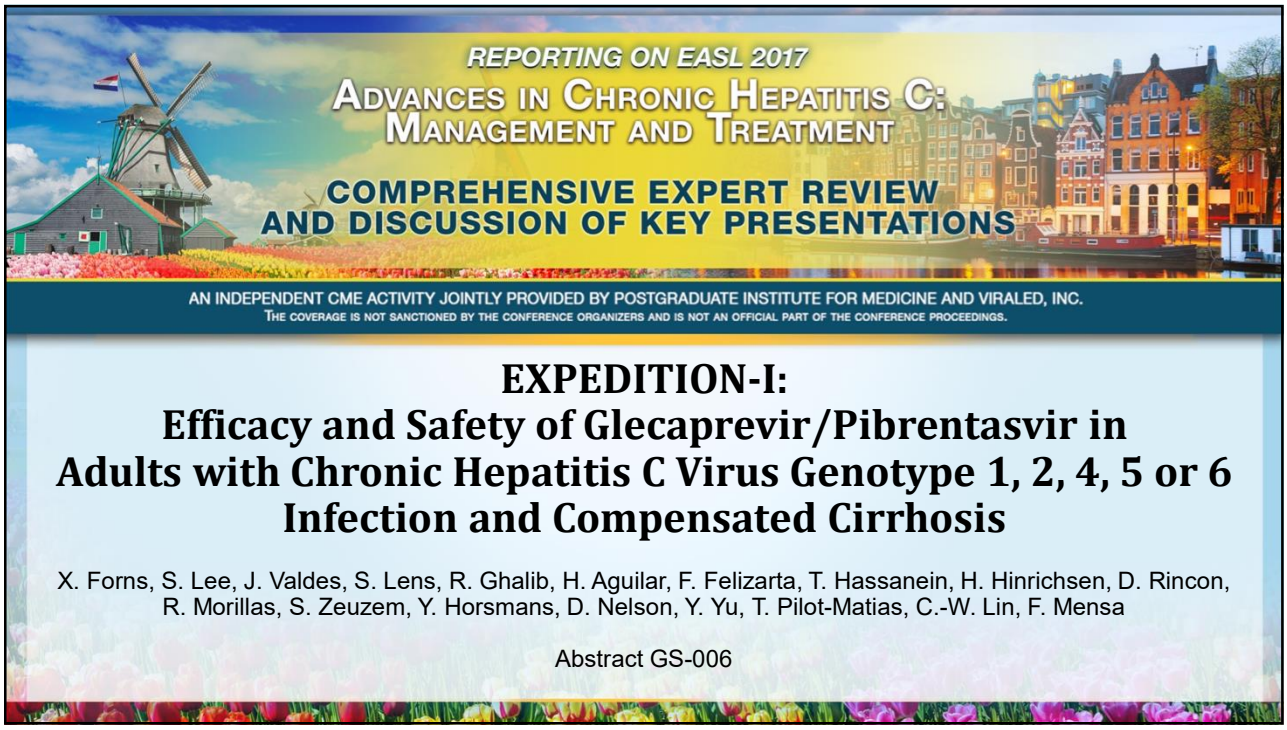
New Data with Glecaprevir/Pibrentasvir

Jürgen Rockstroh, MD
Department of Medicine I
University of Bonn, Germany



EXPEDITION-I: Efficacy and Safety of Glecaprevir/Pibrentasvir in Adults with Chronic Hepatitis C Virus Genotype 1, 2, 4, 5 or 6 Infection and Compensated Cirrhosis

X. Forns, S. Lee, J. Valdes, S. Lens, R. Ghalib, H. Aguilar, F. Felizarta, T. Hassanein, H. Hinrichsen, D. Rincon, R. Morillas, S. Zeuzem, Y. Horsmans, D. Nelson, Y. Yu, T. Pilot-Matias, C.-W. Lin, F. Mensa

Abstract GS-006

EXPEDITION-I Study: Next Generation Direct-Acting Antivirals

Glecaprevir
(formerly ABT-493)
pangenotypic NS3/4A protease inhibitor

Coformulated: G/P

Pibrentasvir
(formerly ABT-530)
pangenotypic NS5A inhibitor

***In vitro*:**[1,2]
- High barrier to resistance
- Potent against common NS3 polymorphisms (e.g., positions 80, 155, and 168) and NS5A polymorphisms (e.g., positions 28, 30, 31 and 93)
- Synergistic antiviral activity

Clinical PK & metabolism:
- Once-daily oral dosing with food
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

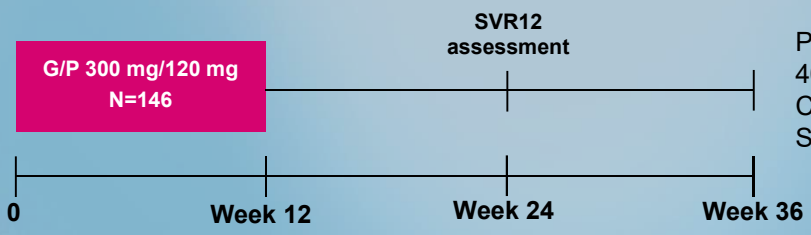
G/P is co-formulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg
Glecaprevir was identified by AbbVie and Enanta.

1. Ng TI, et al. Antimicrobial Agents and Chemotherapy; 2017 (in press).
2. Ng TI, et al. Abstract 636. CROI, 2014

EXPEDITION-1 Study: Objective and Study Design

Objective

- Evaluate the efficacy and safety of G/P for 12 weeks in patients with HCV GT1, 2, 4, 5 or 6 infection and compensated cirrhosis



Patients were enrolled at 40 study sites in Belgium, Canada, Germany, South Africa, Spain, and the United States

Open-label Treatment

G/P is coformulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg.

Forns X, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. GS-006.

EXPEDITION-1 Study: Baseline Demographics and Clinical Characteristics

Characteristic	12-week G/P N = 146
Male, n (%)	90 (62)
Age, median (range), years	60 (26–88)
White race,* n (%)	120 (82)
BMI, median (range), kg/m^2	29 (18–55)
HCV genotype, n (%)†	
1a	48 (33)
1b	39 (27)
2	34 (23)
4	16 (11)
5	2 (1)
6	7 (5)

G/P, glecaprevir/pibrentasvir; BMI, body mass index
*Race and ethnicity are self-reported
†Genotype determined by the Versant HCV Genotype Inno-LiPA Assay Version 2.0

Forns X, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. GS-006.

EXPEDITION-1 Study: Baseline Demographics and Clinical Characteristics (Cont'd)

	12-week G/P N = 146
HCV RNA, median (range) $\log_{10}$ IU/mL	6.1 (3.1–7.4)
Treatment-naïve	110 (75)
Treatment-experienced	36 (25)
IFN-based (IFN/pegIFN ± RBV)	25 (69)
SOF-based (SOF + RBV ± pegIFN)	11 (31)
Platelet count <100,000, 10^9/L	29 (20)
INR <1.7	144 (99)
Total bilirubin ≥2, mg/dL	5 (3)
Albumin ≥LLN	145 (99)
Child-Pugh score at screening	
5	133 (91)
6	13 (9)

IFN, interferon; SOF, sofosbuvir; INR, international normalized ratio; LLN, lower limit of normal (33)

Forns X, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. GS-006.

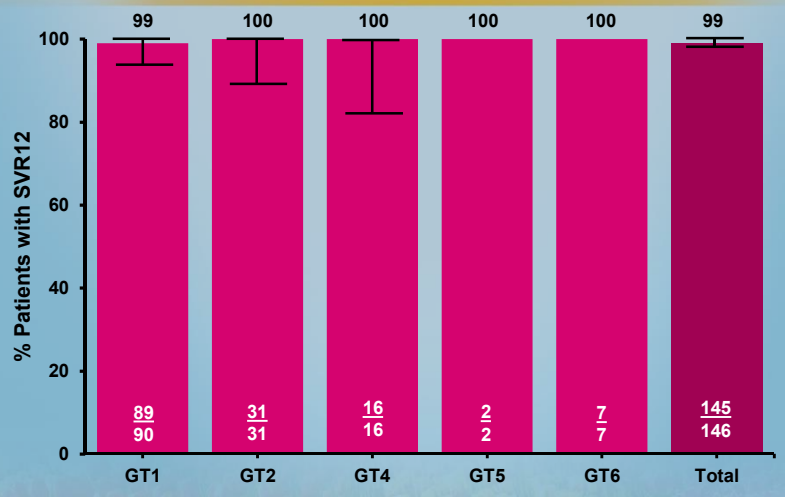
EXPEDITION-1 Study: Key Baseline Polymorphisms

Target(s), n (%)*	12-week G/P N = 133*
None	76 (57)
NS3 only	2 (2)
NS5A only	53 (40)
NS3 + NS5A	2 (2)

*Baseline polymorphisms relative to appropriate subtype specific reference sequence at 15% detection threshold by next generation sequencing in samples that had sequences available for both targets (N) at amino acid positions:
NS3: 155, 156, 168
NS5A: 24, 28, 30, 31, 58, 92, 93

Forns X, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. GS-006.

EXPEDITION-1 Study: SVR12 by Intent-to-Treat (ITT) Analysis



*Patient with HCV GT1a infection relapsed at PTW8 - No treatment-emergent substitutions were present in NS3
- In NS5A, Y93N was present at baseline; Y93N, Q30R and H58D were present at the time of failure

Forns X, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. GS-006.

EXPEDITION-1 Study: Summary of Adverse Events (AE)

Event, n (%)	12-week G/P N=146
Any AE	101 (69)
Any serious AE	11 (8)
DAA-related serious AE	0
Any AE leading to discontinuation of study drug	0
Death*	1 (0.7)
Common AEs (occurring in ≥10% of patients)	
Fatigue	28 (19)
Headache	20 (14)
Pruritus	14 (10)
HCC	2 (1)

DAA, direct-acting antiviral; HCC, hepatocellular carcinoma
*Patient had a history of hemophilia and died post-treatment due to a cerebral hemorrhage assessed by the investigator as not related to the study drug

Forns X, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. GS-006.

Efficacy and Safety of Glecaprevir/Pibrentasvir in Patients Coinfected with Hepatitis C Virus and Human Immunodeficiency Virus-1: the EXPEDITION-2 Study

J. Rockstroh, K. Lacombe, R.M. Viani, C. Orkin, D. Wyles, A. Luetkemeyer, R. Soto-Malave, R. Flisiak, S. Bhagani, K.E. Sherman, T. Shimonova, P. Ruane, J. Sasadeusz, J. Slim, Z. Zhang, T.I. Ng, R. Trinh, M. Sulkowski

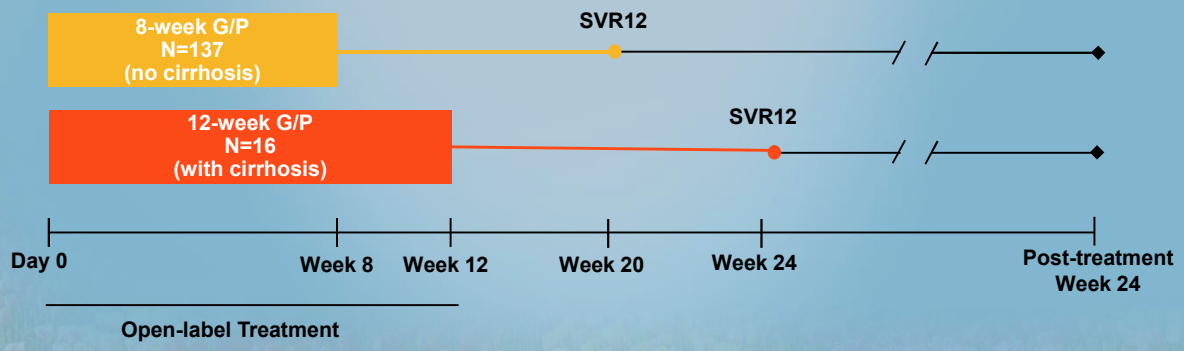
Abstract LBP-522

EXPEDITION-2 Study: Objective and Study Design

Objective

- EXPEDITION-2 is a phase 3, multi-center global study evaluating 8- or 12-week treatment with G/P in HCV/HIV-1 co-infected adults without or with compensated cirrhosis, respectively

Study Design



Rockstroh J, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. LBP-522

EXPEDITION-2 Study: Inclusion Criteria

- Anti retroviral therapy (ART) naïve with CD4+ count ≥500 cells/mm^3 or ≥29% or
- On a stable ART regimen for at least 8 weeks prior to screening, with CD4+ count ≥200 cells/mm^3 or ≥14% and plasma HIV-1 RNA <LLOQ:

Absence or Presence of Cirrhosis Documented by Liver Biopsy or:

	Without Cirrhosis	With Cirrhosis
Fibroscan or	<12.5kPa	≥12.5 kPa
FibroTest and APRI	≤0.48 + <1	≥0.75 + >2

Allowed ART Anchor Agents (All Patients)	Raltegravir (RAL) BID
	Dolutegravir (DTG) QD or BID
	Rilpinvirine (RPV) QD
	Elvitegravir /Cobicistat (EVG/COBI) QD
Allowed ART Regimens (Patients without Cirrhosis)	Darunavir (DRV) + Ritonavir (r) QD
	DRV/COBI QD
	Lopinavir/r BID
Allowed N(t)RTI Backbone (All Patients)	Tenofovir Disoproxil Fumarate (TDF)
	Tenofovir Alafenamide (TAF)
	Abacavir (ABC)
	Emtricitabine (FTC)
	Lamivudine (3TC)

ART, anti retroviral therapy; BID, twice-daily; QD, once-daily; N(t)RTI, nucleoside/nucleoti de reverse transcriptase inhibitor

Rockstroh J, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. LBP-522

EXPEDITION-2 Study: Baseline Demographics and Disease Characteristics

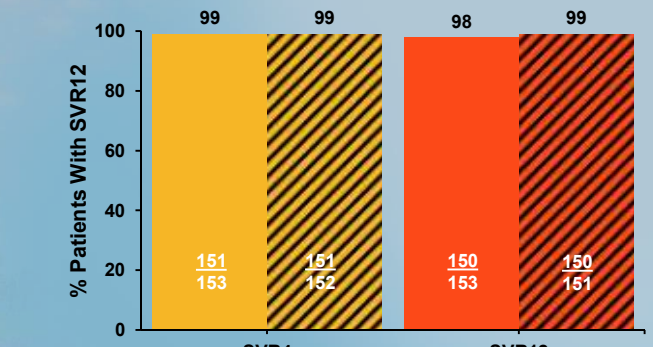
Characteristics	Without Cirrhosis 8 Weeks N = 137	With Cirrhosis 12 Weeks N = 16
Male, n (%)	113 (83)	15 (94)
Age, median (range), years	45 (23-74)	50 (35-62)
BM, median (range), kg/m^2	45 (23-74)	27.6 (21.6-38.2)
Race, n (%)		
White	106 (77)	15 (94)
Black	24 (18)	1 (6)
Genotype, n(%)		
1	84 (61)	10 (63)
Subtype 1a	66 (48)	5 (31)
Subtype 1b	18 (13)	5 (31)
2	12 (9)	1 (6)
3	22 (16)	4 (25)
4	16 (12)	1 (6)
5	0	0
6	3 (2)	0
HCV RNA, median (range), $\log_{10}$ IU/mL	6.2 (4.0-7.4)	6.1 (4.4-7.0)
HCV treatment-naïve, n (%)	111 (81)	14 (87)
HCV treatment-experienced, n(%)	26 (19)	2 (13)
IFN-based	23 (17)	2(13)
SOF-based	3 (2)	0
Fibrosis Stage, n (%)		
F0-F1	120 (88)	0
F2	2 (1)	0
F3	15 (11)	0
F4	0	16 (100)

EXPEDITION-2 Study: Baseline Demographics and Disease Characteristics (Cont'd)

Characteristics	Without Cirrhosis 8 Weeks N = 137	With Cirrhosis 12 Weeks N = 16
CD4+ cell count, median (range), cells/mm^3	588 (154-2103)	545 (222-1806)
No antiretroviral therapy, n (%)	9/137 (7)	0
Anchor ARV Agent, n (%)		
Raltegravir	39 (29)	6 (38)
Dolutegravir	62 (45)	5 (31)
Rilpinvirine	27 (20)	5 (31)
Elvitegravir/cobi	1 (1)	0
Darunavir/r	0	0
Lopinavir/r	0	0
N(t)RTI backbone agent, n (%)		
Tenofovir disoproxil fumarate	74 (54)	13 (81)
Tenofovir alafenamide	6 (4)	0
Abacavir	49 (36)	3 (19)
Concomitant PPI use, n (%)	11 (8)	1 (6)
IDU within 12 months, n (%)	3 (2)	1 (6)
IDU >12 months prior to screening, n (%)	62 (45)	10 (63)
On opiate substitution therapy, n (%)	11 (8)	2 (13)

BMI, body mass index; IFN, interferon; SOF, sofosbuvir; ARV, antiretroviral; N(t)RTI, nucleoside/nucleotide reverse transcriptase inhibitor; PPI, proton pump inhibitor.
*Race was self-reported

EXPEDITION-2 Study: Efficacy Results



	SVR4	SVR12
Breakthrough	1	1
Relapse	0	0
Missing Data	0	1*
Discontinued	1	1

mITT, modified ITT population, which excludes patients with non-virologic failure.
*One patient achieved SVR4 but as lost to follow-up due to homelessness and did not return for PTW12 visit

- The SVR12 rate in the mITT population of patients with cirrhosis treated for 12 weeks was 93% (14/15); 1 patient with GT3a infection and cirrhosis had on-treatment virologic failure at treatment Week 8:
  - NS3: no polymorphisms at baseline; Y56H at failure
  - NS5A: A30V at baseline; S24F & M28K at failure; (A30V not detected)
- The SVR12 rate was 100% (136/136) in patients without cirrhosis treated for 8 weeks

Rockstroh J, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. LBP-522

EXPEDITION-2 Study: Adverse Events and Lab Abnormalties

Event, n (%)	Without Cirrhosis 8 Weeks N = 137	With Cirrhosis 12 Weeks N = 16
Any AE	86 (63)	8 (50)
Serious AE	2 (1.5)*	1 (6)†
DAA-related serious AE	0	0
AE leading to discontinuation	0	1 (6)†
AEs occurring in ≥5% of overall patients		
Fatigue	18 (13)	0
Nausea	12 (9)	1 (6)
Headache	12 (9)	0
Nasopharyngitis	12 (9)	0
Laboratory Abnormalities‡		
ALT, grade ≥3 (>5 x ULN)	0	0
AST, grade ≥3 (>5 x ULN)	0	0
Total Bilirubin, grade ≥3 (>3 x ULN)	1 (0.7)	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
*Upper GI hemorrhage and urolithiasis in 1 patient each, both unrelated to G/P.
†One patient with cerebrovascular accident and cerebral hemorrhage, both unrelated to G/P.
‡Grade must be more extreme than baseline.

Rockstroh J, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. LBP-522

REPORTING ON EASL 2017

ADVANCES IN CHRONIC HEPATITIS C: MANAGEMENT AND TREATMENT

COMPREHENSIVE EXPERT REVIEW AND DISCUSSION OF KEY PRESENTATIONS

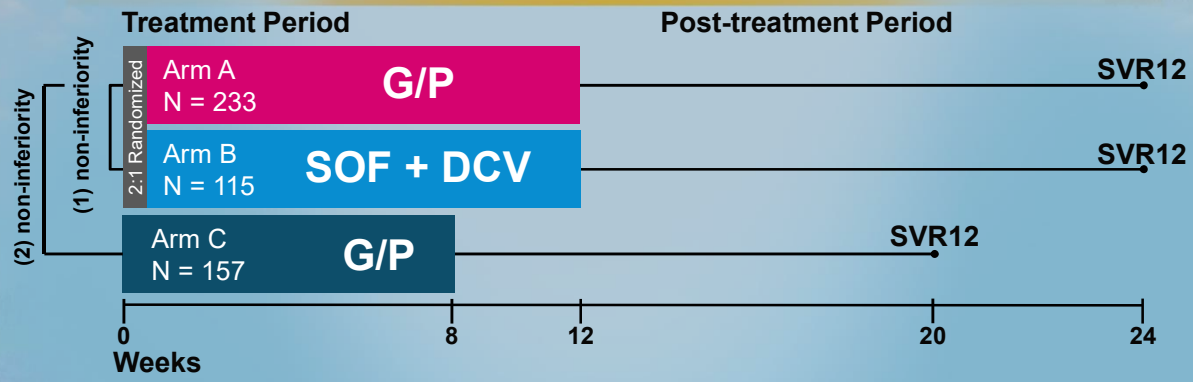
AN INDEPENDENT CME ACTIVITY JOINTLY PROVIDED BY POSTGRADUATE INSTITUTE FOR MEDICINE AND VIRALED, INC.
THE COVERAGE IS NOT SANCTIONED BY THE CONFERENCE ORGANIZERS AND IS NOT AN OFFICIAL PART OF THE CONFERENCE PROCEEDINGS.

ENDURANCE-3: safety and efficacy of glecaprevir/pibrentasvir compared to sofosbuvir plus daclatasvir in treatment-naïve HCV genotype 3-infected patients without cirrhosis

G.R. Foster, E. Gane, A. Asatryan, T. Asselah, P.J. Ruane, S. Pol, F. Poordad, C.A. Stedman, G. Dore, S.K. Roberts, K. Kaita, J. Vierling, H.E. Vargas, J. Kort, C.-W. Lin, R. Liu, T. Ng, F. Mensa

Abstract GS-007

ENDURANCE-3 Study: Objective and Study Design



- Arm C: 8-week treatment duration
- Per discussion with regulatory authorities after phase 2 treatment data became available, an 8 week treatment Arm of G/P was added to the study design
  - SVR12: Non-inferiority of 8 weeks of G/P compared to 12 weeks of G/P*

*Endpoint was tested only after 12 weeks of G/P was determined non-inferior to 12 weeks of SOF + DCV

Foster G, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. GS-007.

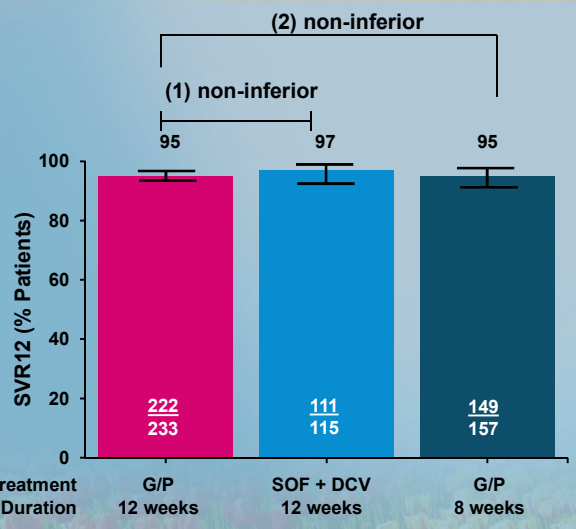
ENDURANCE-3 Study: Baseline Demographics and Clinical Characteristics

Characteristic	2:1 randomized		Non-randomized
	G/P 12 weeks N = 233	SOF + DCV 12 weeks N = 115	G/P 8 weeks N = 157
Male, n (%)	121 (52)	52 (45)	92 (59)
White race, n (%)	205 (88)	103 (90)	134 (85)
Age, median years (range)	48 (22 – 71)	49 (20 – 70)	47 (20 – 76)
BMI, median kg/m^2 (range)	25 (17 – 49)	25 (18 – 42)	26 (18 – 44)
HCV RNA, median $\log_{10}$ IU/mL (range)	6.1 (3.5 – 7.5)	6.0 (3.8 – 7.4)	6.1 (1.2 – 7.6)
History of injection drug use, n (%)	149 (64)	73 (63)	104 (66)
Baseline fibrosis stage, n (%)			
F0 – F1	201 (86)	97 (84)	122 (78)
F2	12 (5)	8 (7)	8 (5)
F3	20 (9)	10 (9)	27 (17)
Subtype GT3a, n/N (%)*	226/229 (99)	113/113 (100)	154/155 (99)

BMI, body mass index; DCV, daclatasvir; G/P, coformulated glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; SOF, sofosbuvir
*HCV subtype determined by phylogenetic analysis; N = total number of patients with sequence data available

Foster G, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. GS-007.

ENDURANCE-3 Study: Results SVR12 by Intent-to-Treat (ITT) Analysis



Non-inferiority:

- Lower bound of the confidence interval (CI) of the difference in SVR12 must be above -6%*
  - **(1)** -1.2% (95% CI -5.6 – 3.1)
  - **(2)** -0.4% (97.5% CI -5.4 – 4.6)
- **Both G/P treatments met non-inferiority criteria for the primary endpoint**

*Conventional statistical methods were used in multiplicity comparison for determining non-inferiority

Foster G, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. GS-007.

ENDURANCE-3 Study: All Treatment Outcomes

	2:1 randomized		Non-randomized
Outcome, n (%)	**G/P 12 weeks N = 233**	**SOF + DCV 12 weeks N = 115**	**G/P 8 weeks N = 157**
Sustained virologic response	222 (95)	111 (97)	149 (95)
Virologic Failure			
Breakthrough	1 (<1)	0	1 (1)
Relapse	3 (1)	1 (1)	5 (3)
Failure due to other reasons			
Discontinuation due to AE	1 (<1)	1 (1)	0
Withdrawal of consent	1 (<1)	0	0
Non-compliance	1 (<1)	0	0
Lost to follow-up / missing SVR12	4 (2)	2 (2)	2 (1)

AE, adverse event; G/P, coformulated glecaprevir/pibrentasvir; DCV, daclatasvir; SOF, sofosbuvir; SVR12, sustained virologic response at post-treatment week 12

Foster G, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. GS-007.

ENDURANCE-3 Study: Resistance Analysis

	2:1 randomized		Non-randomized
SVR12 by baseline polymorphisms, n/N (%)	**G/P 12 weeks**	**SOF + DCV* 12 weeks**	**G/P 8 weeks**
NS3 only	26/26 (100)	–	14/15 (93)
NS5A only	35/36 (97)	20/21 (95)	34/36 (94)
NS3 + NS5A	6/7 (86)	–	5/7† (71)
None	151/153 (99)	89/89 (100)	94/95 (99)

- Overall, 97% (mITT analysis; 371/381) of GT3 infected patients receiving G/P achieved SVR12
- 3% of patients (n = 10) had virologic failure
  - Common baseline polymorphisms: NS3 A166S‡ (n = 3); NS5A A30K‡ (n=5)
  - Common substitutions at failure: A30K+Y93H (n = 5); confers 69-fold resistance to PIB
  - G/P for 8 weeks: 5/5 (100%) patients with Y93H at baseline achieved SVR12

Patients that prematurely discontinued treatment or were lost to follow-up were not included in the analysis
Polymorphisms detected by next-gen sequencing using 15% detection threshold at amino acid positions: NS3: 36, 56, 80, 155, 156, 166, 168; NS5A: 24, 28, 29, 30, 31, 32, 58, 92, 93
*NS3 sequences of samples were not determined
†One patient who had virologic failure had poor adherence and baseline polymorphisms in both NS3 and NS5A
‡Does not confer resistance to GLE or PIB

Foster G, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. GS-007.