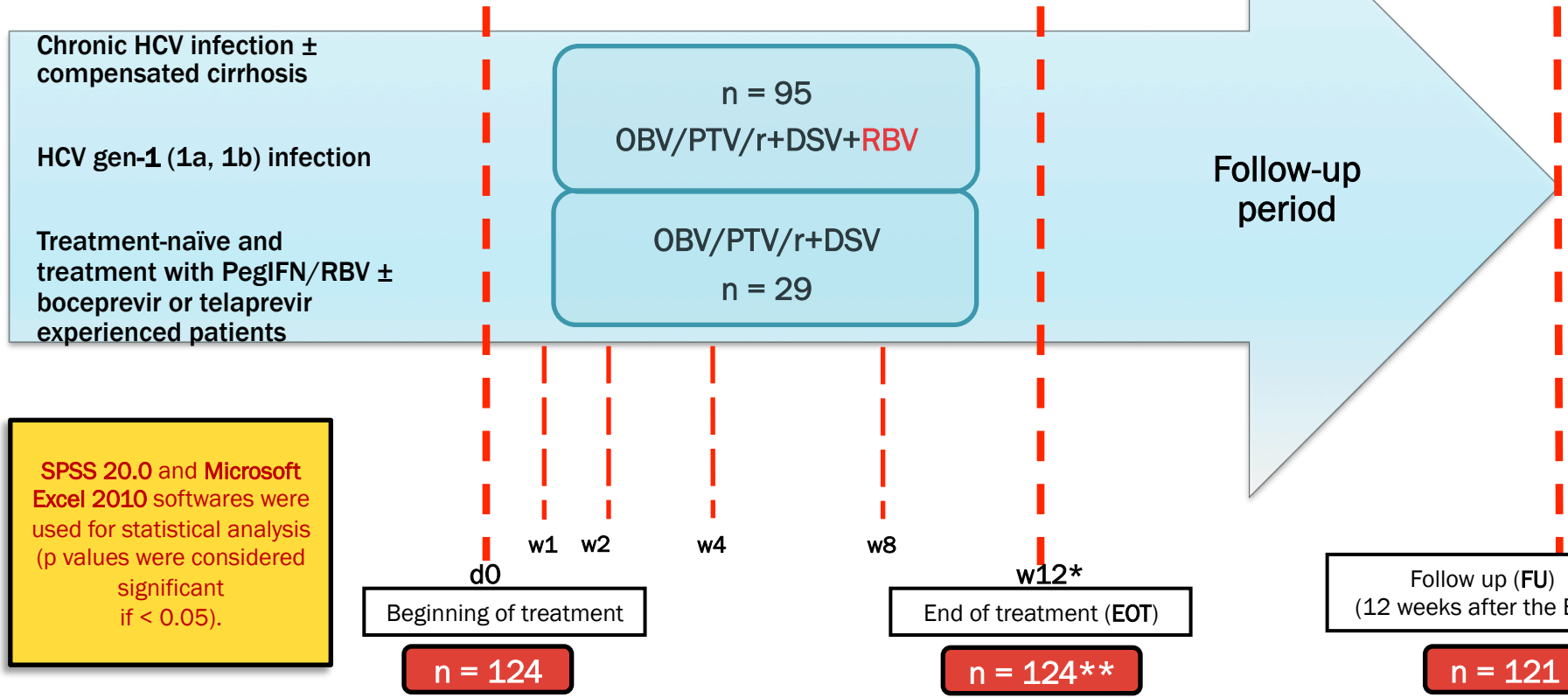


Riga Stradins University Department of Infectology and Dermatology; Infectology Center of Latvia, Department of Hepatology

Vilnius University Hospital Santariskiu klinikos
Centre of Infectious Diseases

Vilnius University Hospital Santariskiu klinikos
Centre of Hepatology, Gastroenterology and Dietetics

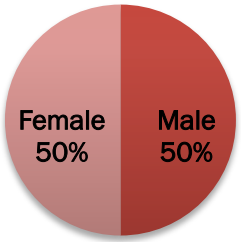
Study Design (2)

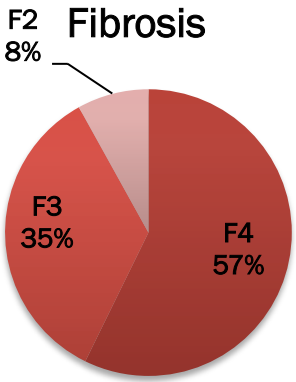


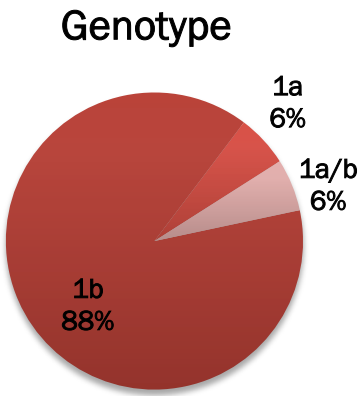
SPSS 20.0 and Microsoft Excel 2010 softwares were used for statistical analysis (p values were considered significant if < 0.05).

*the treatment was scheduled for 24 weeks in 4 patients (HCV subtype 1a infection+cirrhosis);
**the treatment was discontinued in 3 patients.

Baseline characteristics



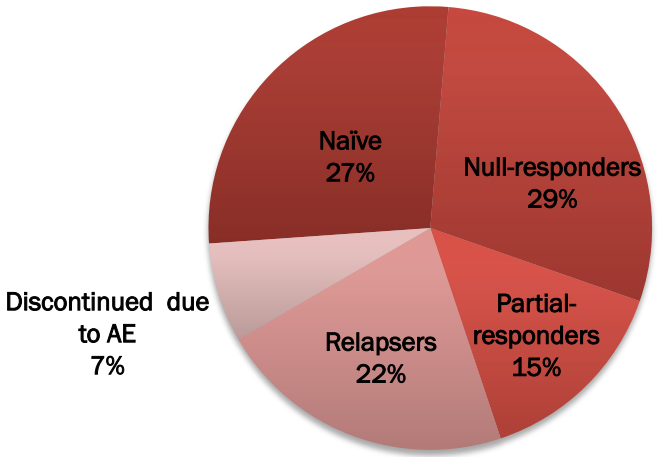




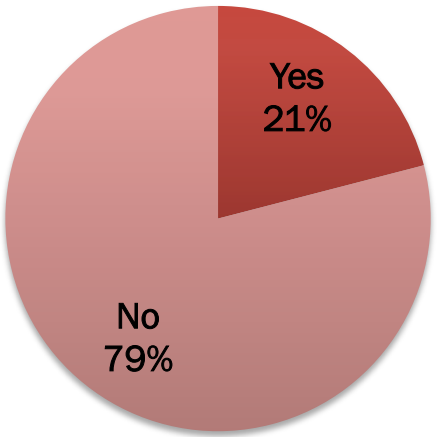
	Mean	±SD	Min	Max
Age, *years*	54,6	11	24	83
BMI, kg/m^2	28.14	4.9	18	42
HCV-RNA, *TV/mL*	5.0×10^6	$9,5 \times 10^6$	$8,7 \times 10^3$	$8,8 \times 10^7$
FibroScan, *kPa*	16.8	11.2	3.5	69.7
AFP, *kIU/L*	16.1	26.8	1	182
INR	1.1	0.2	0.88	2.5
Creatinin, *µmol/L*	70	11.8	25	102
Albumin, *g/L*	41.6	5.2	28	54
Bilirubin, *µmol/L*	18.3	8.8	4	61
ALT, *IU/L*	95.7	70.9	15.8	481.9
AST, *IU/L*	73.6	53.6	15	301.3
γ-GT, *IU/L*	98.9	119.9	15	756

Previous treatment with PegIFN/RBV ± boceprevir or telaprevir characteristics

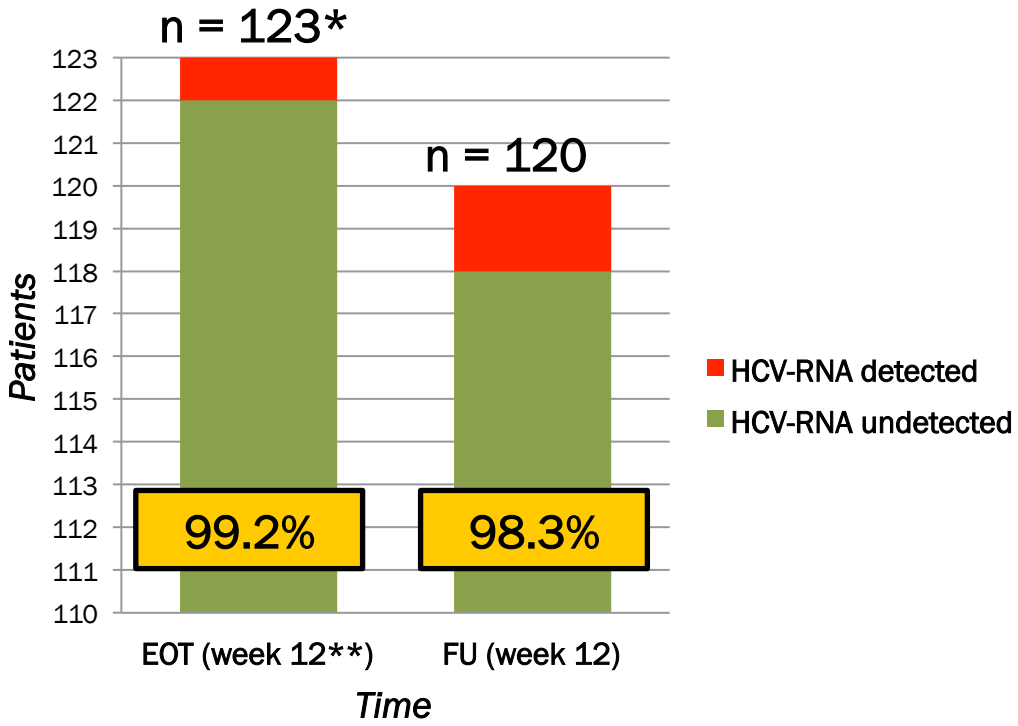
Treatment history



Triple therapy with Boceprevir or Telaprevir previously



Virologic Response



**the treatment was discontinued in 3 patients:*

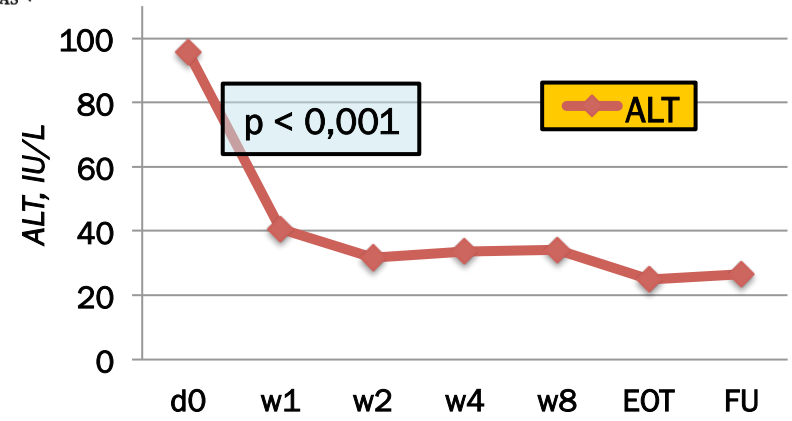
- *one patients' results were not assessed because of the treatment discontinuation on day 3*
- *2 patients had undetectable HCV-RNA at the EOT – all of them has already confirmed SVR12*

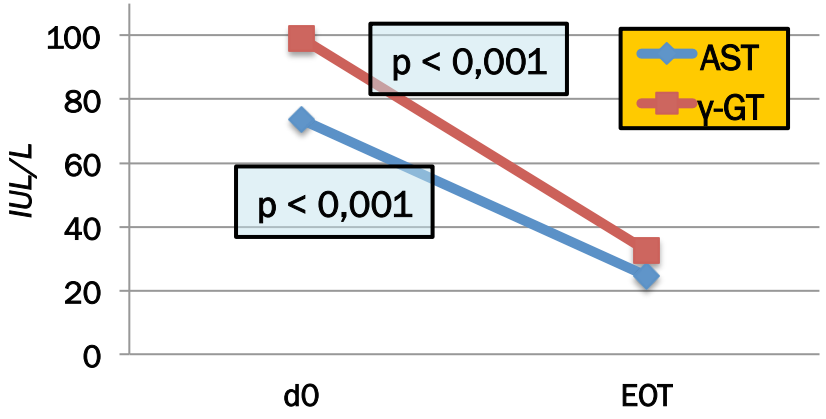
***the treatment was scheduled for 24 weeks in 4 patients (HCV subtype 1a infection+cirrhosis).*

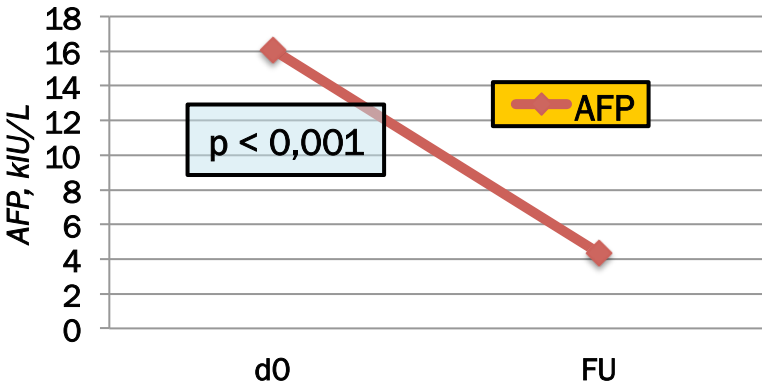
Virologic Failure

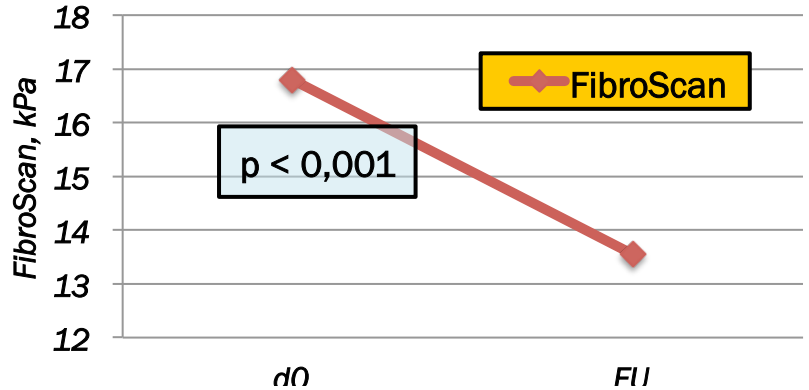
	Patient Nr. 1	*Patient Nr. 2*
Fibrosis	F4	F4
Genotype	1a/b	1b
Previous treatment	PegINF/RBV+Boceprevir – null-responder	PegINF/RBV – null-responder
OBV/PTV/r+DSV±RBV treatment duration	24 weeks	12 weeks
RBV	1200 mg (RBV dose was not reduced)	1200 mg (RBV dose was not reduced)
HCV-RNA (TV/ml): *day 0* *EOT* *FU*	 3490000 374000 –	 2610000 Undetected 3210000
Adverse events	Fatigue Bleeding from the nose	–

Laboratory and Instrumental Data (1)

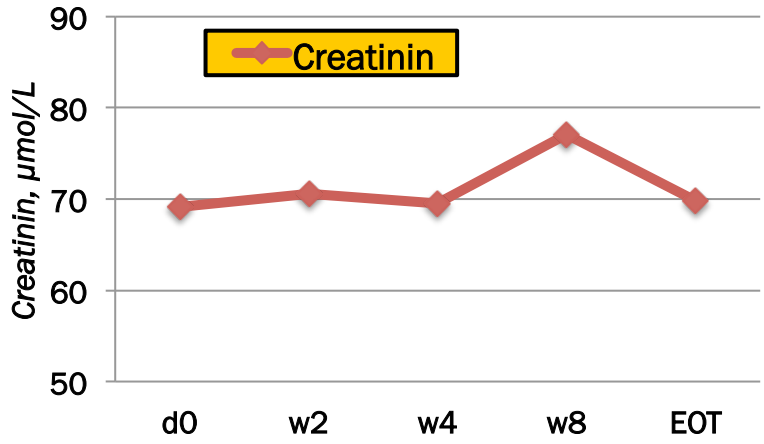


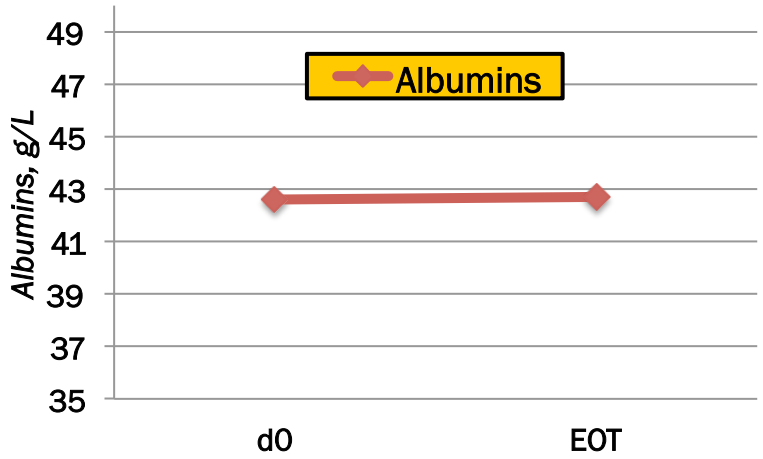


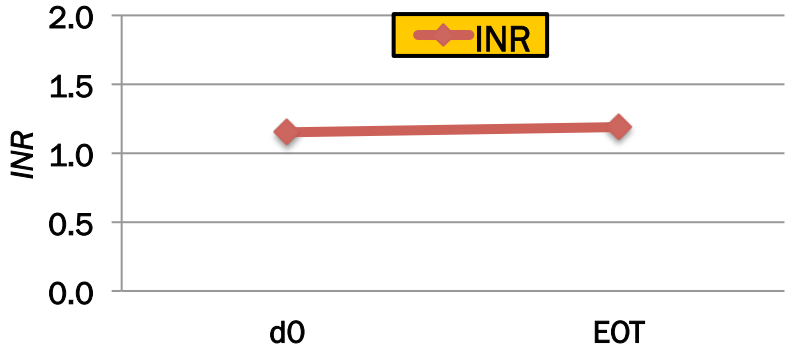


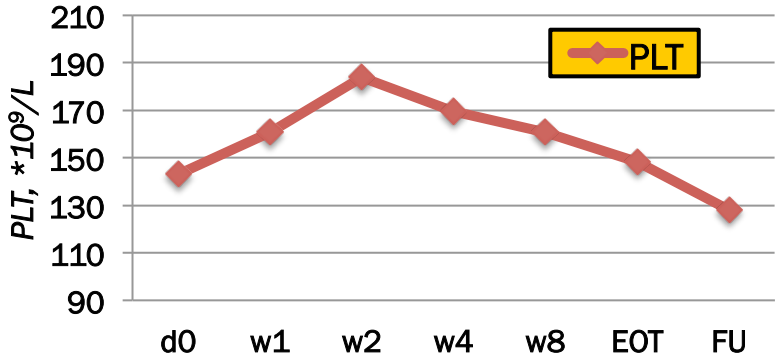


Laboratory and Instrumental Data (2)





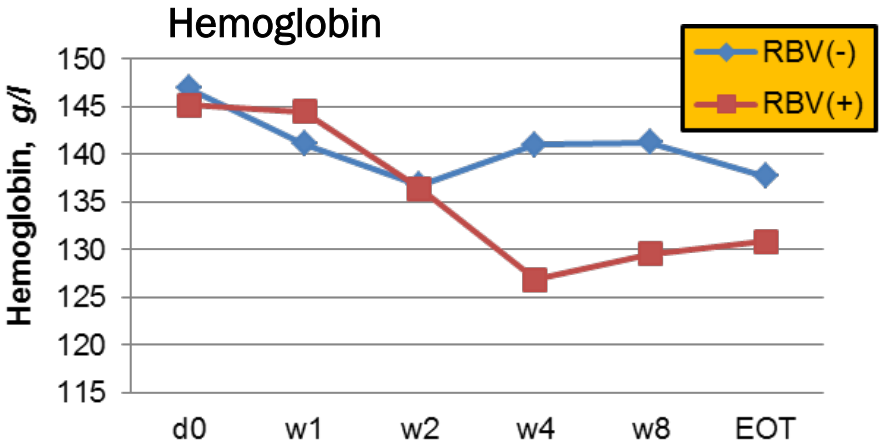


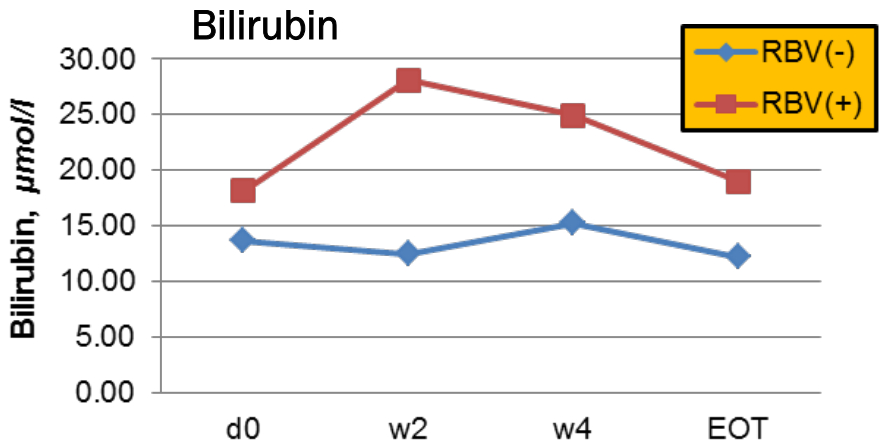


Laboratory and Instrumental Data (3)

	Mean		±SD		Min		Max	
	d0	*EOT/FU*	*d0*	*EOT/FU*	*d0*	*EOT/FU*	*d0*	*EOT/FU*
FibroScan, *kPa*	**16.8**	**13.5**	11.2	8.2	3.5	3.6	69.7	45.7
AFP, *kIU/L*	**16.1**	**4.3**	26.8	2.9	1	0.2	182	14
INR	**1.1**	**1.2**	0.2	0.2	0.88	0.89	2.5	2.3
Creatinin, *μmol/L*	**70**	**67.8**	11.8	10.7	49	45	102	94
Albumins, *g/L*	**41.6**	**42.7**	5.2	4.4	28	52.8	30.8	51.4
Bilirubin, *μmol/L*	**18.3**	**21.6**	8.8	10.7	6.1	8.5	42.4	56.1
PLT, *$*10^9$/L*	**143.2**	**128**	70.3	61	14	40	391	338
Hb, *g/L*	**145.5**	**131.5**	16.4	17.2	102	74	180	171
ALT, *IU/L*	**95.7**	**26.7**	70.9	19.6	15.8	3.8	481.9	26.7
AST, *IU/L*	**73.6**	**24.4**	53.6	9.3	15.4	11	301.3	72
γ-GT, *IU/L*	**98.9**	**32.6**	119.9	3.4	15	12	756	251

RBV (+) versus RBV (-): on-treatment laboratory abnormalities





	RBV (+) n = 95	RBV (-) n = 29
Hemoglobin: 80-100 g/L <80 g/L	6 (6.3%) 5 (5.3%) 1 (1.1%)	0 0 0
Bilirubin: ↑3-10xULN	10 (10.5%)	0
ALT: ↑5xULN	5 (5.3%)	0

Adverse Events

	RBV (+) n = 95	RBV (-) n = 29	All n = 124
Any adverse events	47 (49.5%)	6 (20.7%)	53 (42.7%)
Asthenia	29 (30.5%)	3 (10.3%)	32 (25.8%)
Fatigue	18 (18.9%)	2 (6.9%)	20 (16.1%)
Itchy skin	16 (16.8%)	0	16 (12.9%)
Dyspepsia	13 (13.7%)	1 (3.4%)	14 (11.3%)
Insomnia	10 (10.5%)	2 (6.9%)	12 (9.7%)
Joint, lower extremities pain	9 (9.5%)	0	9 (7.3%)
Headache	8 (8.4%)	1 (3.4%)	9 (7.3%)
Mood disoders	8 (8.4%)	0	8 (6.5%)
Rash	5 (5.3%)	1 (3.4%)	6 (4.8%)
Dizziness	5 (5.3%)	0	5 (4.0%)

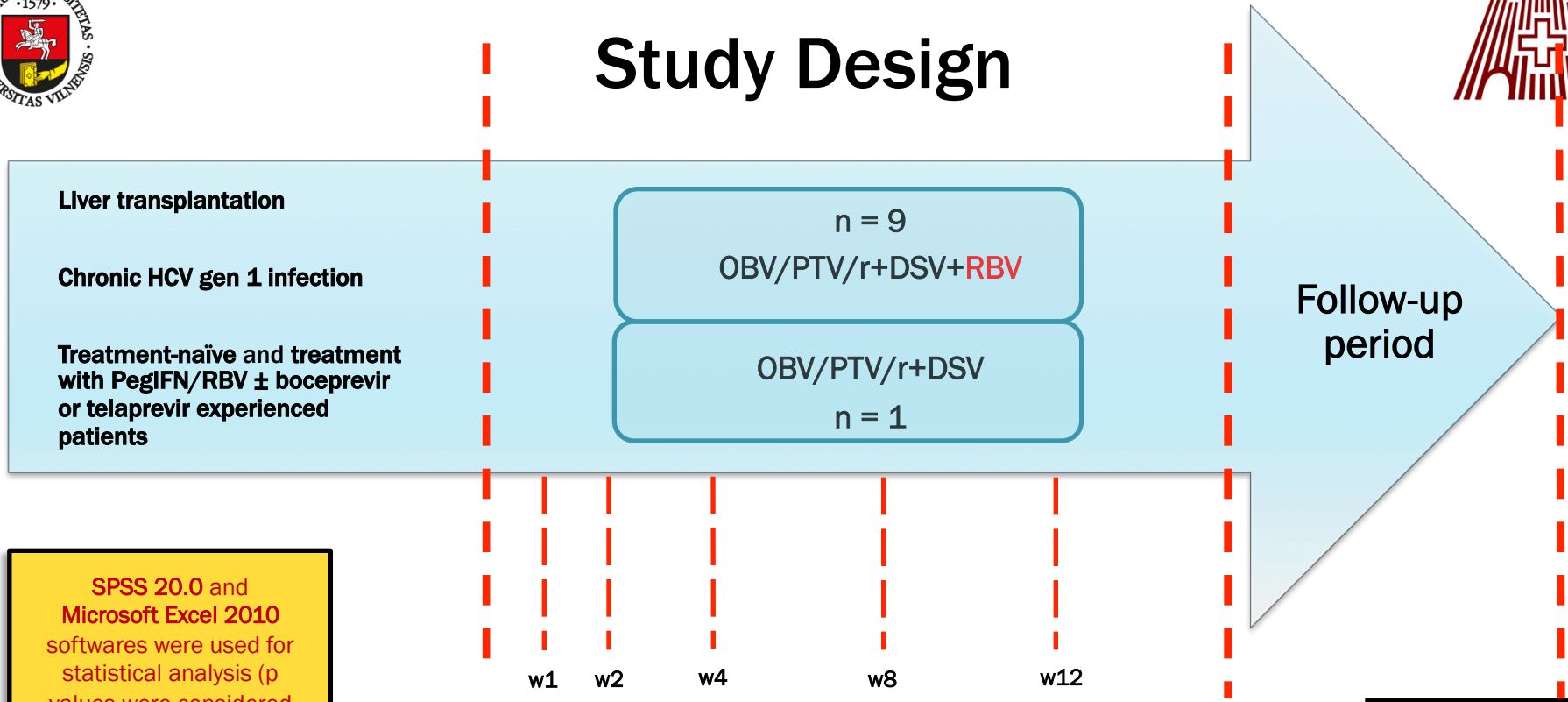
RBV dose was reduced in 27 (28.4%) pacients
RBV was discontinued in 10 (10.5%) pacients

The treatment of OBV/PTV/r+DSV +RBV was discontinued in 3 patients due to:

1. Depression (*week 5 – achieved SVR12*);
2. Elevation of ALT and AST (*week 9 – achieved SVR12*);
3. Severe exacerbation of **psoriasis** (*day 3*).

The **efficacy** and **safety** of **OBV/PTV/r + DSV ± RBV in HCV gen 1 infected treatment-naïve** and **treatment experienced** patients after liver transplantation

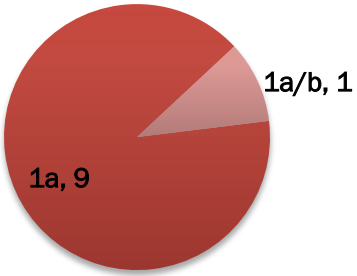
Study Design



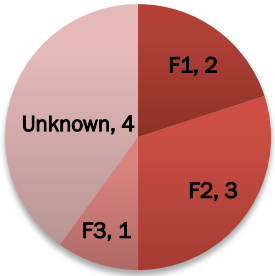
SPSS 20.0 and Microsoft Excel 2010 softwares were used for statistical analysis (p values were considered significant if < 0.05).

Baseline characteristics

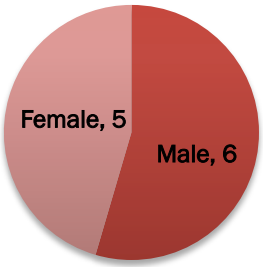
Genotype



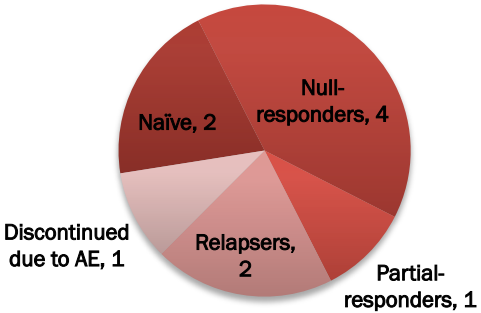
Fibrosis



Sex

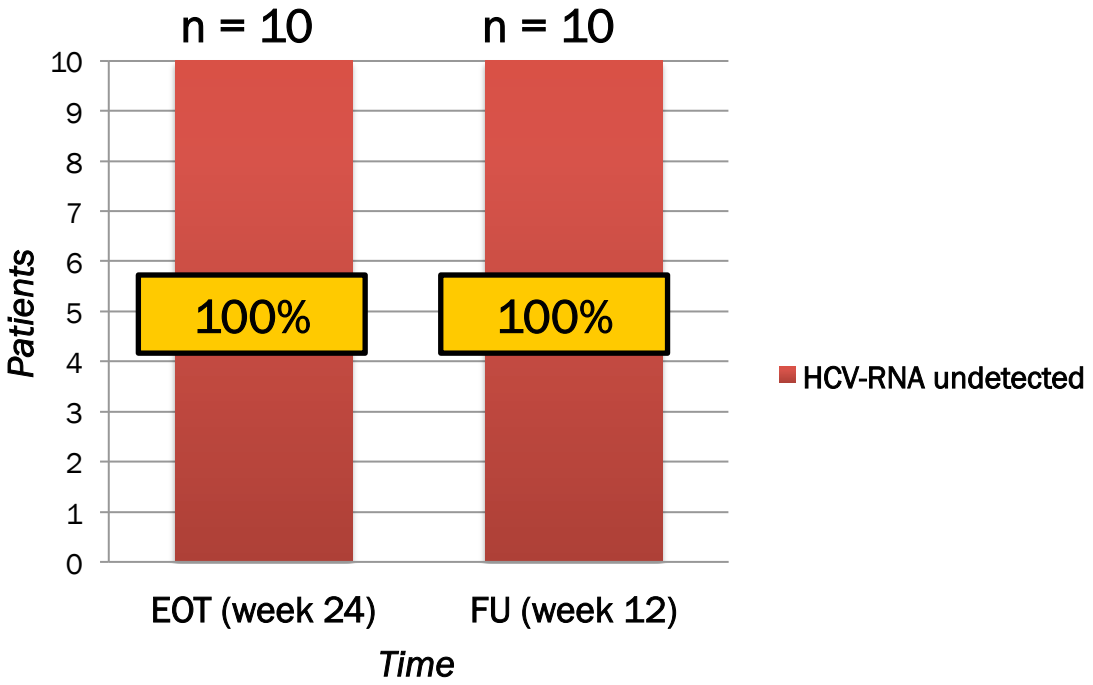


Treatment history

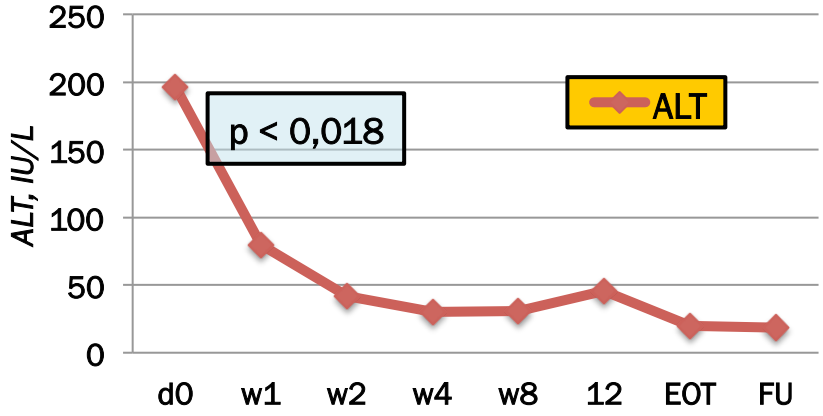


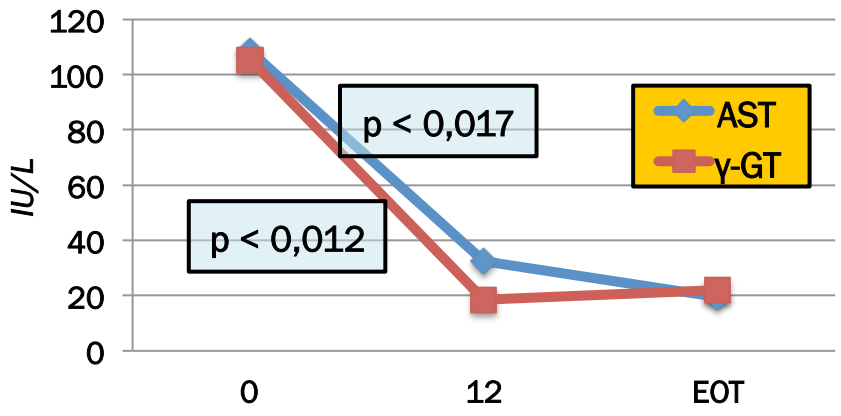
	Mean	±SD	Min	Max
Age, *years*	50.7	8.0	42	63
BMI, *kg/m²*	25.6	4.2	20	31
HCV-RNA, *TV/ml*	8.7×10^6	1.5×10^6	1.6×10^3	5.1×10^7
AFP, *kIU/L*	21	36.3	0.88	116
INR	1.09	0.2	0.92	1.48
Creatinin, *µmol/L*	101.5	60.6	63	271
Albumin, *g/L*	35.3	5.3	27.7	42.8
Bilirubin, *µmol/L*	31.8	35	8	127.4
ALT, *IU/L*	196.4	287.2	13	863
AST, *IU/L*	108.4	95.8	19	301
γ-GT, *IU/L*	135.3	157.2	19	447

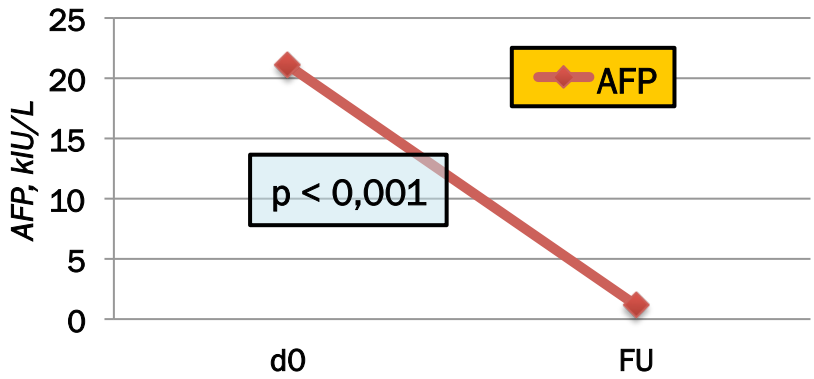
Virologic Response

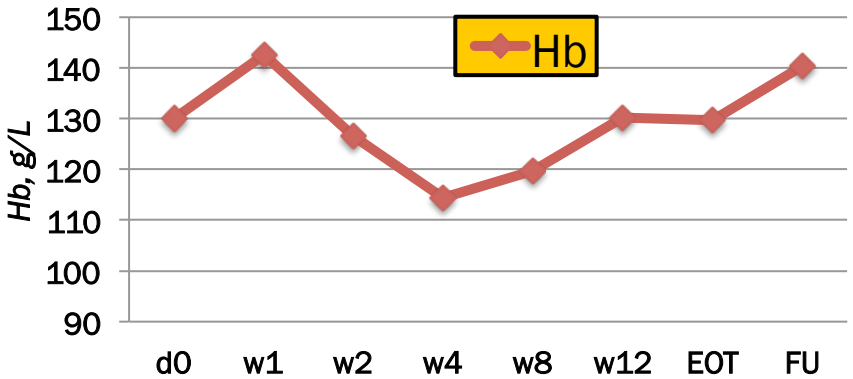


Laboratory and Instrumental Data (1)

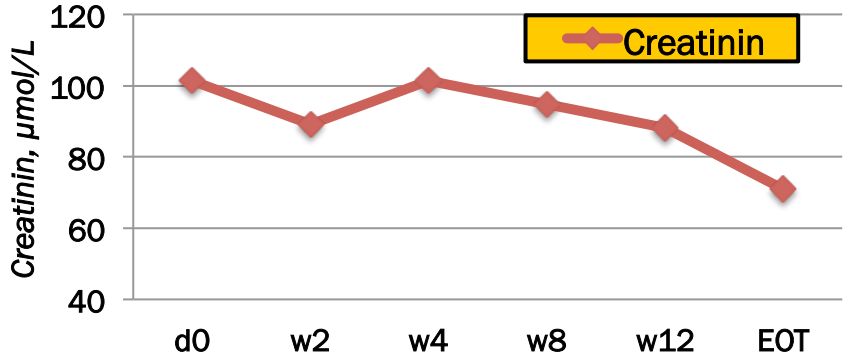


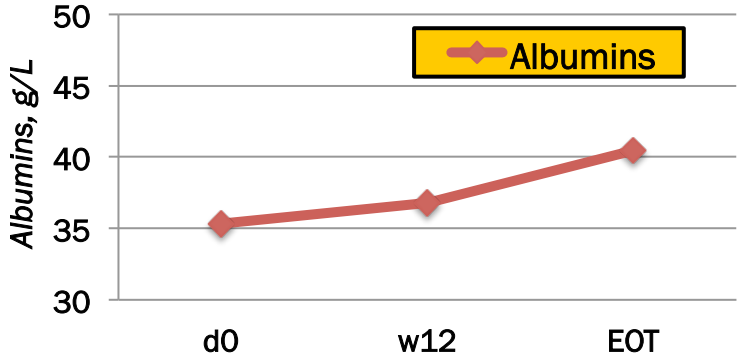


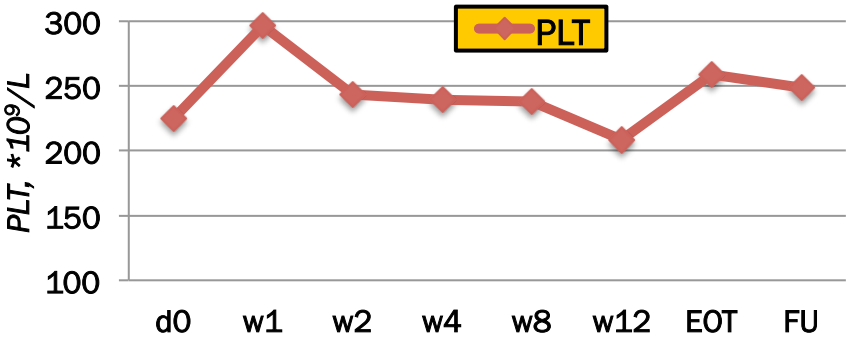


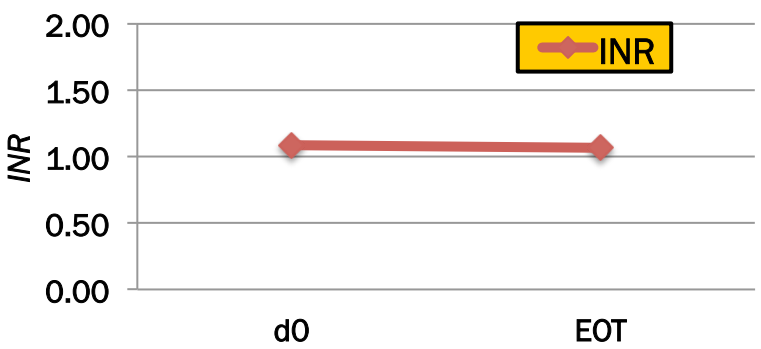


Laboratory and Instrumental Data (2)









Laboratory and Instrumental Data (3)

	Mean		±SD		Min		Max	
	d0	*EOT/FU*	*d0*	*EOT/FU*	*d0*	*EOT/FU*	*d0*	*EOT/FU*
AFP, *kIU/L*	**21**	**1.2**	36.3	1	0.88	0.21	116	3.04
INR	**1.1**	**1.1**	0.2	0.1	0.92	0.91	1.48	1.19
Creatinin, *µmol/L*	**101.5**	**81.9**	60.6	12.3	63	70	271	92
Albumin, *g/L*	**35.3**	**40.5**	5.3	4.4	27.7	31.1	42.8	44.5
Bilirubin, *µmol/L*	**31.8**	**11.9**	35	5.5	8	5	127.4	22.6
PLT, *$*10^9$/L*	**225.4**	**248.8**	95.4	111.6	77	103	366	407
Hb, *g/L*	**130**	**140.3**	20.5	26.8	93	82	163	175
ALT, *IU/L*	**196.4**	**18.4**	287.2	4.1	13	11	863	26
AST, *IU/L*	**108.4**	**19.4**	95.8	2.7	19	14	301	23
γ-GT, *IU/L*	**135.3**	**22.1**	157.2	17.3	19	12	447	64

Adverse Events

	n = 10
Any adverse events	8 (80%)
Asthenia	4 (40%)
Fatigue	4 (40%)
Dyspepsia	2 (20%)
Itchy skin	1 (10%)
Rash	1 (10%)
Joint, lower extremities pain	1 (10%)
Headache	1 (10%)
Cough	1 (10%)
Chest discomfort	1 (10%)
Hemoglobin: *80-100 g/L* *<80 g/L*	8 (80%) 5 (50%) 3 (30%)
Bilirubin ↑3-10xULN	1 (10%)

RBV dose was reduced in 3 patients

RBV was discontinued in 2 patients

No patients discontinued the treatment of OBV/ PTV/r + DSV ± RBV

Conclusions

- The treatment regimen of OBV/PTV/r + DSV ± RBV was highly effective in CHC patient population (SVR12 - 98.3% - 2 treatment failures out of 120 patients) and in liver transplanted patients with recurrent HCV infection (SVR12 - 100%)
- The treatment regimen was generally well tolerated and resulted in low rates of discontinuation due to adverse events
- The most common adverse event – anemia was manageable by RBV discontinuation or dose reduction, which did not impact SVR12 rate
- There were no graft loses or acute graft rejections observed during treatment and at follow up period in this real-life cohort
- These findings confirm safety and efficacy results previously demonstrated in clinical trial for this treatment regimen

The highest number of enrolled patients was in the multicenter Spanish study presented at the ILC-EASL 2016 by Calleja et al.

- The analysis covered 1422 gen 1 (mostly gen 1b) infected patients:
  - 49% - were treatment experienced
  - 47% - were cirrhotics
- The SVR12 rate in this population was 97%
- In a multivariate analysis, a decreased probability of achieving SVR was associated with low baseline albumin
- No statistical differences were associated with genotype, age or stage of fibrosis
- Serious adverse events occurred in 84 patients (5.4%) and 1.8% discontinued early
- The most frequent SAE was anemia, associated with RBV (24 patients, 1.5%), skin lesions (11 patients, 0.7%) and infections (8 patients, 0.5%)
- Occurrence of SAEs was related to MELD score, high transient elastography values and advanced age

Calleja J, Rincon D, Ruiz-Antoran B, et al. Effectiveness and safety of ombitasvir and paritaprevir, ritonavir and dasabuvir patients with genotype 1 chronic hepatitis C virus infection: results from Spanish real world cohort. J Hepatol 2016; 64 (Suppl 2): LBP-512.

AMBER study RWE in Polish Patients with HCV (GT1)

- Final data of AMBER study confirmed the SVR12 rate of 99% in a population of 209 patients consisting mostly of gen 1b infected, cirrhotics and non-responders to previous therapy, including failures of triple regimens
- SAEs were observed in 8 patients (3.8%), and 5 patients (2.4%) discontinued treatment due to AE
- Risk of on-treatment decompensation was associated with a history of decompensation before the treatment and baseline hepatic function
- Adverse events were observed in 151 patients (72%), and they were mostly related to RBV

Flisiak R, Janczewska E, Wawrzynowicz-Syczewska M, et al. Real- world efficacy and safety of ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin in HCV infection: AMBER study. Hepatology 2016, submitted for publication.

Results of other real world studies

- Almost exactly the same efficacy (SVR rate 99%) and safety results were achieved by Zuckerman et al. in a population of mostly cirrhotic Israeli patients infected with genotype 1 (subgenotyping not available)

- In a relatively small but important study Hunyady et al. demonstrated that failure of the interferon-based triple regimen containing the first generation protease inhibitor boceprevir or telaprevir did not affect the high efficacy of OBV/PTV/r ± DSV ± RBV (SVR rate 98%)

Zuckerman E. The real-world Israeli experience treating chronic hepatitis C, genotype 1 patients with advanced fibrosis with paritaprevir/ritonavir/ombitasvir, dasabuvir with or without ribavirin: a large multi-center cohort. J Hepatol 2016; 64 (Suppl 2): PS004.
Hunyady B, Abonyi M, Gervain J, et al. Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir + Rybaviryn (3D+Rybaviryn) treatment of hepatitis C (HCV) genotype 1 (GT1) infected patients (pts) after failure to previous first generation protease- inhibitor (PI) therapy. Interim analysis. J Hepatol 2016; 64 (Suppl 2): SAT-120.

Real-world experience with OBV/PTV/r + DSV ± RBV in HCV infection: meta-analysis results

- Treatment of 5726 patients, including 2390 cirrhotics, with OBV/PTV/r + DSV ± RBV in real-word studies with currently available data was safe and therapeutic success was achieved by 5548 patients, so the SVR rate was 97% in both the general population and in patients with liver cirrhosis
- The discontinuation rate due to AE did not exceed 3%, and SAEs were observed in 2-5.4% of patients
- Anemia and hyperbilirubinemia occurred usually in cirrhotics receiving RBV
- However, due to the exclusion of RBV from the regimen for gen 1b patients, according to the most recent label, this problem should disappear in a large majority of European patients

Pogorzelska J, Flisiak R. Real-world experience **with ombitasvir/paritaprevir boosted with ritonavir and possibly combined with dasabuvir and ribavirin in HCV infection.** Clinical and Experimental Hepatology, 2016; 2: 34–37

Real-world experience with OBV/PTV/r + DSV ± RBV in HCV infection: conclusion

- According to results of randomized clinical trials, the OBV/PTV/r + DSV ± RBV regimen has been found to fulfill the promise of SVR rates close to 100%

- However, the most important requirement is confirmation of such high efficacy in real-world experience in the large, mixed population of patients previously considered as “difficult to treat”

Pogorzelska J, Flisiak R. Real-world experience **with ombitasvir/paritaprevir boosted with ritonavir and possibly combined with dasabuvir and ribavirin in HCV infection.** Clinical and Experimental Hepatology, 2016; 2: 34–37

Direct acting antivirals

DAAs Approved in 2014

- SOFOSBUVIR (All genotypes)
- SIMEPREVIR (Gen 1, 4)
- DACLATASVIR (All genotypes)

DAAs Approved in 2015

- SOFOSBUVIR/LEDIPASVIR (Gen 1, 4, 5, 6)
- OMBITASVIR/PARITAPREVIR/RITONAVIR (Gen 1, 4) + DASABUVIR (Gen 1)

DAAs Approved in 2016

- SOFOSBUVIR/VELPATASVIR (All genotypes)
- GRAZOPREVIR/ELBASVIR (Gen 1, 4)

EASL Recommendations on Treatment of CHC 2016

INF Free Treatment options - 2016

Combination regimen	GT1	GT2	GT3	GT4	GT5-6
SOF + RBV	No	Suboptimal	Suboptimal	No	No
SOF/LDV ± RBV	Yes	No	No	Yes	Yes
SOF/VEL ± RBV	Yes	Yes	Yes	Yes	Yes
OBV/PTV/r + DSV (3D) ± RBV	Yes	No	No	No	No
OBV/PTV/r (2D) ± RBV	No	No	No	Yes	No
GZR/EBR ± RBV	Yes	No	No	Yes	No
SOF + DCV ± RBV	Yes	Yes	Yes	Yes	Yes
SOF + SIM ± RBV	Suboptimal	No	No	Yes	No

EASL Recommendations on Treatment of Hepatitis C 2016. Journal of Hepatology 2016


www.photocamera.lt





