Supplementary Table 1: Summary of clinical trials:

Clinical trial	Patients	Genotype	Treatment Arms
Endurance-1	620, 1:1 randomization across arms A and B	1	Arm A: G/P for 12 weeks Arm B: G/P for 8 weeks
Endurance-2	291-321, 2:1 randomization across arms A and B	2	Arm A: G/P for 12 weeks Arm B: Placebo for 12 weeks
Edurance-3	460, 2:1:1 randomization across arms A, B and C	3	Arm A: G/P for 12 week Arm B: Sofosbuvir co-administered with daclatasvir Arm C: G/P for 8 weeks
Endurance-4	130	4,5 or 6	Single arm of G/P for 12 weeks
Expedition-1	175	1,2,4,5 or 6	Single arm of G/P for 12 weeks
Expedition-4	100, all with CKD stage 4 and 5	1-6	Single arm of G/P for 12 weeks

G/P: glecaprevir + pibrentasvir
CKD: chronic kidney disease

Supplementary Table 2: Patient demographics of all patients who received G/P treatment for 8 or 12 weeks by baseline EHM categories:

	CV		Metabolic			Renal		
	Normal	Elevated	Normal	Pre diabetic	Diabetic	Stage 1	Stage 2	Stage 3
N	1404	149	1500	48	13	791	746	22
Age (mean; years)	51.4	52.9	51.4	55.0	61.3	48.3	54.8	62.1
Gender - male	51.5%	62.4%	52.1%	64.6%	61.5%	58%	47%	50%
Race								
White	81.3%	73.2%	80.9%	70.8%	53.8%	79%	82%	77%
Asian	13.1%	17.4%	13.4%	18.8%	23.1%	15%	13%	9%
Black or African American	3.6%	8.1%	3.7%	6.3%	23.1%	4%	3%	9%
Others	1.9%	1.3%	1.7%	4.2%	0.0%	2%	2%	5%
Fibrosis								
F0–F1	76.1%	67.1%	76.3%	56.3%	23.1%	75.60%	75%	59%
F2	5.7%	8.1%	5.7%	8.3%	23.1%	5.31%	7%	5%
F3	9.2%	9.4%	9.2%	14.6%	0.0%	9.61%	9%	5%
F4	8.8%	15.4%	8.6%	20.8%	53.8%	9.36%	9%	32%
Genotype								
1	51.6%	47.7%	51.3%	47.9%	38.5%	48.5%	54%	55%
2	14.1%	16.1%	14.5%	14.6%	38.5%	14.2%	15%	14%
3	25.3%	22.8%	25.2%	22.9%	0.0%	26.9%	23%	23%
Others (4,5,6)	9.0%	13.4%	9.1%	14.6%	23.1%	10.4%	8%	9%
BMI (>=30)	16.2%	34.2%	17.3%	35.4%	30.8%	16.4%	19%	36%
Prior diabetes history - Yes	5.6%	14.8%	3.9%	66.7%	92.3%	6.7%	6%	14%
History of metabolic syndrome - Yes	12.3%	69.1%	16.1%	60.4%	61.5%	16.6%	18%	45%
Prior cardiovascular disease - Yes	27.1%	38.9%	27.1%	52.1%	76.9%	24.0%	32%	73%
HOMA - IR								

< 2	51.0%	22.8%	50.1%	8.3%	0.0%	46.4%	51%	27%
≥ 2	32.3%	49.0%	32.1%	75.0%	84.6%	34.8%	32%	59%
Missing	16.7%	28.2%	17.7%	16.7%	15.4%	18.5%	17%	14%
HCV History								
DAA experienced	1.1%	2.7%	1.2%	2.1%	7.7%	1.6%	1%	0%
Naïve-all	74.5%	71.1%	74.6%	62.5%	69.2%	74.7%	74%	68%
P/R experienced	24.4%	26.2%	24.2%	35.4%	23.1%	23.6%	25%	32%
Treatment arm								
12 weeks	67.2%	67.8%	67.1%	72.9%	92.3%	68.0%	67%	68%
8 weeks	32.8%	32.2%	32.9%	27.1%	7.7%	32.0%	33%	32%
SVR12								
Yes	99.1%	100.0%	99.3%	97.9%	100.0%	99.1%	99%	100%
No	0.9%	0.0%	0.7%	2.1%	0.0%	0.9%	1%	0%

Note: Includes patients with or without cirrhosis treated with G/P for 8 or 12 weeks across five Phase 3 clinical trials (ENDURANCE-1, ENDURANCE-2, ENDURANCE-3, ENDURANCE-4 and EXPEDITION-1).

Supplementary Table 3: Patient demographics of the all patients who received G/P treatment regimen by treatment naïve non cirrhotic status:

	CV				Metabolic				Renal			
	Naïve, F0-F3	Naïve, F4	Experienced, F4	Experienced, F0-F3	Naïve, F0-F3	Naïve, F4	Experienced, F4	Experienced, F0-F3	Naïve, F0-F3	Naïve, F4	Experienced, F4	Experienced, F0-F3
N	1039	110	36	364	1045	110	36	366	1037	110	36	364
Age (mean; years)	49.4	60.0	60.4	54.1	49.5	59.9	60.4	54.1	49.4	60.0	60.4	54.1
Gender - male	49.6%	59.1%	69.4%	58.0%	49.6%	59.1%	69.4%	58.2%	49.6%	59.1%	69.4%	58.2%
Race												
White	82.0%	80.9%	86.1%	75.3%	81.9%	80.9%	86.1%	75.1%	82.1%	80.9%	86.1%	75.3%
Asian	12.2%	8.2%	2.8%	20.1%	12.3%	8.2%	2.8%	20.2%	12.2%	8.2%	2.8%	20.1%
Black or African American	3.5%	10.0%	11.1%	3.0%	3.4%	10.0%	11.1%	3.0%	3.5%	10.0%	11.1%	3.0%
Others	2.2%	0.9%	0.0%	1.1%	2.2%	0.9%	0.0%	1.1%	2.2%	0.9%	0.0%	1.1%
Fibrosis												
F0–F1	84.6%	0.0%	0.0%	79.4%	84.6%	0.0%	0.0%	79.2%	84.6%	0.0%	0.0%	79.4%
F2	6.3%	0.0%	0.0%	7.4%	6.2%	0.0%	0.0%	7.4%	6.3%	0.0%	0.0%	7.4%
F3	9.1%	0.0%	0.0%	13.2%	9.2%	0.0%	0.0%	13.4%	9.2%	0.0%	0.0%	13.2%
F4	0.0%	100.0%	100.0%	0.0%	0.0%	100.0%	100.0%	0.0%	0.0%	100.0%	100.0%	0.0%
Genotype												
1	41.8%	60.0%	66.7%	73.6%	41.5%	60.0%	66.7%	73.5%	41.9%	60.0%	66.7%	73.6%
2	12.9%	21.8%	19.4%	15.7%	13.4%	21.8%	19.4%	15.8%	12.9%	21.8%	0.0%	15.7%
3	37.4%	0.0%	0.0%	0.0%	37.2%	0.0%	0.0%	0.0%	37.5%	0.0%	19.4%	0.0%
Others (4,5,6)	7.9%	18.2%	13.9%	10.7%	7.8%	18.2%	13.9%	10.7%	7.7%	18.2%	13.9%	10.7%
BMI (>=30)	15.5%	40.9%	50.0%	14.6%	15.6%	40.9%	50.0%	14.5%	15.4%	40.9%	50.0%	14.6%
Prior diabetes history - Yes	3.6%	20.0%	22.2%	9.1%	3.6%	20.0%	22.2%	9.3%	3.5%	20.0%	22.2%	9.1%
History of metabolic syndrome - Yes	14.4%	37.3%	47.2%	18.4%	14.5%	37.3%	47.2%	18.6%	14.4%	37.3%	47.2%	18.4%
Prior cardiovascular disease - Yes	22.6%	50.0%	69.4%	34.1%	22.7%	50.0%	69.4%	34.2%	22.6%	50.0%	69.4%	34.1%
HOMA - IR												
< 2	51.8%	21.8%	19.4%	48.9%	51.9%	21.8%	19.4%	49.2%	51.9%	21.8%	19.4%	48.9%

≥ 2	28.0%	63.6%	69.4%	38.5%	28.0%	63.6%	69.4%	38.3%	28.1%	63.6%	69.4%	38.5%
Missing	20.2%	14.5%	11.1%	42.9%	20.1%	14.5%	11.1%	12.6%	20.1%	14.5%	11.1%	12.6%
HCV History												
DAA experienced	0.0%	0.0%	30.6%	2.5%	0.0%	0.0%	30.6%	2.5%	0.0%	0.0%	30.6%	2.5%
Naïve-all	100.0%	100.0%	0.0%	0.0%	100.0%	100.0%	0.0%	0.0%	100.0%	100.0%	0.0%	0.0%
P/R experienced	0.0%	0.0%	69.4%	97.5%	0.0%	0.0%	69.4%	97.5%	0.0%	0.0%	69.4%	97.5%
Treatment arm												
12 weeks	64.0%	100.0%	100.0%	64.0%	64.2%	100.0%	100.0%	64.2%	63.9%	100.0%	100.0%	64.0%
8 weeks	36.0%	0.0%	0.0%	36.0%	35.8%	0.0%	0.0%	35.8%	36.1%	0.0%	0.0%	36.0%
SVR12												
Yes	99.0%	100.0%	97.2%	99.7%	99.0%	100.0%	97.2%	99.7%	99.0%	100.0%	97.2%	99.7%
No	1.0%	0.0%	2.8%	0.3%	1.0%	0.0%	2.8%	0.3%	1.0%	0.0%	2.8%	0.3%

Note: Includes patients with or without cirrhosis treated with G/P for 8 or 12 weeks across five Phase 3 clinical trials (ENDURANCE-1, ENDURANCE-2, ENDURANCE-3, ENDURANCE-4 and EXPEDITION-1).

Supplementary Table 4: Impact of treatment with 8 week G/P on studied biomarkers by treatment history and cirrhotic status

	N	Adjusted baseline	W1	W2	W4	W8	PTW4
	Triglycerides						
All 8 week treated patients	505	165.8	-13.7*	-15.2*	-17.8*	-17.8*	-5.5*
Naïve, F0 – F3	374	166.3	-11.2*	-14.3*	-19.3*	-17.7*	-2.2
P/R Experienced, F0 - F3	131	153.8	-29.4*	-26.6*	-22.0*	-26.9*	-24.2*
	Glucose						
All 8 weeks treated patients	505	129.9	-2.6	-3.3	-3.2	-11.1*	-13.4*
Naïve, F0 - F3	374	130.9	-11.5*	-17.7*	-15.6*	-31.6*	-31.3*
P/R Experienced, F0 - F3	131	126.8	-0.9	6.2	3.1	3.2	-1.1
	eGFR						
All 8 weeks treated patients	505	95.9	0.9	0.3	0.3	-0.5	-0.8
Naïve, F0 - F3	374	98.1	-1.3	-1.8	-1.4	-2.5	-2.8
P/R Experienced, F0 - F3	131	92.3	2.7	2.1	1.1	1.1	0.7

*indicate statistical significance at alpha = 0.05; BL: baseline; W: week; PTW4: Post treatment week 4; P/R: Peg-interferon + ribavirin

Supplementary Table 5a: Impact of treatment with G/P on triglycerides by treatment history and cirrhotic status and by baseline EHM level

				Adjusted change from baseline			
Normal							
	N	**Adjusted baseline**	**W1**	**W2**	**W4**	**EOT**	**PTW4**
Naïve, F0-F3	945	96.1	12.6*	10.6*	9.6*	8.7*	18.6*
Naïve, F4	98	106.1	20.8*	12.3	11.3	13.9	20.2*
Experienced, F4	25	112.6	1.6	16.9	15.8	10.8	20.1
Experienced, F0-F3	332	99.9	0.06	1.3	-1.2	-0.3	9.9
Elevated							
Naïve, F0-F3	94	194.7	-54.8*	-54.9*	-39.3*	-47.4*	-36.1*
Naïve, F4	12	195.3	-57.1*	-89.1*	-92.8*	-88.6*	-96.7*
Experienced, F4	11	202.5	-54.2*	-80.9*	-9.4	-70.2*	-44.8*
Experienced, F0-F3	32	188.2	-41.4*	-46.9*	-39.9*	-47.3*	-50.6*

*indicate statistical significance at alpha = 0.05; BL: baseline; W: week; PTW4: Post treatment week 4

Supplementary Table 5b: Impact of treatment with G/P on glucose by treatment history and cirrhotic status and by baseline EHM level

				Adjusted change from baseline			
Normal							
	N	**Adjusted baseline**	**W1**	**W2**	**W4**	**EOT**	**PTW4**
Naïve, F0-F3	1012	93.9	5.1*	4.6*	4.1*	4.5*	5.1*
Naïve, F4	97	104.5	6.7	4.7	1.9	2.6	2.3
Experienced, F4	32	103.1	4.2	-1.9	-1.4	-3.7	-1.1
Experienced, F0-F3	346	95.7	0.7	1.6	0.9	0.9	0.9
Pre-diabetic							
Naïve, F0-F3	21	137.1	-12.9*	-6.3*	-15.1*	-30.1*	-39.7*
Naïve, F4	8	139.6	-23.7	-35.7*	-30.9*	-45.5*	-33.9*
Experienced, F4	2	134.1	-8.7	-14.8	-28.8*	-29.8*	-21.8
Experienced, F0-F3	15	152.8	-3.6	-1.3	-8.6*	-8.1*	-21.2*
Diabetic							
Naïve, F0-F3	4	205.4	12.9	-34.4*	-1.9	-80.6*	-93.5*
Naïve, F4	5	232.2	-101.5*	-100.5*	-111.7*	-146.2*	-71.3*
Experienced, F4	2	179.1	-11.1	-65.3*	-107.4*	-90.8*	-77.5*
Experienced, F0-F3	2	182.6	-26.5*	-18.6*	-42.1*	-42.7*	-50.9*

*indicate statistical significance at alpha = 0.05; BL: baseline; W: week; PTW4: Post treatment week 4

Supplementary Table 5c: Impact of treatment with G/P on eGFR by treatment history and cirrhotic status and by baseline EHM level

				Adjusted change from baseline			
CKD Stage 1							
	N	**Adjusted baseline**	**W1**	**W2**	**W4**	**EOT**	**PTW4**
Naïve, F0-F3	529	102.4	-3.4*	-2.8*	-3.2*	-3.3*	-4.3*
Naïve, F4	59	104.8	-5.4*	-1.3	-5.9*	-3.7	-5.2*
Experienced, F4	15	108.1	-8.8*	-11.4*	-7.5	-12.5*	-7.1
Experienced, F0-F3	184	102.1	-5.3*	-6.1*	-6.9*	-9.4*	-9.1*
CKD Stage 2							
Naïve, F0-F3	497	80.7	2.4*	2.8*	2.9*	2.1*	2.3*
Naïve, F4	47	77.6	0.8	1.6	1.6	2.2	1.7
Experienced, F4	18	76.2	-5.3	-2.5	-3.2	-7.6	-4.2
Experienced, F0-F3	176	80.6	0.8	1.1	-0.2	-0.4	0.6
CKD Stage 3							
Naïve, F0-F3	11	61.4	10.9*	12.2*	10.1*	4.5	12.3*
Naïve, F4	4	53.9	0.7	7.2	7.4	-1.1	4.2
Experienced, F4	3	58.2	-8.1	2.1	1.6	3.6	3.3
Experienced, F0-F3	4	57.5	6.1	3.8	4.1	6.8	7.3

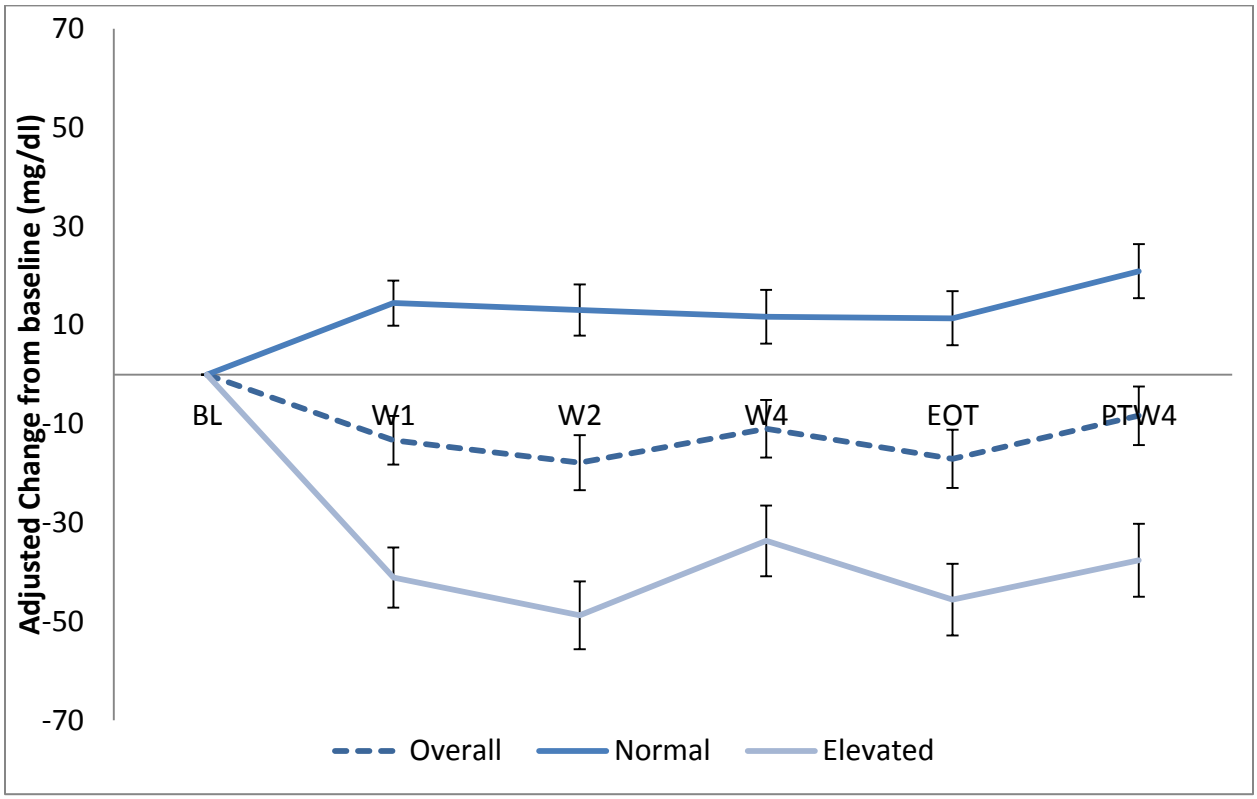
*indicate statistical significance at alpha = 0.05; BL: baseline; W: week; PTW4: Post treatment week 4

Supplementary Table 6: Descriptive mean change from baseline for various study populations

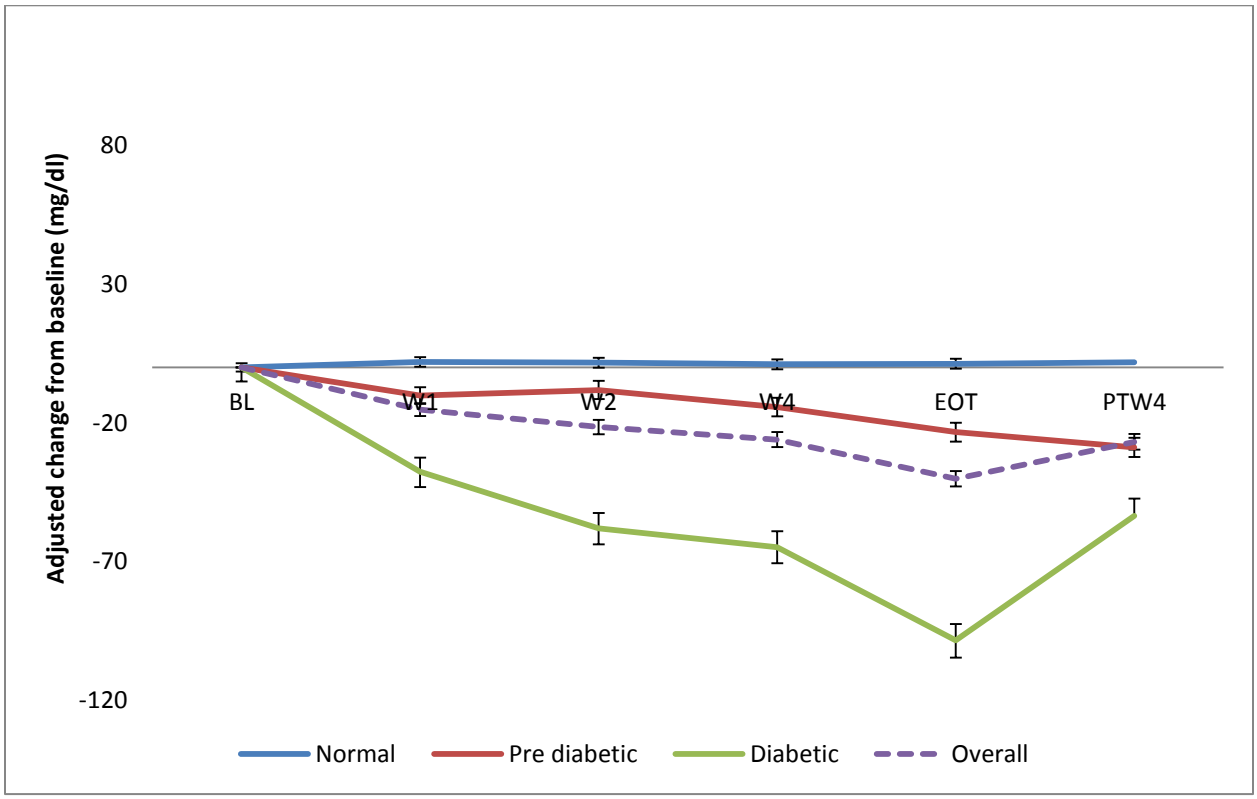
	N	Unadjusted baseline	Change from BL to EOT	Change from BL to PTW4
	Glucose			
Overall - G/P treated	1550	97.0	-0.1	0.6
Normal	1491	93.8	1.5*	2.0*
Pre- diabetic	59	178.7	-38.7*	-36.2*
Diabetic				
	Triglycerides			
Overall - G/P treated	1553	103.6	1.0	10.7*
Normal	1490	89.9	6.7*	16.6*
Elevated	150	232.9	-52.9*	-45.5*
	eGFR			
Overall - G/P treated	1551	93.0	-2.6*	-2.4*
Normal	788	106.8	-5.5*	-5.9*
Stage 2 and stage 3	763	78.8	0.4	1.2*
Stage 4 and 5	104	10.6	-0.2	-0.16

*indicate statistical significance at alpha = 0.05; BL: baseline; W: week; PTW4: Post treatment week 4

Supplementary Figure 1: Predicted change in triglycerides from baseline: Overall all HCV patients treated with G/P



Supplementary Figure 2: Predicted change in glucose from baseline: Overall all HCV patients treated with G/P



Supplementary Figure 3: Predicted change in eGFR from baseline: Overall all HCV patients treated with G/P