Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Zeuzem S, Foster GR, Wang S, et al. Glecaprevir–pibrentasvir for 8 or 12 weeks in HCV genotype 1 or 3 infection. N Engl J Med 2018;378:354-69. DOI: 10.1056/NEJMoa1702417

ONLINE SUPPLEMENTARY APPENDIX

8- or 12-week Glecaprevir/Pibrentasvir in Non-cirrhotic HCV Genotype 1 or 3

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COMPLETE ELIGIBILITY CRITERIA ARE LISTED IN THE ONLINE PROTOCOL

HCV GENOTYPING

HCV genotype and subtype were determined at screening using the Versant® HCV Genotype Inno LiPA Assay, version 2.0 (Siemens Healthcare Diagnostics, Tarrytown, NY), and confirmed by phylogenetic analysis of HCV NS3 and NS5A sequences. If the LiPA assay was unable to genotype a sample, its genotype was determined by a Sanger sequencing assay of a region of NS5B (Covance). HCV genotype and subtype were confirmed by phylogenetic analysis of HCV NS3 and NS5A sequences.

DETERMINATION OF CIRRHOSIS & BREAKDOWN OF PATIENTS DIAGNOSED

Patients must have been documented as having no cirrhosis defined as meeting one of the following criteria (per local standard):

- A liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis, e.g., a METAVIR Score of ≤3, Batts-Ludwig, Knodell (Histologic Activity Index; Fibrosis component), IASL, Scheuer, or Laennec fibrosis score of ≤3, Ishak (modified Knodell) fibrosis score of ≤ 4; or
- A FibroScan score of <12.5 kPa within 6 months prior to Screening or during the Screening Period; or
    - Patients with indeterminate FibroScan score (12.5 ≤ score <14.6) must have qualifying liver biopsy.
- A screening FibroTest score of ≤ 0.48 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) <1;

Patients with non-qualifying/conflicting FibroTest and APRI results (e.g., FibroTest ≤0.48, but APRI ≥1) must have a qualifying liver FibroScan or biopsy.

51/703 (7.3%) patients had biopsy results

520/703 (74.0%) patients had results of liver elastography

276/703 (39.3%) patients had FibroTest results.

All patients (with or without FibroTest results) had APRI scores, which were calculated with the equation below.

$$\text{APRI} = \frac{\frac{\text{AST Level (U/L)}}{\text{AST (Upper Limit of Normal)(U/L)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

Eligibility Criteria for Co-infected Patients

Co-infected patients were either antiretroviral therapy (ART) naïve, with HIV-1 RNA less than 1000 copies per milliliter and CD4+ count greater than or equal to 500 cells per mm^3 or 29%, or on a stable ART regimen with HIV-1 RNA below the lower limit of quantification and CD4+ count greater than or equal to 200 cells per mm^3 or at least 14% of total T cells. The following antiretrovirals were permitted: the integrase strand transfer inhibitors raltegrevir and dolutegravir, the non-nucleoside reverse transcriptase inhibitor rilpivirine, and the nucleoside or nucleotide reverse transcriptase inhibitors tenofovir disoproxil fumarate, emtricitabine, lamivudine, abacavir and zidovudine. Patients not on qualifying ART regimens could switch to a qualifying regimen at least 8 weeks prior to beginning DAA treatment.

Table S1. ART Regimens of Co-infected Patients

ART Regimen	8-Week Treatment Arm N=15	12-Week Treatment Arm N=18
DTG/ABC/3TC	4 (27)	8 (44)
TDF/FTC + RAL	6 (40)	3 (17)
RPV/TDF/FTC	3 (20)	3 (17)
DTG+ TDF/FTC	1 (7)	4 (22)
ABC/3TC + RAL	1 (7)	0

3TC, lamivudine; ABC, abacavir; DTG, dolutegravir; FTC, emtricitabine; RAL, raltegravir; RPV, rilpivirine; TDF, Tenofovir disoproxil fumarate

RESISTANCE ANALYSES

For HCV resistance analysis, we define a polymorphism as a baseline amino acid difference relative to the appropriate reference sequence, and a substitution as a treatment-emergent amino acid difference relative to the patient's baseline viral sequence. Regions encoding full-length NS3/4A or NS5A were sequenced by next generation sequencing from available baseline samples from all patients, and on the first available post-baseline sample with HCV RNA ≥ 1000 IU per milliliter from patients who experienced virologic failure. Detection of baseline polymorphisms and treatment-emergent substitutions was done using a 15% detection threshold.

Baseline polymorphisms relative to a subtype-specific reference sequence were analyzed using a key subset of amino acid positions, whereas treatment-emergent substitutions relative to a patient's baseline sequence were analyzed using an extended set of amino acid positions at which substitutions have been observed in vitro or clinically in NS3 or NS5A with drugs for the respective inhibitor classes (eTable 2).

Table S2. Key Subset and Extended Set of Amino Acid Positions

Target	Genotype	Key Subset of Amino Acid Positions	Extended Set of Amino Acid Positions
NS3	1a	155, 156, 168	36, 43, 54, 55, 56, 80, 155, 156, 168
	1b		36, 54, 55, 56, 80, 155, 156, 168
	3	155, 156, 166, 168	36, 43, 54, 55, 56, 80, 155, 156, 166, 168
NS5A	1a	24, 28, 30, 31, 58, 92, 93	24, 28, 29, 30, 31, 32, 58, 62, 92, 93
	1b		24, 28, 29, 30, 31, 32, 54, 58, 62, 92, 93
	3	24, 28, 30, 31, 58, 92, 93	24, 28, 29, 30, 31, 32, 58, 92, 93

MONITORING OF HIV-1 SUPPRESSION AND LYMPHOCYTE/LYMPHOCYTE SUBSETS

The following endpoints were also assessed for patients with co-infection:

- The percentage of patients with plasma HIV-1 RNA suppression at the end of treatment and at Post-Treatment Week 12 using the FDA Snapshot Algorithm;
- The number and percentage of patients with plasma HIV-1 RNA <20 copies/milliliter at each applicable time point;
- Change from baseline in CD4+ T-cell count (absolute and percent) to each applicable post-baseline time point;
- Change from baseline in lymphocytes (count) and CD8+ T-cell count (absolute and percent) to each applicable post-baseline time point

VIROLOGIC STOPPING AND FUTILITY CRITERIA

Patients were required to stop treatment with study drugs if they met any of the following criteria:

- Confirmed increase from nadir in HCV RNA, defined as 2 consecutive HCV RNA measurements >1 $\log_{10}$ IU/mL above nadir at any time point during treatment
- Confirmed HCV RNA ≥100 IU/mL, defined as 2 consecutive HCV RNA measurements ≥100 IU/mL, after HCV RNA was measured at less than LLOQ during treatment

INTENT-TO-TREAT POPULATION AND CONFIDENCE INTERVALS

The intent-to-treat population was used for all efficacy analyses, and the safety population was used for all safety analyses. All subjects who received at least one dose of study drug were included in the intent-to-treat population and safety population. The data from the intent-to-treat population were presented by the treatment arm assigned at the time of randomization, while the data from the safety population were presented according to actual treatment received during the entire treatment period.

For the primary analyses of non-inferiority tests, the percentage of patients achieving SVR12 in each arm or difference in percentages of patients achieving SVR12 between treatment arms in the intent-to-treat population was calculated with confidence intervals (CI) using the normal approximation to the binomial distribution.

For other analyses of SVR (except superiority tests in ENDURANCE-3) or virologic failure, the percentage of subjects was calculated with a two-sided 95% confidence interval (CI) using the Wilson score method.

Table S3. Outcomes and Endpoints

ENDURANCE-1	Reason not included
Primary Endpoints	
Efficacy (SVR12) of the 12-week treatment duration	Included
Non-inferiority of 8-week to 12-week treatment (per protocol)	Included
Non-inferiority of 8-week to 12-week treatment (primary subset)	Included
Secondary Endpoints	
SVR12 in mono-infected HCV GT1 patients	Included
SVR12 in all HCV GT1 patients in the ITT population	Included
SVR12 in patients with HCV GT1/HIV-1 co-infection	Included
SVR12 in SOF-treatment experienced HCV GT1 patients	Included
On-treatment virologic failure	Included
Post-treatment relapse	Included
Additional Pre-specified Outcomes	
Change from baseline in patient reported outcome summary measures	Data to be presented elsewhere
Presence of baseline polymorphisms	Included
Presence of treatment-emergent substitutions in patients with virologic failure	Included
Plasma concentration of glecaprevir and pibrentasvir, and possible glecaprevir and pibrentasvir metabolites	Data to be presented elsewhere

Adverse events	Included
Laboratory abnormalities	Included
Ad-hoc Outcomes (None)	
ENDURANCE-3	**Reason not included**
Primary Endpoints	
Non-inferiority of 12 weeks of G/P to 12 weeks of SOF+DCV	Included
Non-inferiority of 8-weeks of G/P to 12 weeks of G/P	Included
Secondary Endpoints	
Superiority of 12 weeks of G/P to 12 weeks of SOF+DCV	Included
On-treatment virologic failure	Included
Post-treatment relapse	Included

SAMPLE SIZE AND THE NON-INFERIORITY THRESHOLD AND MARGIN

ENDURANCE-1

The 91% threshold for non-inferiority of 12 weeks of glecaprevir/pibrenatsvir was based on a historical SVR12 rate of 97% derived from the standard-of-care at the time of study design, ombitasvir/paritaprevir/ritonavir plus dasabuvir or sofobuvir/ledipasvir, minus a 6% non-inferiority margin.

ENDURANCE-3

The study was designed to enroll a total of 460 patients: 230 in Arm A and 115 each in Arms B and C. The primary efficacy endpoint of SVR12 was assessed within each Arm, and the primary comparison of SVR12 rates was for non-inferiority of Arm A to Arm B, and Arm C to Arm A. With these patient numbers, the study would have 90% power to show non-inferiority to a current standard of care (sofosbuvir plus daclatasvir for 12 weeks) with a lower confidence bound for the Arm A SVR12 rate greater than 92% or with a lower confidence bound for the difference (Arm A – Arm B) in SVR12 rates greater than –6% (assuming the SVR12 rate is 97% in both arms). Similarly, the study had approximately 80% power to demonstrate non-inferiority of the 8-week duration to the 12 week duration of glecaprevir/pibrentasvir (Arm C), with identical assumptions.

The 6% non-inferiority margin was identified based on the benefit of sofosbuvir plus daclatasvir over the previous standard-of-care, interferon/ribavirin. The SVR12 rate for treatment-naïve patients with HCV genotype 3 without cirrhosis, when treated with interferon/ribavirin, was 68%.[1,2] Given the 97.6% SVR12 rate in the ALLY-3 clinical trial[3] observed for these patients treated with sofosbuvir plus daclatasvir, the benefit over the previous standard-of-care was approximately 30%. A margin of 6%, therefore, preserves 80% of the benefit of the current standard-of-care over the previous standard-of-care.

The 92% threshold used for the within-arm comparison was derived by applying the 6% non-inferiority margin to the SVR rate in the ALLY-3 clinical trial. In that study, the SVR12 rate of treatment-naïve patients with HCV genotype 3 without cirrhosis was 80/82 (97.6%). Using the 6% non-inferiority margin this results in a 92% threshold (97.6% – 6% = 91.6%).

The use of the fixed sequence testing procedure and Hochberg procedure for multiplicity adjustment in the primary analysis (non-inferiority test) and first secondary analysis (superiority test) is explained as follows:

Arm A was treatment with 12 weeks of glecaprevir/pibrentasvir, Arm B was treatment with 12 weeks of sofosbuvir plus daclatasvir, and Arm C was treatment with 8 weeks of glecaprevir/pibrentasvir.

The three tests in fixed sequence testing procedure are:

Test 1: non-inferiority of Arm A to Arm B;

Test 2: non-inferiority of Arm C to Arm A;

Test 3: superiority of Arm A to Arm B

Only if success was demonstrated for Test 1 would the testing proceed to Test 2, and only if successes have been demonstrated for both Test 1 and 2 would the testing proceed to Test 3.

To adjust for the multiple comparisons (lower confidence bound within arm > 92% and lower confidence bound of difference between arms > -6%) within Test 1 or Test 2, prespecified use of the Hochberg procedure demonstrated non-inferiority within each test if:

1. The lower bound of the 95% confidence interval for the difference was above –6% **and** the lower bound of the 95% confidence interval for the SVR12 rate within Arm A (or Arm C) was greater than 92%

   or;
2. The lower bound of the 97.5% confidence interval for the SVR12 rate within Arm A (or Arm C) was greater than 92% but the lower bound of the 95% confidence interval for the difference was below –6%

   or;
3. The lower bound of the 97.5% confidence interval for the difference was above –6% but the lower bound of the 95% confidence interval for the SVR12 rate within Arm A (or Arm C) was below 92%

Non-inferiority of Arm A to B was demonstrated by achieving condition 1; and non-inferiority of Arm C to A was demonstrated by achieving condition 3. Thus, 95% confidence intervals were used in reporting non-inferiority of Arm A to B, but a 97.5% confidence interval was used in reporting non-inferiority of Arm C to A.

ADDITIONAL INFORMATION ON ASSESSMENTS

Plasma samples were collected at each treatment (weeks 1, 2, 4, 8 and 12) and post-treatment visit (post-treatment weeks 2, 4, 8, 12, and 24). Samples were used for quantifying levels of HCV RNA, analyzing plasma concentrations of study drugs and liver biomarkers, as well as next-generation sequencing to identify the emergence and persistence of viral substitutions, where applicable.

- **Efficacy:** A patient with confirmed increase in HCV RNA to at least 100 international units per milliliter after it had been measured at less than the lower limit of quantitation during treatment or had a confirmed increase greater than 1 $\log_{10}$ international units per milliliter above nadir during treatment was considered to have on-treatment virologic failure and mandated to stop treatment. Any patient that completed treatment as planned with HCV RNA less than the lower limit of quantification at the end of treatment and had confirmed HCV RNA greater than or equal to the lower limit of quantitation at any time between end-of-treatment and post-treatment week 12 was considered to have relapsed (excluding reinfection confirmed by phylogenetic analysis). Patients that achieved SVR12 were those with HCV RNA less than the lower limit of quantification throughout the SVR12 window (post treatment day 57 to 126) without confirmed quantifiable HCV RNA before or after that window. For determination of virologic relapse, completion of treatment is defined as at least 77 days of treatment for the 12-week arms or at least 52 days for patients in the 8-week treatment arm.
- **Safety:** Patients that received at least one dose of study drug were included in safety analyses. All adverse events were collected between the first administration of study drug and 30 days after study drug discontinuation. Assessment of the relatedness of each adverse event was made with respect to study drugs and the event was classified using the MedDRA system organ class and preferred term, as assigned by the study investigator. Change from baseline in

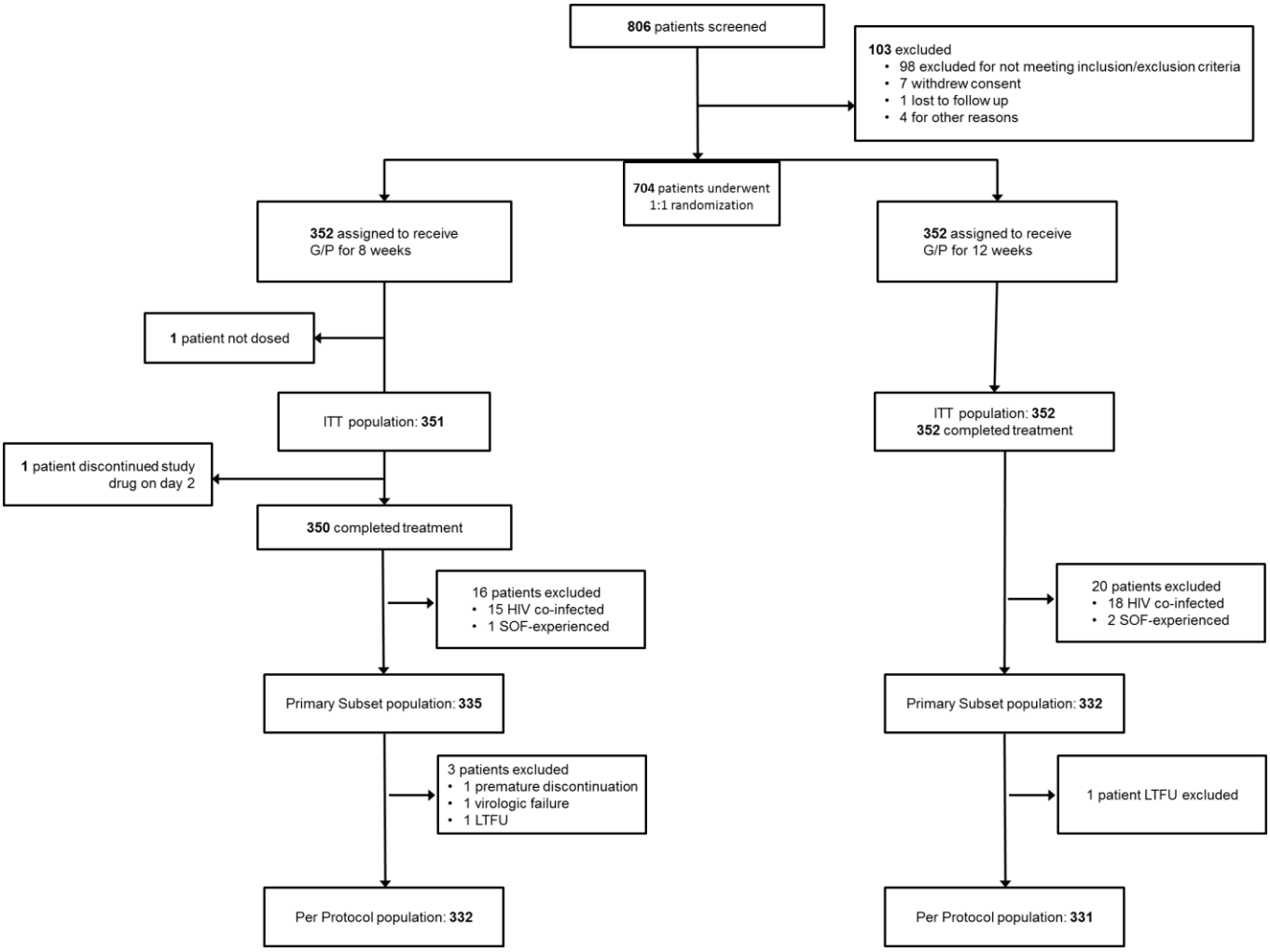
laboratory tests and vital sign measurements were assessed at each clinical visit and compared between treatment arms.

DETAILS ON THE ADDITION OF 8-WEEK TREATMENT (NON-RANDOMIZED ARM C) AND PATIENT RANDOMIZATION (ENDURANCE-3)

Initial study design was a two arm comparison between 12 week durations of glecaprevir/pibrentasvir and sofosbuvir plus daclatasvir with genotype 3 infected patients. However, during the 2:1 randomization of patients into these arms, additional phase 2 data became available that suggested 8 weeks of glecaprevir/pibrentasvir could be a viable option for the treatment of patients with HCV GT3 infection.

After discussion with regulatory authorities, Arm C (8 weeks of glecaprevir/pibrentasvir treatment) was added to the ENDURANCE-3 study design without randomization. After all patients were randomized into Arms A and B (12 weeks of glecaprevir/pibrentasvir and sofosbuvir plus daclatasvir, respectively), Arm C enrollment was opened. Patients for Arm C were enrolled at the same study sites as those for Arms A and B.

Figure S1a. Patient Disposition, ENDURANCE-1



Flow chart shows dispersal of patients screened, randomized, dosed and who completed treatment. Intention-to-treat population: includes all patients who received one dose of study drug; Primary Subset: ITT population excluding co-infected and sofosbuvir-experienced patients; Per Protocol, primary subset population excluding patients lost to follow-up, or with premature discontinuation or virologic failure prior to week 8. Abbreviations: ITT, intention-to-treat; LTFU, lost to follow-up.

Figure S1b. Patient Disposition, ENDURANCE-3

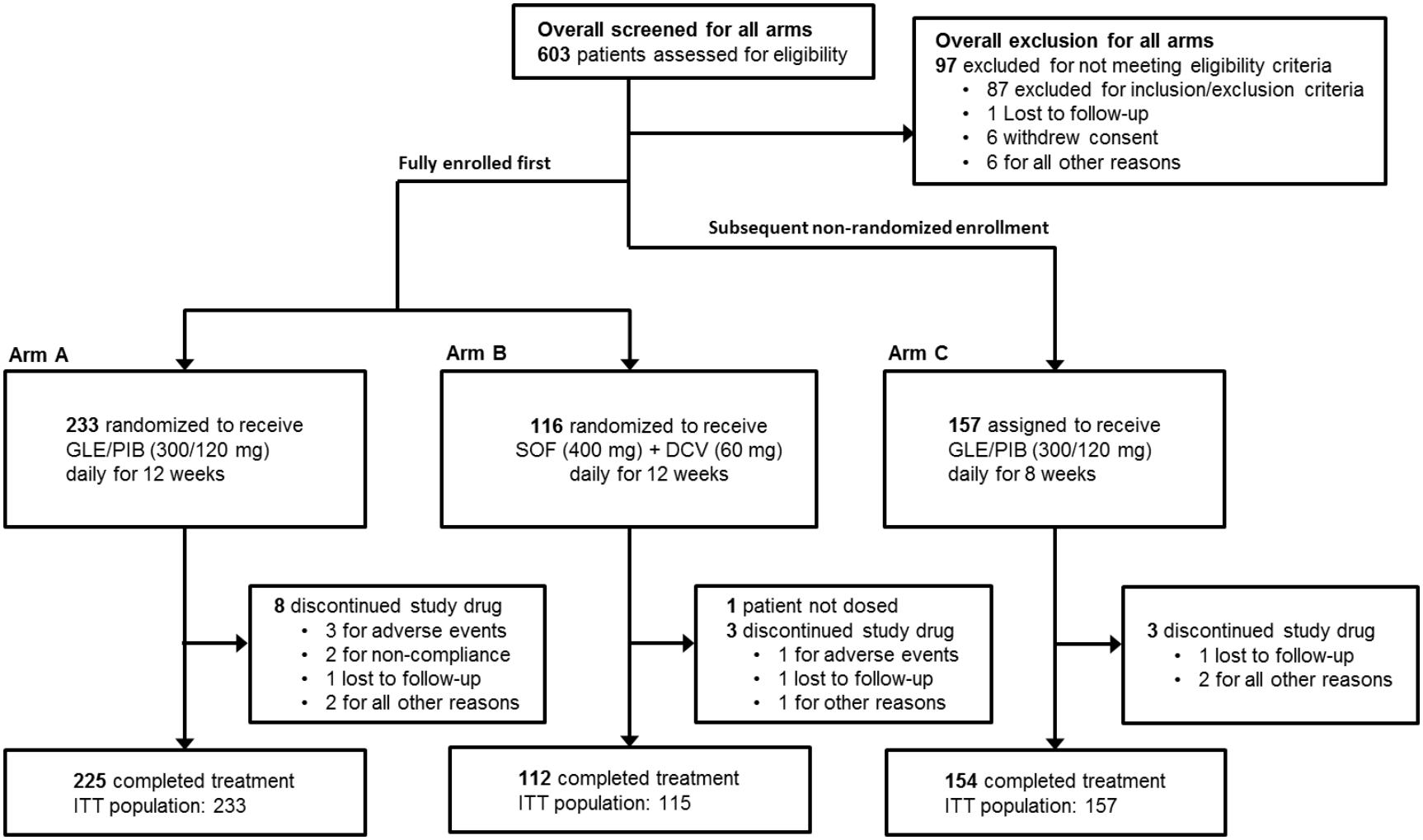


Table S4. Prevalence of Baseline Polymorphisms in NS3 or NS5A in Patients with Genotype 3 Infection

Polymorphism, n (%)	G/P 8 weeks N=155	G/P 12 weeks N=228/229*	SOF + DCV 12 weeks N=113
Any NS3	22 (14)	33 (14)	ND
A166S/T	22 (14)	30 (13)	ND
Q168K/R	2 (1)	4 (2)	ND
Any NS5A	43 (28)	43 (19)	21 (19)
S24A	4 (3)	7 (3)	3 (3)
M28V	2 (1)	2 (1)	0
A30K	16 (10)	12 (5)	5 (4)
A30L/M/S/T/V	9 (6)	14 (6)	4 (4)
P58A/R/S/T/Y	9 (6)	6 (3)	1 (1)
Y93H	5 (3)	11 (5)	8 (7)

n = number of patients with the indicated polymorphism relative to subtype-specific reference sequences; N = total number of patients sequenced in the respective Arms; ND = sequence not determined
Specific polymorphisms listed were detected in at least 4 patients in G/P treatment arms
Amino acid positions included in the analysis: 155, 156, 166, 168 in NS3; 24, 28, 30, 31, 58, 92, 93 in NS5A
*Of 233 samples in this arm, 228 or 229 sequences were available for NS3 or NS5A, respectively

Table S5. Patients with Virologic Failure: NS3 and NS5A Polymorphisms/Substitutions at Baseline and Time of Failure

				NS3 Variants		NS5A Variants	
Arm	**Treatment Duration**	**HCV Subtype**	**Failure**	**Baseline**	**At Failure**	**Baseline**	**At Failure**
Glecaprevir/pibrentasvir (ENDURANCE-1)							
B	8 weeks	1a	Breakthrough	None	A156V	None	Q30R + L31M + H58D
Glecaprevir/pibrentasvir (ENDURANCE-3)							
A	12 weeks	3a	Breakthrough	Q168R	Y56H + Q168R	A30K, A30V, Y93H	A30K + Y93H
A	12 weeks	3a	Relapse	None	None	None	A30G, Y93H
A	12 weeks	3a	Relapse	None	Reinfection	None	Reinfection
A	12 weeks	3b	Relapse	None	Q80K	V31M	V31M + Y93H
C	8 weeks	3a	Relapse	T54S	T54S	None	None
C	8 weeks	3a	Relapse	None	Q168L	A30K	A30K + Y93H
C	8 weeks	3a	Relapse	A166S	Y56H, Q168L	A30K	A30K + Y93H
C	8 weeks	3a	Failed to Suppress	A166S, Q168R	Q80R, A156G	A30K	A30K + Y93H
C	8 weeks	3a	Relapse	A166S	A166S	None	Y93H
C	8 weeks	3a	Relapse	None	Y56H	A30K	A30K + Y93H
Sofosbuvir plus daclatasvir (ENDURANCE-3)							
B	12 weeks	3a	Relapse	ND	ND	Y93H	Y93H

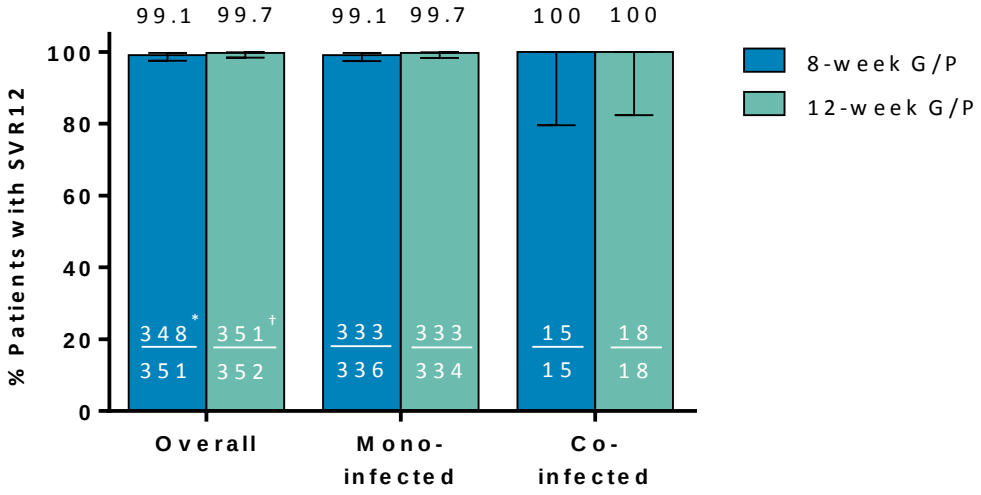
ND, Sequence Not Determined: patients in ENDURANCE-3 treated with sofosbuvir plus daclatasvir were not treated with an NS3/4A protease inhibitor

For samples with multiple variants (polymorphisms/substitutions) within a target, if individual variants were detected at ≥90% prevalence , they are considered to be linked and denoted by "+", whereas if one or more of the variants was detected at <90% prevalence, the variants are separated by a comma

Amino acid positions included in analysis of patients with GT1: 36, 43, 54, 55, 56, 80, 155, 156, 168 in NS3; 24, 28, 29, 30, 31, 32, 58, 62, 92, 93 in NS5A

Amino acid positions included in analysis of patients with GT3: 36, 43, 54, 55, 56, 80, 155, 156, 166, 168 in NS3; 24, 28, 29, 30, 31, 32, 58, 92, 93 in NS5A

Figure S2. ENDURANCE-1 Secondary Endpoint Analysis, ITT Population



*One patient with GT1a infection in the eight-week treatment arm experienced on-treatment virologic failure at day 29 of treatment, one patient discontinued on day 2 due to non-compliance, one patient missing SVR12 data

† One patient missing SVR12 data

All patients with prior sofosbuvir treatment experience (N=3) achieved SVR12 (not shown); In the ITT population, there was no significant difference in treatment outcome amongst mono-infected, or coinfected patient subgroups between the eight- (blue) and twelve- (turquoise) week treatment duration.

Table S6. SVR12 in Genotype 1 Patient Subgroups, ITT Analysis

Subgroup	G/P 8 weeks N=351	G/P 12 weeks N=352
	SVR12 n/N (%; 95% CI)	
Subtype 1a	150/153 (98; 94.4 –99.3)	148/149 (99; 96.3 – 99.9)
Female	183/184 (99; 97.0 – 99.9)	175/176 (99; 96.9 – 99.9)
Black race	14/14 (100; 78.5 – 100)	12/13 (92; 66.7 – 98.6)
≥65 years old	42/42 (100; 91.6 – 100)	35/35 (100; 90.1 – 99.9)
BMI ≥30	51/51 (100; 93.0 – 100)	53/53 (100; 93.2 – 100)
HCV RNA ≥6,000,000	49/49 (100; 92.7 – 100)	42/43 (98; 87.9 – 99.6)
HCV RNA≥10,000,000	16/16 (100; 80.6 – 100)	15/16 (94; 71.7 – 98.9)
F2 fibrosis	22/22 (100; 85.1 – 100)	24/24 (100; 86.2 – 100)
F3 fibrosis	30/30 (100; 88.6 – 100)	29/29 (100; 88.3 – 100)
Treatment-experienced	131/132 (99.2; 95.8 – 99.9)	135/135 (100; 97.2 – 100)
IL28B non-CC genotype	246/249 (99; 96.5 – 99.6)	265/266 (99.6; 97.9 – 99.9)
Recent IDU	2/2 (100; NA)	5/5 (100; NA)
History of IDU	94/96 (98; 92.7 – 99.4)	92/92 (99; 94.2 – 99.8)
On OST	12/12 (100; 75.8 – 100)	15/16 (94; 71.7 – 98.9)

BMI, body mass index; HCV, hepatitis C virus; IDU, injection drug use; OST, opioid substitution therapy
Recent IDU was classified as within 12 months prior to enrollment; history of IDU was more than 12 months prior to enrollment

Table S7. Primary reason for premature discontinuation of study drugs (ENDURANCE-3)

Reason for discontinuation, n (%)	Arm A G/P 12 weeks N=233	Arm B SOF + DCV 12 weeks N=115	Arm C G/P 8 weeks N=157
Premature discontinuation	**8 (3)**	**3 (3)**	**3 (2)**
Adverse event	3 (1)	1 (1)	0
Non-compliance	2 (1)	0	0
Withdrew consent	1 (<1)	0	0
Lost to follow-up	1 (<1)	1 (1)	1 (1)
Other	1 (<1)	1 (1)	2 (1)

Table S8. SVR12 in Genotype 3 Patient Subgroups, ITT Analysis

	2:1 Randomized		
Subgroup	G/P 12 weeks N = 233	SOF + DCV 12 weeks N = 115	G/P 8 weeks N = 157
	SVR12 n/N (%; 95% CI)		
Subtype 3a	220/230 (96; 92–98)	111/115 (97; 91–99)	148/156 (95; 90–97)
Female	110/112 (98; 94–99)	63/63 (100; 94–100)	63/65 (97; 90–99)
Black race	4/4 (100)	3/4 (75)	3/3 (100)
≥65 years old	9/9 (100)	4/4 (100)	5/5 (100)
BMI ≥30	36/36 (100; 90–100)	20/20 (100; 84–100)	24/24 (100; 86–100)
HCV RNA ≥6,000,000	60/65 (92; 83–97)	14/14 (100; 79–100)	30/34 (88; 73–95)
HCV RNA≥10,000,000	34/39 (87; 73–94)	5/5 (100)	19/20 (95; 76–99)
F2 fibrosis	11/12 (92; 65–99)	6/8 (75)	6/8 (75)
F3 fibrosis	19/20 (95; 76–99)	10/10 (100; 72–100)	24/27 (89; 72–96)
IL28B non-CC genotype	135/142 (95; 90–98)	75/76 (99; 93–99)	93/97 (96; 90–98)
Recent IDU	6/8 (75)	4/4 (100)	8/9 (89)
History of IDU	133/141 (94; 89–97)	66/69 (96; 88–99)	90/95 (95; 88–98)
On OST	34/38 (90; 76–96)	17/17 (100; 82–100)	30/31 (97; 84–99)

BMI, body mass index; HCV, hepatitis C virus; IDU, injection drug use; OST, opioid substitution therapy
Recent IDU was classified as within 12 months prior to enrollment; history of IDU was more than 12 months prior to enrollment

Table S9. SVR12 in Genotype 3-infected Patients by Baseline Polymorphisms in NS3 or NS5A

SVR12, n/N (%)	G/P 12 weeks N=221/222*	SOF + DCV 12 weeks N=110	G/P 8 weeks N=153
NS3 polymorphisms			
With any	32/33 (97)	ND	19/22 (86)
Without any	185/188 (98)	ND	128/131 (98)
NS5A polymorphisms			
With any	41/43 (95)	20/21 (95)	39/43 (91)
Without any	177/179 (99)	89/89 (100)	108/110 (98)
With A30K	9/10 (90)†	5/5 (100)	12/16 (75)
Without A30K	209/212 (99)	104/105 (99)	135/137 (99)
With Y93H	10/11 (91)†	7/8 (88)	5/5 (100)
Without Y93H	208/211 (99)	102/102 (100)	142/148 (96)
NS3+NS5A polymorphisms	6/7 (86)	ND	5/7 (71)

n = number of patients with SVR12 with the indicated polymorphism relative to subtype-specific reference sequence; N = total number of patients with sequence data available (patients that prematurely discontinued treatment or were lost to follow-up not included in analysis); DCV, daclatasvir; G/P, coformulated glecaprevir and pibrentasvir; SOF, sofosbuvir; ND, sequence not determined

Amino acid positions included in the analysis: 155, 156, 166, 168 in NS3; 24, 28, 30, 31, 58, 92, 93 in NS5A

*221 or 222 sequences were available for NS3 or NS5A, respectively

†Single patient with virologic breakthrough had A30K and Y93H at baseline

Table S10. Rates of SVR24, n/N (%)

	ENDURANCE-1		ENDURANCE-3		
Population	G/P 8 weeks N=351	G/P 12 weeks N=352	G/P 12 weeks N=233	SOF + DCV 12 weeks N=115	G/P 8 weeks N=157
ITT	343/351 (98)	345/352 (98)	214/233 (92)	110/115 (96)	143/157 (91)
VFs*	1	0	3	1	6
Non-VFs	7	7	16	4	8
mITT	343/344 (99.7)	345/345 (100)	214/217 (99)	110/111 (99)	143/149 (96)

ITT, intent-to-treat; mITT, modified intent-to-treat; VF, virologic failure

The ITT population included all patients that received at least one dose of study drug. The mITT population excluded all patients that failed to achieve SVR due to reasons other than virologic failure

*There were no post-SVR12 relapses; all VFs were the same as those reported for SVR12 time point

Table S11. Safety and Laboratory Abnormalities in HCV/HIV-1 Co-infected Patients (ENDURANCE-1)

Event, n (%)	Glecaprevir/Pibrentasvir 8 Weeks N = 15	Glecaprevir/Pibrentasvir 12 Weeks N = 18
Any adverse event	6 (40)	11 (61)
Any DAA-related adverse event	4 (27)	4 (22)
Adverse events leading to study drug d/c	0	0
Serious adverse events	0	1 (6)*
ALT Grade ≥2 (>5 × ULN), post nadir	0	0
AST Grade ≥2 (>5 × ULN)	0	0
Total Bilirubin Grade 3 (>3-10 × ULN)	1 (7)	0

DAA, direct-acting antiviral; ALT, alanine aminotransferase; AST, aspartate aminotransferase; d/c, discontinuation

*One patient with HIV-1 co-infection had a SAE of bronchitis on post-treatment day 18 that was unrelated to study drug.

Table S12. Serious Adverse Events for Glecaprevir/Pibrentasvir Treated Patients

Treatment Duration	Serious Adverse Event	Study Day Onset	Toxicity Grade	Considered Related to DAA?
Genotype 1 (ENDURANCE-1)				
8 weeks	Suicide attempt, arterial injury	82 (24), 82 (24)	4, 4	No
8 weeks	Angina unstable	26	3	No
8 weeks	Radius fracture	2	3	No
8 weeks	Uterine leiomyoma	64 (8)	3	No
8 weeks	Transient ischemic attack	4	3	No
12 weeks	Irritable bowel syndrome	81	1	No
12 weeks	Pneumonia aspiration, Death	54, 99 (14)	3, 5	No
12 weeks	Bronchitis	106 (18)	3	No
12 weeks	Atrial fibrillation	29	2	No
Genotype 3 (ENDURANCE-3)				
8 weeks	Ulcerative keratitis due to herpes simplex I	25	3	No
8 weeks	Accidental overdose	51	3	No
8 weeks	Substance-abuse dependence	51	3	No
12 weeks	Pneumonia Infection	67	3	No
12 weeks	Limb injury	38	3	No
12 weeks	Paranasal sinus cancer	72	3	No
12 weeks	Abortion missed	72	3	No
12 weeks	Acute respiratory failure with hypoxia	48	4	No

Numbers in parentheses are days since last dose of study drug

Table S13. Mean Change from Baseline for Select Laboratory Values in Genotype 1 Patients

	ALT Visit mean (change from baseline ± SD)		AST (U/L) Visit mean (change from baseline ± SD)		Bilirubin (µmol/L) Visit mean (change from baseline ± SD)		eGFR* Visit mean (change from baseline ± SD)		CrCl (mL/sec) Visit mean (change from baseline ± SD)	
	Treatment Duration									
	8	**12**	**8**	**12**	**8**	**12**	**8**	**12**	**8**	**12**
Baseline	62.3 (NA)	69.1 (NA)	46.7 (NA)	48.7 (NA)	10.2 (NA)	9.6 (NA)	1.515 (NA)	1.546 (NA)	1.76 (NA)	1.81 (NA)
Treatment week 4	17.7 (-44.5 ± 49.0)	18.5 (-50.5 ± 74.1)	20.5 (-26.1 ± 29.5)	20.8 (-27.8 ± 36.9)	10.1 (-0.1 ± 4.51)	9.3 (-0.3 ± 4.12)	1.496 (-0.02 ± 0.20)	1.503 (-0.04 ± 0.2)	1.73 (-0.03 ± 0.20)	1.77 (-0.04 ± 0.18)
End of treatment	16.9 (-44.2 ± 45.63)	17.1 (-50.9 ± 73.4)	20.3 (-25.9 ± 29.5)	20.6 (-26.8 ± 35.4)	10.5 (0.2 ± 5.45)	9.3 (-0.3 ± 4.16)	1.486 (-0.03 ± 0.19)	1.495 (-0.05 ± 0.20)	1.72 (-0.04 ± 0.17)	1.76 (-0.04 ± 0.20)

*GFR from creatinine adjusted for BSA (mL/sec/1.73 m^2)

Table S14. Coinfected Patients with Plasma HIV-1 RNA Suppression using the FDA Snapshot Algorithm (<40 Copies/mL) at End of Treatment and Post-Treatment Week 12, n/N (%)

Treatment Visit	G/P 8 Weeks N = 15	G/P 12 Weeks N = 18
Final Treatment Visit*	12/12 (100)	13/13 (100)
Post-treatment Week 12	14/14 (100)	15/15 (100)

Table includes only patients with available data at each study visit

*The final treatment visit value is defined as the last non-missing measurement collected during treatment period.

Table S15. Coinfected Patients with Plasma HIV-1 RNA <20 Copies/mL , n/N (%)

Treatment Visit	G/P 8 Weeks N = 15	G/P 12 Weeks N = 18
Baseline	15/15 (100)	18/18 (100)
Week 2	13/13 (100)	16/16 (100)
Week 4	15/15 (100)	16/16 (100)
Week 8	11/12 (92)	15/16 (94)
Week 12	N/A	13/13 (100)
Final Treatment Visit*	14/15 (93)	18/18 (100)
Post-treatment Week 4	13/15 (87)	17/18 (94)
Post-treatment Week 12	14/15 (93)	15/15 (100)
Final Post-treatment Visit^	14/15 (93)	18/18 (100)

Table includes only patients with available data at each study visit

* The final treatment visit value is defined as the last non-missing measurement collected during treatment period.

^ The final post-treatment treatment visit value is defined as the last non-missing measurement collected during post-treatment period.

Table S16. Mean Change from Baseline in CD4+ T Cell Absolute Count and Percent in Coinfected Patients

	G/P 8 Weeks N = 15		G/P 12 Weeks N = 18	
Treatment Visit	**Cells per microliter Visit mean (change from baseline ± SD)**	**Percent Visit mean (change from baseline ± SD)**	**Cells per microliter Visit mean (change from baseline ± SD)**	**Percent Visit mean (change from baseline ± SD)**
Baseline	652.9	29.8	783.3	35.1
Week 4	695.3 (42.3 ± 128.0)	31.2 (1.4 ± 2.3)	800.8 (36.6 ± 174.3)	35.4 (-0.4 ± 3.2)
Week 8	669.1 (87.6 ± 154.2)	31.2 (2.8 ± 3.9)	991.4 (85.9 ± 258.7)	36.7 (0.6 ± 5.0)
Week 12	N/A	N/A	848.9 (42.2 ± 200.1)	36.4 (0.5 ± 4.1)
Final Treatment Visit*	691.7 (38.7 ± 171.8)	32.0 (2.1 ± 3.6)	835.0 (51.7 ± 199.0)	35.8 (0.7 ± 3.8)
Post-treatment Week 4	652.3 (-0.7 ± 153.8)	30.7 (0.9 ± 4.2)	946.1 (155.9 ± 485.1)	34.8 (-0.2 ± 5.0)
Post-treatment Week 12	663.1 (10.2 ± 211.4)	30.3 (0.5 ± 4.3)	871.0 (102.2 ± 197.7)	34.3 (0.4 ± 5.2)
Final Post-treatment Visit^	663.1 (10.2 ± 211.4)	30.3 (0.5 ± 4.3)	910.0 (126.7 ± 207.8)	35.4 (0.3 ± 5.1)

Table includes only patients with available data at each study visit

* The final treatment visit value is defined as the last non-missing measurement collected during treatment period.

^ The final post-treatment treatment visit value is defined as the last non-missing measurement collected during post-treatment period.

Table S17. Mean Change from Baseline in Lymphocyte Count in Coinfected Patients

Treatment Visit	G/P 8 Weeks N = 15	G/P 12 Weeks N = 18
	Lymphocytes × 10^9 per liter, Visit mean (change from baseline ± SD)	
Baseline	2.0	2.2
Week 1	2.4 (0.4 ± 0.4)	2.4 (0.2 ± 0.3)
Week 2	2.2 (0.1 ± 0.4)	2.5 (0.3 ± 0.6)
Week 4	2.2 (0.1 ± 0.4)	2.3 (0.1 ± 0.3)
Week 8	2.1 (0.1 ± 0.4)	2.4 (0.2 ± 0.5)
Week 12	N/A	2.3 (0.05 ± 0.4)
Final Treatment Visit*	2.1 (0.1 ± 0.4)	2.3 (0.1 ± 0.5)
Post-treatment Week 4	2.0 (-0.02 ± 0.3)	2.3 (0.1 ± 0.6)
Final Post-treatment Visit^	2.0 (-0.02 ± 0.3)	2.3 (0.1 ± 0.6)

Table includes only patients with available data at each study visit

* The final treatment visit value is defined as the last non-missing measurement collected during treatment period.

^ The final post-treatment treatment visit value is defined as the last non-missing measurement collected during post-treatment period.

Table S18. Mean Change from Baseline in CD8+ T Cell Count and Percent in Coinfected Patients

	G/P 8 Weeks N = 15		G/P 12 Weeks N = 18	
Treatment Visit	**Cells per microliter Visit mean (change from baseline ± SD)**	**Percent Visit mean (change from baseline ± SD)**	**Cells per microliter Visit mean (change from baseline ± SD)**	**Percent Visit mean (change from baseline ± SD)**
Baseline	955.7	42.5	893.9	38.4
Week 4	956.0 (0.3 ± 166.0)	42.4 (-0.01 ± 2.6)	879.2 (28.8 ± 238.8)	37.6 (-0.7 ± 4.4)
Week 8	917.4 (7.6 ± 168.5)	41.9 (-0.2 ± 4.1)	1051.9 (37.9 ± 260.9)	36.9 (-1.3 ± 2.4)
Week 12	N/A	N/A	888.1 (0.1 ± 260.8)	35.6 (-1.1 ± 2.1)
Final Treatment Visit*	928.4 (-27.3 ± 167.1)	42.3 (-0.1 ± 3.5)	923.8 (29.9 ± 273.5)	37.6 (-0.8 ± 2.2)
Post-treatment Week 4	941.1 (-14.5 ± 187.6)	43.1 (0.6 ± 3.0)	1086.9 (174.2 ± 500.7)	38.6 (-0.3 ± 3.4)
Post-treatment Week 12	950.1 (-5.5 ± 280.4)	43.2 (0.7 ± 4.7)	1023.5 (87.4 ± 254.1)	38.6 (-0.6 ± 2.6)
Final Post-treatment Visit^	950.1 (-5.5 ± 280.4)	43.2 (0.7 ± 4.7)	1006.1 (112.2 ± 260.0)	38.1 (-0.3 ± 3.1)

Table includes only patients with available data at each study visit

* The final treatment visit value is defined as the last non-missing measurement collected during treatment period.

^ The final post-treatment treatment visit value is defined as the last non-missing measurement collected during post-treatment period.

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