SUPPLEMENT TO:

Six-week Combination Directly Acting Anti-HCV Therapy Induces Moderate Rates of Sustained Virologic Response in Patients with Advanced Liver Disease

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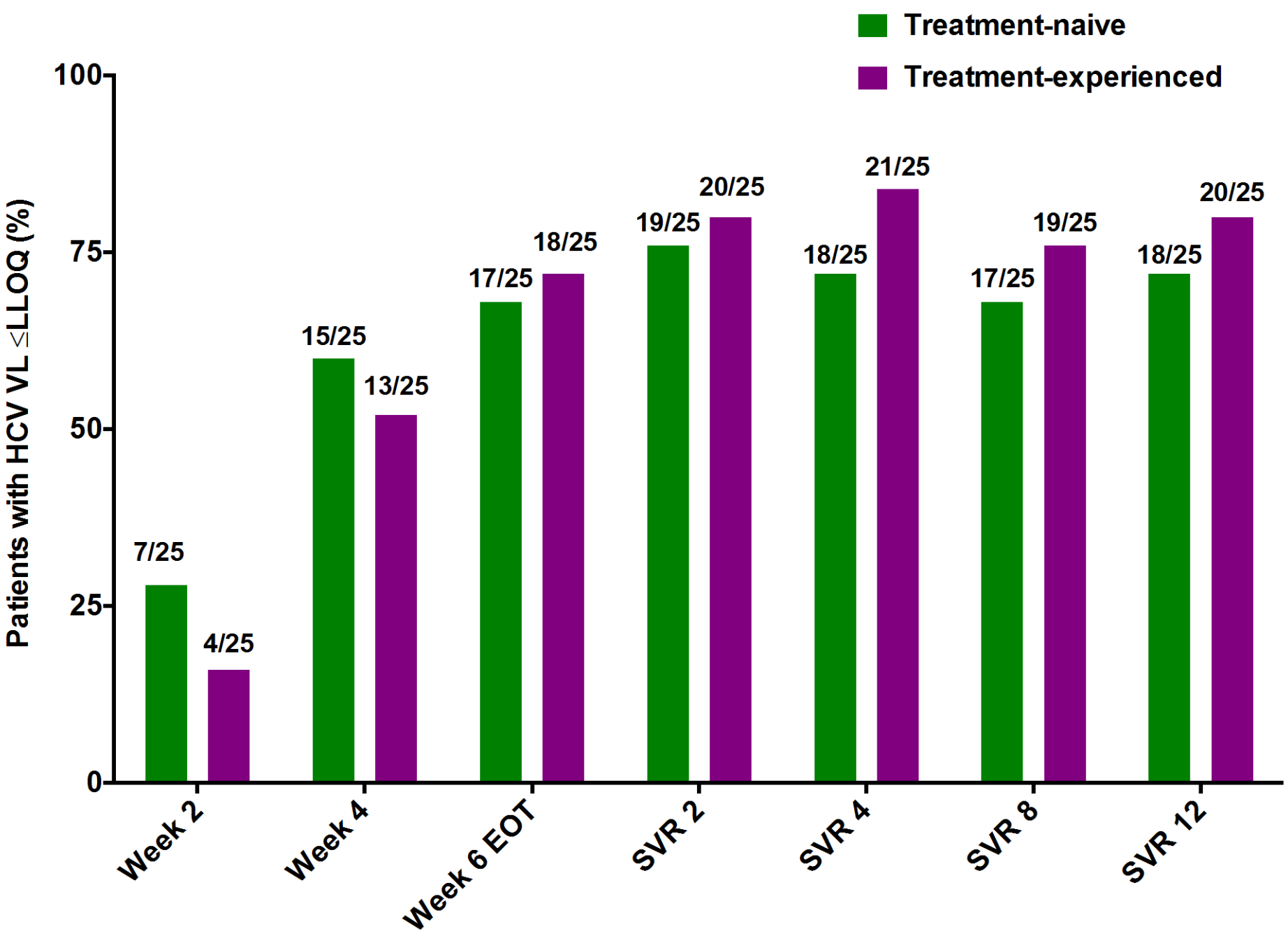
Treatment-naive
Treatment-experienced
Patients with HCV VL <LLOQ (%)
100
75
50
25
0
7/25
4/25
15/25
13/25
17/25
18/25
19/25
20/25
18/25
21/25
17/25
19/25
18/25
20/25
Week 2
Week 4
Week 6 EOT
SVR 2
SVR 4
SVR 8
SVR 12

(A) Treatment Naïve Patients with Advanced Liver Disease Treated with Sofosbuvir + Ledipasvir + GS-9451

Patient		NS3/4 Baseline		NS3/4 at Relapse		NS5A Baseline		NS5A at Relapse		NS5B Baseline		NS5B at Relapse	
	GT	Mutant (% population)	Fold change	Mutant (% population)	Fold change	Mutant (% population)	Fold change	Mutant (% population)	Fold change	Mutant (% population)	Fold change	Mutant (% population)	Fold change
1	1a	T54A (>99%) Q80K (>99%)	3 to 5			None				None			
2	1a	None		None		L31M (57.96%)	554	L31M (>99%)	554	None		None	
3	1b	None		None		None		None		None		None	
4	1b	None				None				None			
5	1a	None				Q30H (>99%)	183			None			
6	1b	None				None				None			
7	1b	None				L31M (35.14%)				None			
8	1a	None		None		None		None		None		None	
9	1a	None				None				None			
10	1a	Q80L (1.76%)	3 to 5	None		None		None		None		None	
11	1a	Q80K (>99%)	3 to 5	None		None		None	-----	None		None	-----
12	1a	Q80K (88.45%)	3 to 5			H58D (10.11%)	>1000			None			
13	1a	Q80K (>99%)	3 to 5			None				None			
14	1b	None				None				None			
15	1b	None				L31M (>99%)	12			None			
16	1a	None				None				None			
17	1b	Q80L (>99%)	3 to 5			L31M (13.61%)	12			None			
18	1a	Q80K (>99%)	3 to 5			None				None			
19	1b	None				None				None			
20	1a	None				None				None			
21	1a	None		None		None		Q30R (1.82%) Y93C (4.31%)	>1000	None		None	
22	1a	None				None				None			
23	1b	None				None				None			
24	1a	None				None				None			
25*	1a	Q80K (>99%)	3 to 5	**LTF**		None		**LTF**		None		**LTF**	

There was no FTN 19, so 19=FTN20, so on.

***Patient was lost to follow up after week 8 and SVR vs. viral relapse could not be assessed**

(B) Treatment-experienced Patients with Advanced Liver Disease and received 6 weeks of Sofosbuvir + Ledipasvir + GS-9451

Patient	GT	NS3/4 Baseline		NS3/4 at Relapse		NS5A Baseline		NS5A at Relapse		NS5B Baseline		NS5B at Relapse	
		Mutant (% population)	Fold change	Mutant (% population)	Fold change	Mutant (% population)	Fold change	Mutant(% population)	Fold change	Mutant (% population)	FC	Mutant (% population)	Fold change
1	1a	Q80K (84.4%)	3 to 5			None				None			
2	1a	Q80K (>99%)	3 to 5			None				None			
3	1a	None		None		L31M (>99%)	554	L31M (>99%)	**554**	None		None	
4	1a	None				None				None			
5	1b	Q80L (>99%)	3 to 5			Y93H (36.25%)	>1000			None			
6	1a	Q80L (>99%)	3 to 5			None				None			
7	1a	None				Q30L (31.43%) Y93H	>1000			None			
8	1a	None				None				None			
9	1a	R155K (5.19%)	>100			None				None			
10	1a	None		None		None		None		None		None	
11	1a	None				None				None			
12	1a	None		None		None		Q30R (7.4%) Q30E (15.8%) L31V (29.5%) L31M (37.0%) H58D (7.6%)	>1000	None		None	
13	1a	Q80K (>99%)	3 to 5			None				None			
14	1a	None		None		None		None		None		None	
15	1a	None				None				None			
16	1a	Q80K (>99%)	3 to 5			None				None			
17	1b	None				None				None			
18	1a	None				None				None			
19	1a	None				None				None			
20	1a	None				None				None			
21	1a	Q80K (>99%)	3 to 5			None				None			

22	1a	Q80K (>99%)	3 to 5			Q30R (2.79%)	632			None			
23	1a	Q80K (>99%)	3 to 5			None				None			
24	1a	None				None				None			
25	1a	R155K (>99%)	>100	R155K (>99%)	>100	L31M (92.91%)	554	M28T (1.95%) Q30H (23.09%) Q30R (71.52%) L31M (>99%) Y93C (2.1%)	>1000	None		None	

APPENDIX: Inclusion/Exclusion Criteria

1. Participant is eighteen years of age or older at screening

2. Participant is willing to practice either:

a) Abstinence from sexual intercourse or
b) One or more forms of effective contraception throughout dosing and for 30 day following the last dose. This cannot include hormonal contraceptives for female subjects.

3. Participant has Chronic HCV GT1 infection as documented by at >1 measurement of serum HCV RNA >2,000 IU/mL during screening and at least one of the following:

a) Positive anti-HCV antibody, HCV RNA, or
b) HCV genotype test result >12 months prior to the baseline (day 0) visit together with current positive HCV RNA and anti-HCV antibody test results or
c) Positive HCV RNA test and anti-HCV antibody test results together with a liver biopsy consistent with chronic HCV infection or a liver biopsy performed before enrollment with evidence of chronic hepatitis C infection disease, such as the presence of fibrosis.

4. Participant has advanced liver disease.
NOTE: In the absence of a definitive diagnosis of presence or absence of cirrhosis, a liver biopsy is required

5. IF Participant has cirrhosis, the participant had liver imaging within 6 months of Day 0 to exclude hepatocellular carcinoma (HCC)

6. Participant is able to communicate effectively with the study investigator and other key personnel

7. Participant is willing to comply with the study restrictions and requirements

8. If opioid-dependent, Participant is participating in a supervised treatment program

9. Participant does not have substance abuse which in the opinion of the investigator is likely to interfere with medication adherence or study compliance

10. Participant has an external primary care doctor (outside of the Clinical Center and the NIH) for their medical management

11. Participant has a healthy status as determined by medical history, physical examination, electrocardiogram (ECG) and clinical laboratory measurements performed at screening

12. Participant is willing to have blood or tissue samples stored for future use to study liver disease and immune function?

13. Participant is willing to undergo HLA typing

14. Participant does not have a positive test at screening for hepatitis B virus (HBV) surface antigen (HBsAg), IgM antibody subclass to hepatitis B core antigen, HBV DNA (if medically indicated) or anti-HIV antibody

15. Participant does not have prior exposure to any direct-acting antivirals for HCV infection.

16. Participant is without a history of any other clinically significant chronic liver disease (e.g. hemochromatosis, autoimmune hepatitis, Wilson's disease, a1-antitrypsin deficiency, alcoholic liver disease, >grade 1 stage 1 non-alcoholic steatohepatitis and toxin exposures)

17. Participant denies the use of unlicensed herbal/natural remedies for potential benefit to the liver within 21 Days of Day 0

18. Participant is without a history of ascites, variceal hemorrhage, hepatic encephalopathy, or conditions consistent with decompensated liver disease.

19. Participant at screening or baseline is without an ECG with clinically significant ECG findings
OR
Participant is without a personal/first degree relative history of Torsade de pointes?

20. Participant has no abnormal hematological and biochemical parameters at screening, including:
a) Neutrophil count <750 cells/mm^3
b) Hemoglobin level <9 g/dL. Or non-normocytic Hgb < 11g/dL in women and < 12 g/dL in men requiring additional exploration of medical cause prior to enrollment
c) Platelet count <50,000 cells/mm^3
d) Estimated GFR, calculated by the CKD-EPI equation: <50 mL/min/1.73 m^2
e) ALT or AST level >10 times upper limit of normal (ULN)
f) Serum lipase level >1.5 times ULN at screening or during the screening period
g) Total bilirubin level >2.0 times ULN, except in subjects with Gilbert's syndrome
h) Albumin level <3.0 g/dL

21. Participant does not have poorly controlled diabetes mellitus indicated by hemoglobin A1C >9% at screening

22. Participant has not donated or lost more than 400mL of blood within 8 weeks prior to the first dose of the study drugs

23. Participant is without a history of major organ transplantation with an existing functional graft

24. No known hypersensitivity to, GS-5885, GS-7977, GS-9669 or formulation recipients.

25. If female, not pregnant or breastfeeding

26. Participant does not have the need for use of the following medications from 21 days prior to the start of study drugs through the end of treatment:

- Hematologic stimulating agents (e.g. erythropoiesis-stimulating agents (ESAs); granulocyte colony stimulating factor (GCSF); thrombopoietin (TPO) mimetics).

- Chronic systemic antineoplastic or immunomodulatory treatment including supraphysiologic doses of immunosuppressants, such as corticosteroids (e.g. prednisone equivalent >10mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (e.g. infliximab).

- Investigational agents or devices for any indication.

- Medications for disease conditions excluded from the protocol (e.g. , active cancer, transplantation) or not listed under the Concomitant Medication section and are disallowed in the study

- Participation in a previous clinical study in which an investigational drug, biologic, or device was received within 12 weeks prior to the first dose of the study drugs.

27. Participant is not co-enrolled in other clinical trials, other than enrollment in observational studies or those evaluating the use of a licensed medication