REPORTING ON AASLD 2017

ADVANCES IN CHRONIC HEPATITIS C: MANAGEMENT AND TREATMENT

COMPREHENSIVE EXPERT REVIEW AND DISCUSSION OF KEY PRESENTATIONS

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NEXT GENERATIONS DAAS – WHY DISCONTINUED

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RUZASVIR AND UPRIFOSBUVIR

REPORTING ON AASLD 2017

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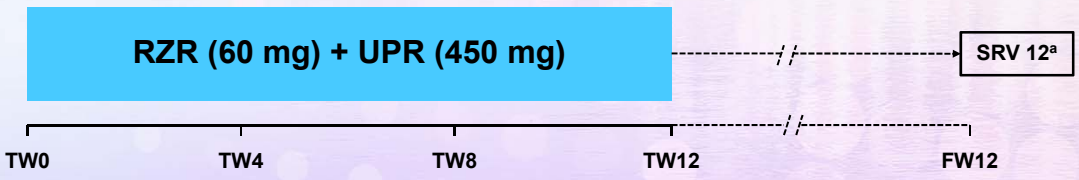
C-BREEZE 1: EFFICACY AND SAFETY OF RUZASVIR 60 MG PLUS UPRIFOSBUVIR 450 MG FOR 12 WEEKS IN ADULTS WITH CHRONIC HEPATITIS C VIRUS (HCV) GENOTYPE (GT)1, 2, 3, 4, OR 6 INFECTION
Lawitz E, et al – Abstract 1175

C-BREEZE 2: EFFICACY AND SAFETY OF A TWO-DRUG DIRECT-ACTING ANTIVIRAL AGENT (DAA) REGIMEN RUZASVIR 180 MG AND UPRIFOSBUVIR 450 MG FOR 12 WEEKS IN ADULTS WITH CHRONIC HEPATITIS C VIRUS (HCV) GENOTYPE (GT)1, 2, 3, 4, OR 6
Lawitz E, et al – Abstract 61

C-BREEZE-1: STUDY DESIGN

- Phase 2, 12-week, open-label, clinical trial
- All participants received RZR 60mg + UPR 450mg once daily as separate medications, administered under fasting conditions
- 160 patients were enrolled (GT1a, n=54); GT1b, n=15; GT2, n=29; GT3, n=39; GT4, n=20; GT5, n=0; GT6, n=3), of whom 50 (31%) had cirrhosis



FW, follow-up week; SVR12, sustained virologic response at 12 weeks; TW, treatment week.
a HCV RNA <15 IU/mL (primary endpoint).

Lawitz E, et al. 68th AASLD; Washington, DC; October 20-24, 2017; Abst. 1175.

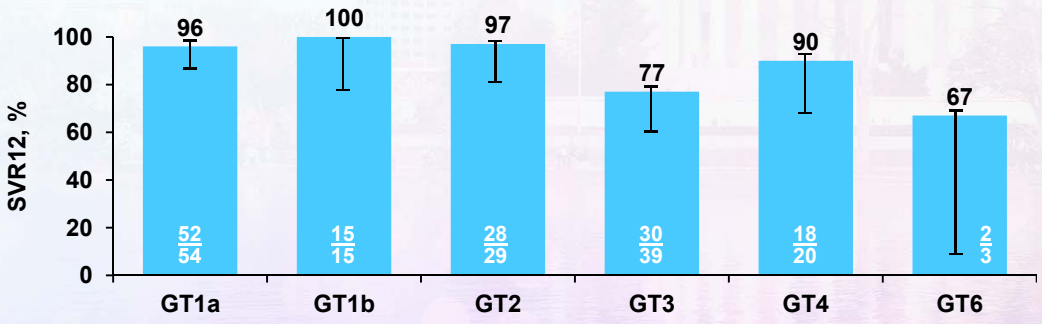
C-BREEZE-1 STUDY: BASELINE DEMOGRAPHICS BY GENOTYPE

Characteristic	GT1a (n = 54)	GT1b (n = 15)	GT2 (n = 29)	GT3 (n = 39)	GT4 (n = 20)	GT6 (n = 3)	All Participants[a] (N = 160)
Male, n (%)	32 (59.3)	4 (26.7)	19 (65.5)	21 (53.8)	15 (75.0)	2 (66.7)	93 (58.1)
Age, years, mean (SD)	49.3 (10.0)	51.7 (13.1)	57.2 (6.8)	48.7 (10.3)	56.5 (8.5)	61.3 (1.5)	51.9 (10.3)
Race, n (%)							
White	51 (94.4)	13 (86.7)	27 (93.1)	39 (100.0)	19 (95.0)	0 (0)	149 (93.1)
Asian	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (100.0)	3 (1.9)
Black	3 (5.6)	1 (6.7)	2 (6.9)	0 (0)	1 (5.0)	0 (0)	7 (4.4)
Multiple	0 (0)	1 (6.7)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.6)
Ethnicity, n (%)							
Hispanic/Latino	30 (55.6)	10 (66.7)	16 (55.2)	25 (64.1)	7 (35.0)	0 (0)	88 (55.0)
Not Hispanic or Latino	24 (44.4)	5 (33.3)	13 (44.8)	14 (35.9)	13 (65.0)	3 (100.0)	72 (45.0)
Cirrhotic, n (%)	17 (31.5)	5 (33.3)	7 (24.1)	10 (25.6)	10 (50.0)	1 (33.3)	50 (31.3)
HIV/HCV co-infected, n (%)	0 (0)	0 (0)	0 (0)	1 (2.6)	1 (5.0)	0 (0)	2 (1.3)
Baseline viral load, n (%)							
>800,000 IU/mL	37 (68.5)	8 (53.3)	21 (72.4)	18 (46.2)	13 (65.0)	3 (100.0)	100 (62.5)
>2,000,000 IU/mL	27 (50.0)	4 (26.7)	18 (62.1)	14 (35.9)	7 (35.0)	2 (66.7)	72 (45)
Treatment history, n (%)							
Treatment-naïve	45 (83.3)	15 (100.0)	27 (93.1)	34 (87.2)	19 (95.0)	3 (100.0)	143 (89.4)
Treatment-experienced	9 (16.7)	0 (0)	2 (6.9)	5 (12.8)	1 (5.0)	0 (0)	17 (10.6)

SD, standard deviation.
a All participants were enrolled from sites in North America.

Lawitz E, et al. 68th AASLD; Washington, DC; October 20-24, 2017; Abst. 1175.

C-BREEZE-1 STUDY: SVR12 RESULTS IN ALL PARTICIPANTS (FULL ANALYSIS SET POPULATION)



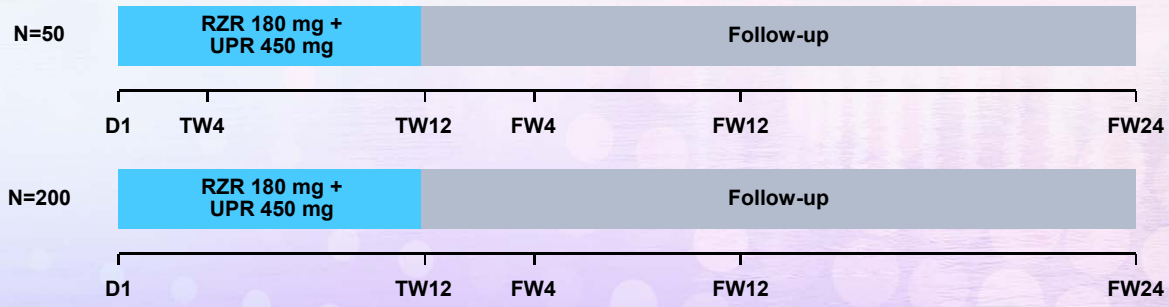
	GT1a	GT1b	GT2	GT3	GT4	GT6
Virologic failure	2	0	0	9	1	1
Discontinuation due to DRAE	0	0	0	0	1[a]	0
Administrative failure	0	0	1[b]	0	0	0

DRAE, drug-related adverse event.
a One GT4-infected participant discounted after day 7 due to DRAEs of worsening hypertension, intermittent chest pressure, urinary tract infection, and hypoesthesia.
b One GT2-infected participant discontinued afterTW4 due to drug abuse relapse and noncompliance with treatment.

Lawitz E, et al. 68th AASLD; Washington, DC; October 20-24, 2017; Abst. 1175.

C-BREEZE-2: STUDY DESIGN

- This is an open-label, single-arm trial of combination regimen of 12 weeks of RZR 180 mg and UPR 450 mg administered as single entities
- 2 enrollment cohorts: initial enrollment of 50 participant, pause to assess safety, and if no safety criteria are met, continue enrollment for a total n=250



TE, treatment-experienced; TN, treatment-naive, TW, treatment week.

Lawitz E, et al. 68th AASLD; Washington, DC; October 20-24, 2017; Abst. 61.

C-BREEZE-2 STUDY: BASELINE DEMOGRAPHICS

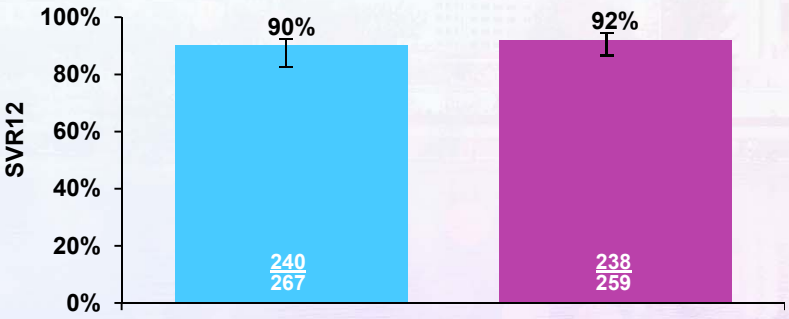
Total Population (N=282)	n (%)
Male	156 (55)
Average mean age, years	49.5
Race	
White	221 (78)
Asian	29 (10)
Black	22 (8)
Cirrhotic (F4)	58 (21)
Baseline VL >2,000,000 IU/mL	157 (56)
Interferon treatment-experienced	45 (16)
HBcAb positive	104 (37)

Total Population (N=282)	n (%)
Genotype	
1a	48 (17)
1b	30 (11)
2	47 (17)
3	61 (22)
4	56 (21)
5	18 (6)
6	22 (8)

HBcAb, hepatitis B core antibody; VL, viral load.

Lawitz E, et al. 68th AASLD; Washington, DC; October 20-24, 2017; Abst. 61.

C-BREEZE-2 STUDY: OVERALL EFFICACY



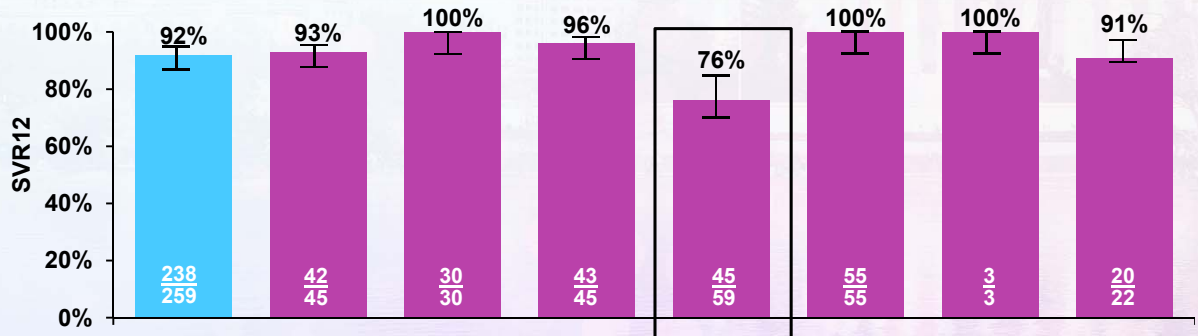
Overall efficacy of 92% in the mFAS
19 virologic failures;
14 of whom were GT3

	Overall FAS	Overall mFAS	Notes
Excluded	0	8	7 discontinued; 1 LTFU
Relapses	19	19	14 GT3, 3 GT1, 1 GT2, 1 GT6
Discontinuation due to DRAEs	2	2	Anxiety and nausea; insomnia and fatigue

LTFU, lost to follow-up.

Lawitz E, et al. 68th AASLD; Washington, DC; October 20-24, 2017; Abst. 61.

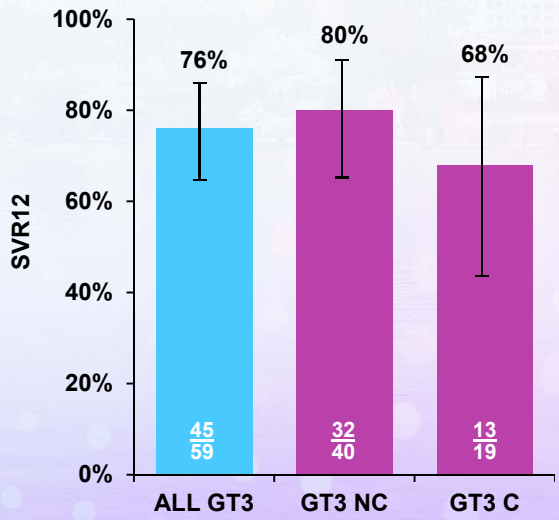
C-BREEZE-2 STUDY: EFFICACY - MFAS



	Overall	GT1a	GT1b	GT2	GT3	GT4	GT5	GT6
Excluded	8	3	0	2	2	1	0	0
VFs								
Relapses	19	3	0	1	14	0	0	1
D/c due to DRAEs	2	0	0	1	0	0	0	1

Lawitz E, et al. 68th AASLD; Washington, DC; October 20-24, 2017; Abst. 61.

C-BREEZE-2 STUDY: GT 3



Overall efficacy of 76%

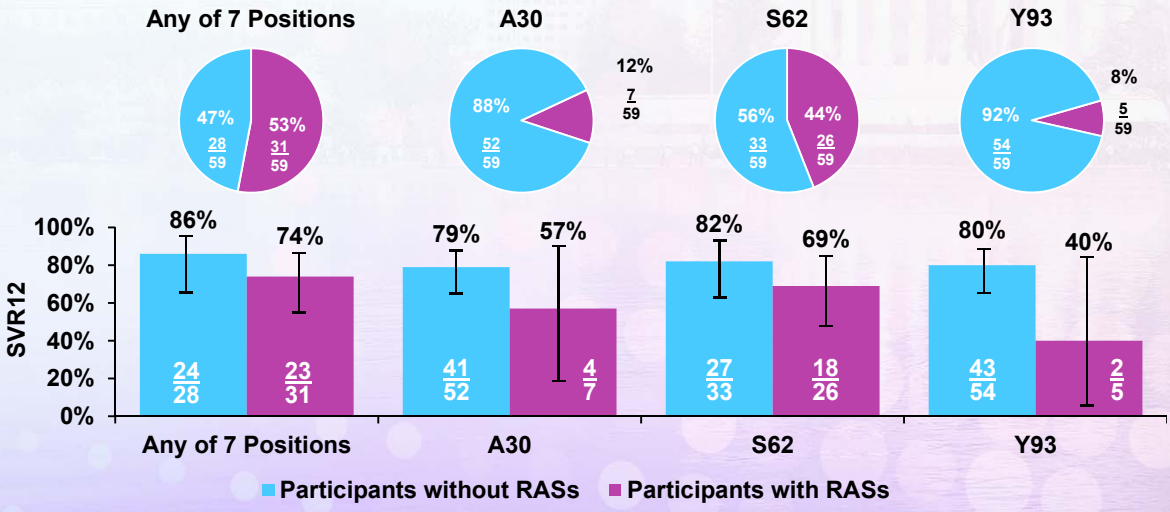
- Eighty percent in noncirrhotics
- Sixty-eight percent in cirrhotics

Failures

- Fourteen virologic failures, all relapses
  - Eight noncirrhotics
  - Six cirrhotics

Lawitz E, et al. 68th AASLD; Washington, DC; October 20-24, 2017; Abst. 61.

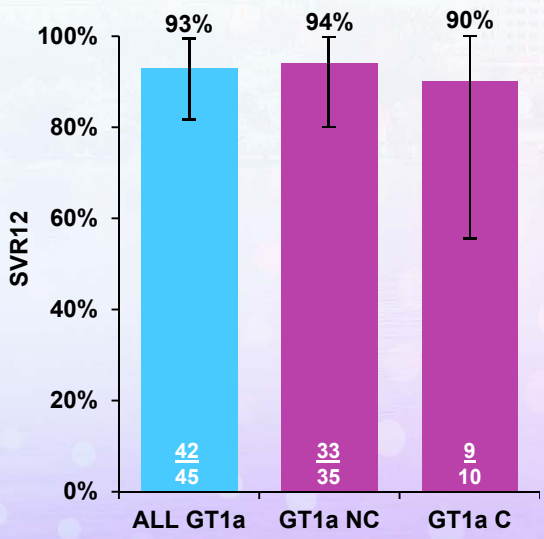
C-BREEZE-2 STUDY: LOWER EFFICACY IN GT3-INFECTED PARTICIPANTS WITH AND WITHOUT BASELINE RASS†



†RASs detected by next-generation sequencing with 15% sensitivity. NS5A RAS was any change from wild type at 7 positions: 24, 28, 30, 31, 58, 62, or 93. There were no RASs detected at 24, 28, 31, or 58.

Lawitz E, et al. 68th AASLD; Washington, DC; October 20-24, 2017; Abst. 61.

C-BREEZE-2 STUDY: GT 1



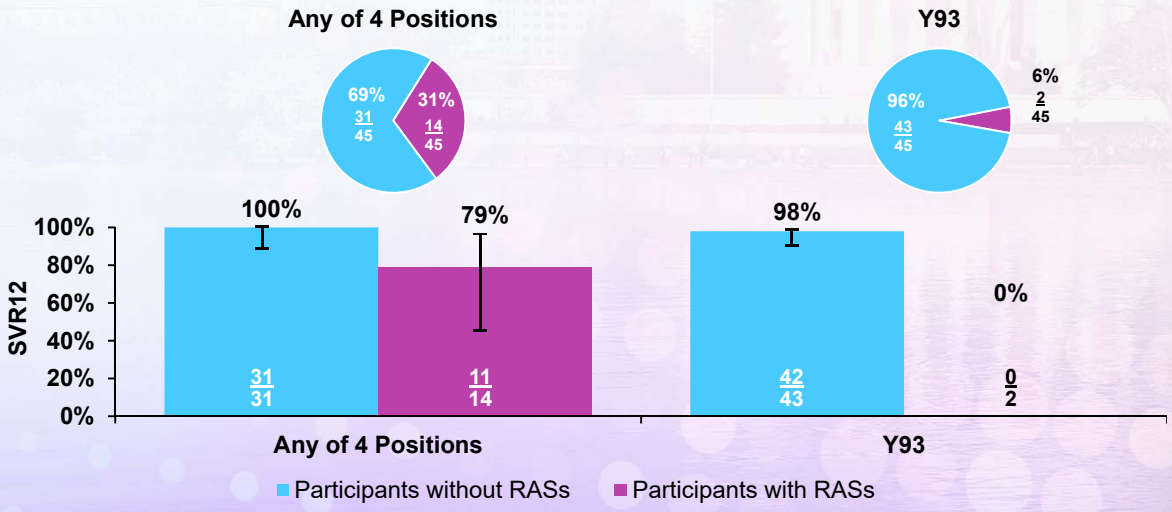
Overall efficacy of 93%

Failures

- Three virologic failures, all relapses
  - Two GT1a
  - One GT1l (categorized as GT1a for mFAS)

Lawitz E, et al. 68th AASLD; Washington, DC; October 20-24, 2017; Abst. 61.

C-BREEZE-2 STUDY: LOWER EFFICACY IN ONLY THOSE GT1A-INFECTED PARTICIPANTS WITH Y93 BASELINE RAS†



†RASs detected by next-generation sequencing with 15% sensitivity. NS5A RAS was any change from wild type at 4 positions (28, 30, 31, or 93).

Lawitz E, et al. 68th AASLD; Washington, DC; October 20-24, 2017; Abst. 61.

C-BREEZE-2 STUDY: SAFETY - ADVERSE EVENT SUMMARY

- 282 participants were in the safety population

	N (%)
≥1 AEs	172 (61.0)
DRAEs	94 (33.3)
Fatigue	22 (7.8)
Headache	21 (7.4)
Discontinued due to DRAE	2 (0.7)
SAEs	7 (2.5)
Discontinued die to SAE	0

Lawitz E, et al. 68th AASLD; Washington, DC; October 20-24, 2017; Abst. 61.

AL-335 + ODALASVIR + SIMEPREVIR

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ADVANCES IN CHRONIC HEPATITIS C: MANAGEMENT AND TREATMENT

COMPREHENSIVE EXPERT REVIEW AND DISCUSSION OF KEY PRESENTATIONS

EVALUATION OF THE EFFICACY AND TOLERABILITY OF JNJ-4178 (AL-335, ODALASVIR, AND SIMEPREVIR) IN HEPATITIS C VIRUS-INFECTED PATIENTS WITHOUT CIRRHOSIS: THE PHASE IIB OMEGA-1 STUDY

Stefan Zeuzem, Stefan Bourgeois, Susan Greenbloom, Maria Buti, Alessio Aghemo, Ewa Janczewska, Seng Gee Lim, Chris Corbett, Wouter Willems, Leen Vijgen, Sivi Ouwerkerk-Mahadevan, Maria Beumont, Rekha Sinha, Ronald Kalmeijer, Michael Biermer

Abstract 65

OMEGA-1 STUDY: COMPONENTS OF JNJ-4178

AL – 335
800 mg QD
Novel uridine-based nucleotide analogue HCV NS5B polymerase inhibitor

Nanomolar potency against GT1-6

+

Odalasvir (ACH-3102)
25 mg QD
Novel HCV NS5A inhibitor

Picomolar potency against GT1, 2, 4, 5 & 6

Nanomolar potency against GT3

+

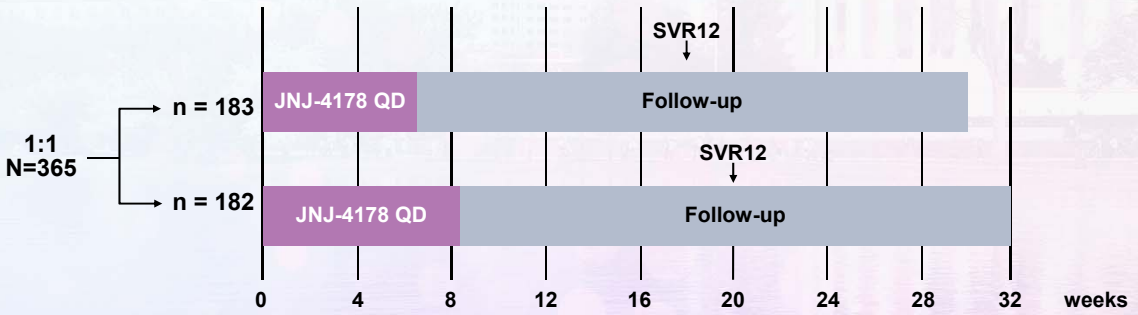
Simeprevir
75 mg QD

HCV NS3/4A protease inhibitor

Nanomolar potency against GT1, 2, 4, 5 & 6

Zeuzem S, et al. 68th AASLD; Washington, DC; October 20-24, 2017; Abst. 65.

OMEGA-1 STUDY: PHASE IIB STUDY IN GT1-, 2-, 4-, 5- & 6-INFECTED PATIENTS WITHOUT CIRRHOSIS (F0–F3)



- Stratified by HCV GT1a/2 versus other GTs and by prior treatment history
  - Non-inferiority testing performed against a historical control rate of 98% (12 weeks of sofosbuvir / velpatasvir; ASTRAL studies)[1-3]

1. Curry MP et al. N Eng J Med 2015;373:2618–2628; 2. Feld JJ et al. N Eng J Med 2015;373:2599–2607; 3. Foster GR et al. N Eng J Med 2015;373:2608–2617

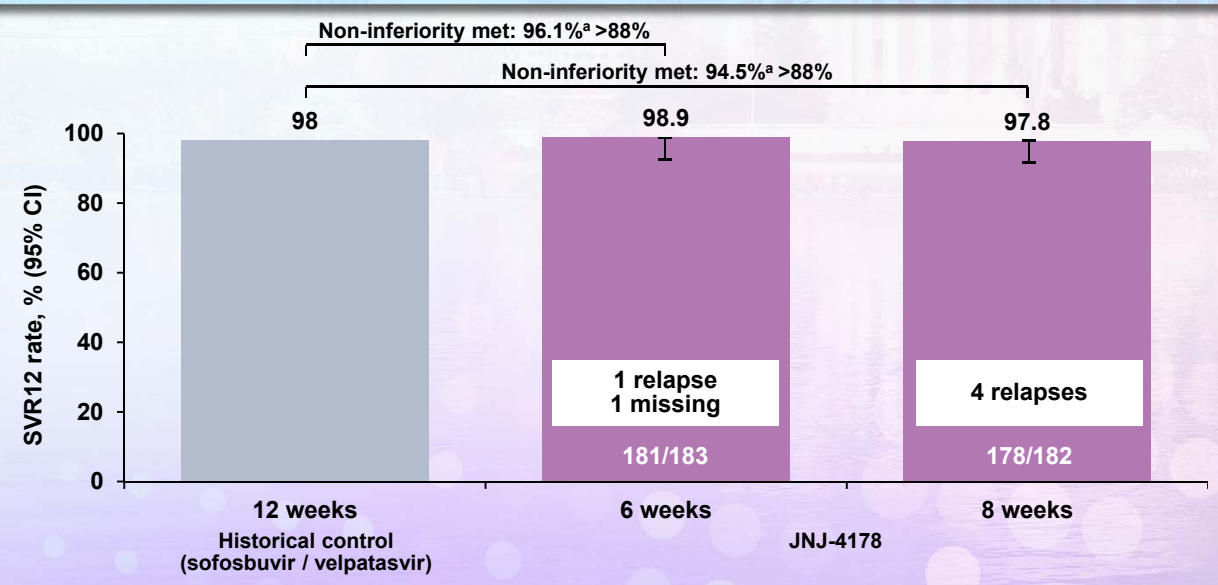
OMEGA-1 STUDY: BASELINE DEMOGRAPHIC AND DISEASE CHARACTERISTICS

	6 weeks (n=183)	8 weeks (n=182)
Age, years, median (range)	48 (19-69)	49 (18-70)
Male, n (%)	95 (52)	88 (48)
White, n (%)	161 (88)	153 (84)
BMI, kg/m^2, median (range)	25 (18-35)	25 (18-35)
HCV Gt, n 1a/1b 2/4/5/6	60/74 18/28/3/0	47/81[a] 27/24/2/0
HCV RNA, $\log_{10}$ IU/mL, median (range)	6.20 (3.1-7.1)	6.33 (3.8-7.3)
Fibrosis stage, n F0-F2 F3	177 6	174 8
IL28B non-CC, n (%)	131[b] (73)	139 (76)
Treatment history, n (%) Treatment-naïve (peg)IFN±RBV-experienced	145 (79) 38 (21)	144 (79) 38 (21)

HCV geno/subtype is NS5B sequence-based or, if not available, LiPAv2.0-based
a One additional patient had HCV GT1e infection
b Data were available for 180 patients

Zeuzem S, et al. 68th AASLD; Washington, DC; October 20-24, 2017; Abst. 65.

OMEGA-1 STUDY: SVR12 (ITT POPULATION)



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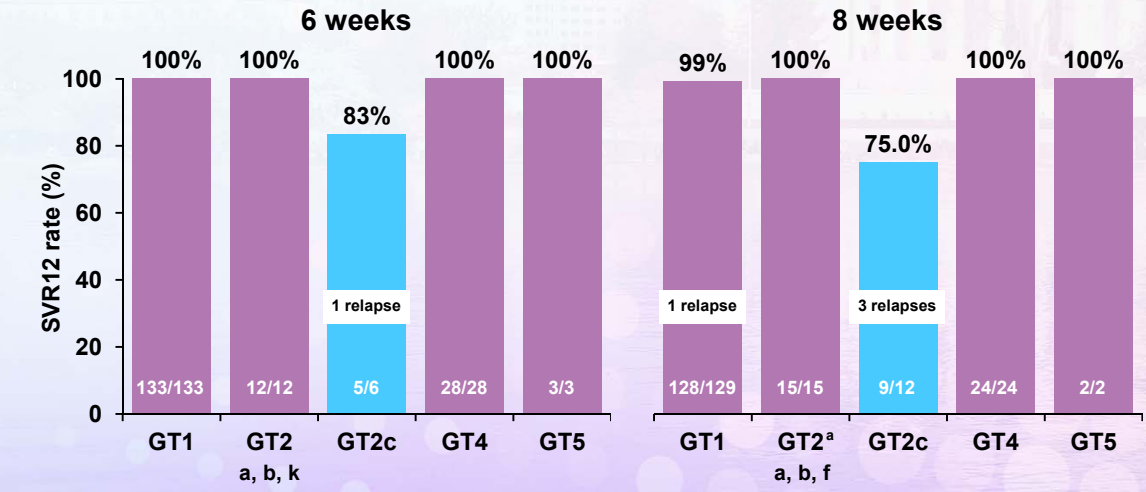
OMEGA-1 STUDY: SVR12 BY GENO/SUBTYPE (EXCLUDING NON-VIROLOGIC FAILURES)

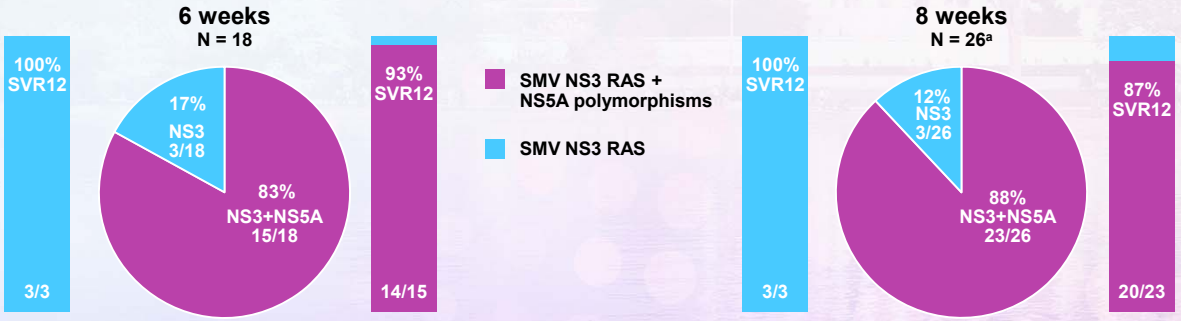


One patient in the 6-week group had non-virologic failure (defined as viral relapse and/or on-treatment virologic failure)
a Genotype2 subtype not defined for 1 patient HCV geno/subtype is NS5B sequence-based or, if not available, LIPA v2.0-based

Zeuzem S, et al. 68th AASLD; Washington, DC; October 20-24, 2017; Abst. 65.

OMEGA-1 STUDY: GT2-INFECTED PATIENTS - PREVALENCE AND IMPACT OF BASELINE SMV NS3 RASS AND NS5A POLYMORPHISMS

- All GT2 infected patients had baseline SMV NS3 RASs and NS5A polymorphisms



- All GT2-infected patients who relapsed had at baseline an NS5A F28C polymorphism in addition to SMV RASs; not all patients with F28C had a relapse (7/11 SVR12)

The SMV RASs observed in the GT2-infected patients were K122R and/or I132L
Based on next-generation sequencing using a 15% read frequency cut-off, and considering NS5A positions 28, 29, 30, 31, 32, 58, 92, 93,and NS3 SMV RASs (ie amino acid substitutions with a fold change in SMV EC50>2 when tested in a transient replicon assay in GT1a or GT1b)
a Including1 GT2-infected patient without sequencing information

Zeuzem S, et al. 68th AASLD; Washington, DC; October 20-24, 2017; Abst. 65.

OMEGA-1 STUDY: ADVERSE EVENTS OF INTREST

	6 weeks (n=183)	8 weeks (n=182)
Pruritus, n (%)	11 (6)	9 (5)
Rash (any type), n (%)	6 (3)	7 (4)
Photosensitivity conditions, n (%)	0	1 (0.5)
Cardiac events[a], n (%)	6 (3.3)	8 (4.4)
Blood creatine phosphokinase increased	0	2 (1.1)
Dyspnea	1 (0.5)	2 (1.1)
Electrocardiogram PR prolongation	0	1 (0.5)
Edema peripheral	1 (0.5)	0
Palpitations	3 (1.6)	3 (1.6)
Peripheral swelling	1 (0.5)	1 (0.5)
Tachycardia	0	1 (0.5)

- Isolated asymptomatic increases in PR interval (>200 ms) were seen in a low number of patients (n=8, 2.2%) and were not considered clinically relevant

Zeuzem S, et al. 68th AASLD; Washington, DC; October 20-24, 2017; Abst. 65.