ADVANCES IN CHRONIC HEPATITIS C:
MANAGEMENT AND TREATMENT
INDEPENDENT REPORTING ON AASLD 2016
COMPREHENSIVE EXPERT REVIEW AND DISCUSSION OF KEY PRESENTATIONS
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Surveyor-II, Part 3: Efficacy and Safety of Glecaprevir/Pibrentasvir (Abt-493/Abt-530) in Patients with Hepatitis C Virus Genotype 3 Infection with Prior Treatment Experience and/or Cirrhosis

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Abstract 113

Next Generation Direct-Acting Antivirals

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

Pibrentasvir (formerly ABT-530)
pangenotypic NS5A inhibitor

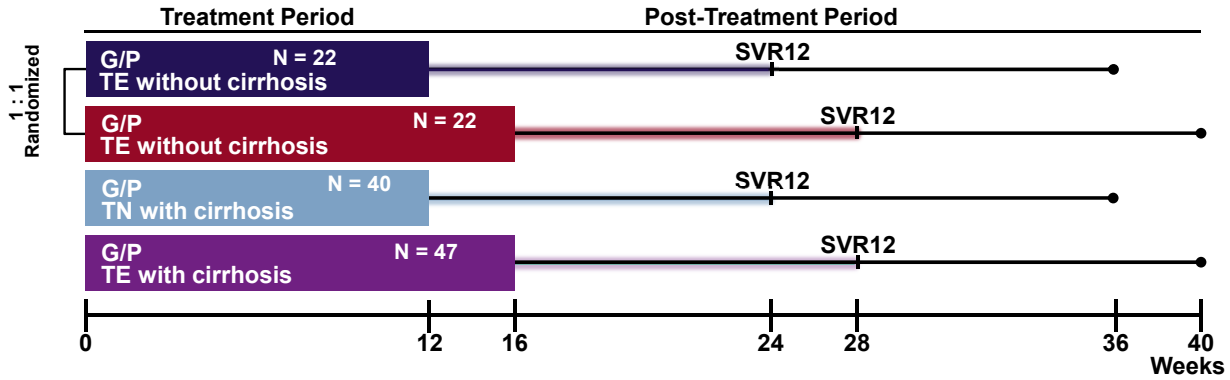
Collectively: G/P

In vitro:[1,2]
- High barrier to resistance
- Potent against common NS3 polymorphisms (eg, positions 80, 155, and 168) and NS5A polymorphisms (eg, positions 28, 30, 31 and 93)
- Additive/synergistic antiviral activity

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

G/P is coformulated 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. Abstract 636. CROI, 2014. 2. Ng TI, et al. Abstract 639. CROI, 2014.
2. Wyles D, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 113.

SURVEYOR-II Part 3: Study Design and Patient Population



- Included GT3
- Patients without cirrhosis or with compensated cirrhosis
- Excluded prior treatment with HCV DAA other than SOF
- Excluded HBV or HIV coinfection

Wyles D, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 113.

Baseline Demographics and Clinical Characteristics

	1:1 Randomized			
Characteristic	**Treatment Experienced – Cirrhosis 12 Weeks N = 22**	**Treatment Experienced – Cirrhosis 16 Weeks N = 22**	**Treatment Naïve + Cirrhosis 12 Weeks N = 40**	**Treatment Experienced + Cirrhosis 16 Weeks N = 47**
Male, n (%)	14 (64)	14 (64)	24 (60)	36 (77)
White race, n (%)	17 (77)	20 (91)	37 (93)	42 (89)
Age, median years (range)	56 (35 – 68)	59 (29 – 66)	56 (36 – 70)	59 (47 – 70)
BMI, median kg/m^2 (range)	26 (19 – 42)	28 (22 – 48)	29 (21 – 51)	27 (21 – 42)
***IL28B* non-CC genotype, n (%)**	15 (68)	19 (86)	20 (50)	34 (72)
HCV RNA, median $\log_{10}$ IU/mL (range)	6.6 (5.1 – 7.5)	6.1 (4.7 – 7.3)	6.2 (4.2 – 7.1)	6.5 (4.6 – 7.2)
HCV RNA ≥6,000,000 IU/mL, n (%)	9 (41)	7 (32)	4 (10)	10 (21)
Prior treatment history, n (%)				
Naïve	0	0	40 (100)	0
IFN/pegIFN ± RBV	14 (64)	13 (59)	0	22 (47)
SOF + RBV ± pegIFN	8 (36)	9 (41)	0	25 (53)
Baseline Fibrosis Stage*, n (%)				
F0-F1	11 (50)	15 (68)	0	0
F2	4 (18)	2 (9)	0	0
F3	7 (32)	5 (23)	0	0
F4	0	0	40 (100)	47 (100)

BMI, body mass index; G/P, coformulated glecaprevir and pibrentasvir; HCV, hepatitis C virus; IFN, interferon; *IL28B*, interleukin 28; NS, non-structural protein; pegIFN, pegylated interferon; SOF, sofosbuvir
*Data missing for 1 patient in Arm A (column 1) and 1 patient in Arm B (column 3)

Wyles D, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 113.

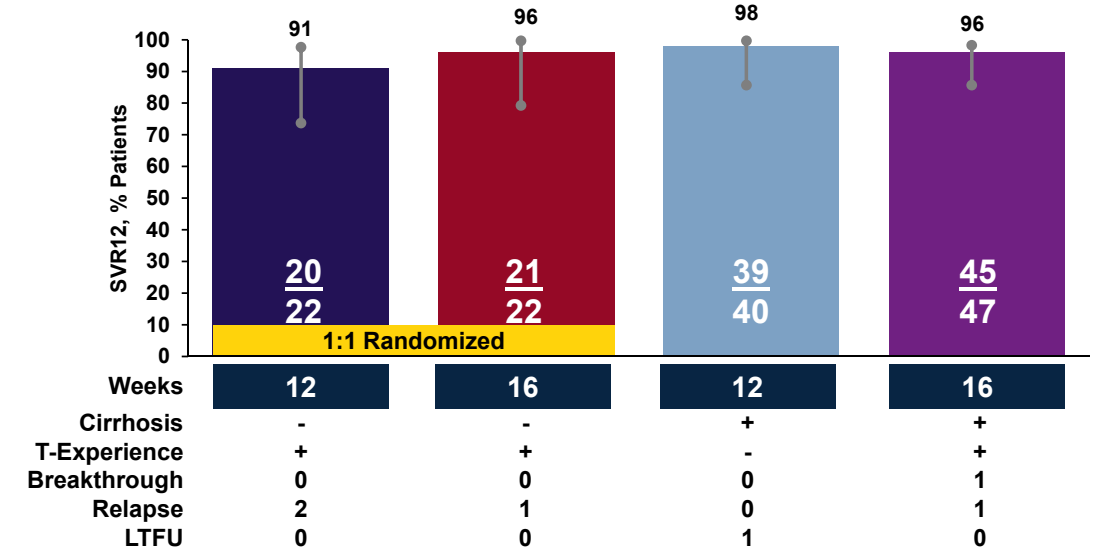
Baseline Polymorphisms

Baseline Polymorphism, n (%)	Treatment Experienced – Cirrhosis 12 Weeks N = 22	Treatment Experienced – Cirrhosis 16 Weeks N = 21	Treatment Naïve + Cirrhosis 12 Weeks N = 39	Treatment Experienced + Cirrhosis 16 Weeks N = 47
None	16 (73)	18 (86)	29 (74)	40 (85)
NS3 only	0	0	1 (3)	1 (2)
NS5A only	6 (27)	3 (14)	9 (23)	6 (13)
Both NS3 and NS5A	0	0	0	0

*Baseline polymorphisms detected at 15% next-generation sequencing threshold only within samples that had sequences available for both targets at key amino acid positions:
NS3: 155, 156, 168
NS5A: 24, 28, 30, 31, 58, 92, 93

Wyles D, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 113.

SURVEYOR-II, Part 3: SVR12



98% of patients had HCV RNA <LLOQ by treatment week 4

Wyles D, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 113.

Virologic Failure: Patient Details

Characteristic	Patient A	Patient B	Patient C	Patient D	Patient E
SURVEYOR-II Treatment	12 weeks	12 weeks	16 weeks	16 weeks	16 weeks
Virologic Failure	Relapse	Relapse	Relapse	Relapse	BT
Compensated Cirrhosis	No	No	No	Yes	Yes
Prior Treatment Experience	Yes	Yes	Yes	Yes	Yes
Fibrosis Stage	F1-F2	F2	F0-F1	F4	F4
Baseline HCV RNA, IU/mL	8,140,000	9,410,000	18,900,000	2,840,000	17,400,000
Treatment Compliance	Yes	Yes	Yes	Yes	NA*

Sequence Analysis†		Patient A	Patient B	Patient C	Patient D	Patient E
NS3	Baseline	None	None	None	None	A166S
	Failure	None	None	Y56H, Q168R	None	A156G, A166S
NS5A	Baseline	Y93H	A30K	A30K	None	None
	Failure	Y93H	A30K, Y93H	A30K, Y93H	L31F, Y93H	A30K, Y93H

BT, breakthrough
NA, not available; *Patient E had drug exposures 85% lower than average at week 4
†Substitutions detected by next-generation sequencing at 15% detection threshold
NS3: 36, 43, 54, 55, 56, 80, 155, 156, 166, and 168
NS5A: 24, 28, 29, 30, 31, 32, 58, 92, and 93

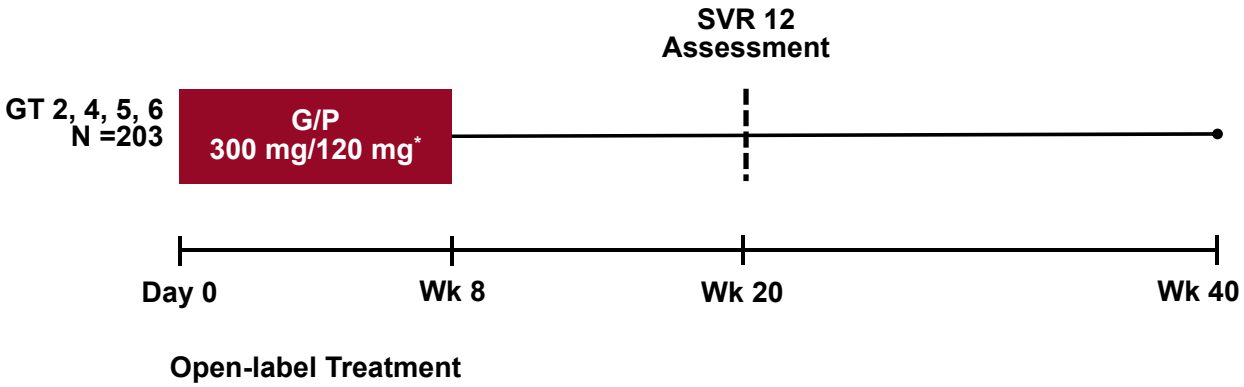
Wyles D, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 113.

SURVEYOR-II, Part 4: Glecaprevir/Pibrentasvir Demonstrates High SVR Rates in Patients with HCV Genotype 2, 4, 5, or 6 Infection without Cirrhosis Following an 8-Week Treatment Duration

T.I. Hassanein, D.L. Wyles, S. Wang, R. Liu, T. Ng, C. Lin, F.J. Mensa, P.Y. Kwo, M.L. Shiffman, Z. Younes, S. Greenbloom, C.A. Stedman, J. Sasadeusz, H.I. Aguilar, J. Heo,

Abstract LB-15

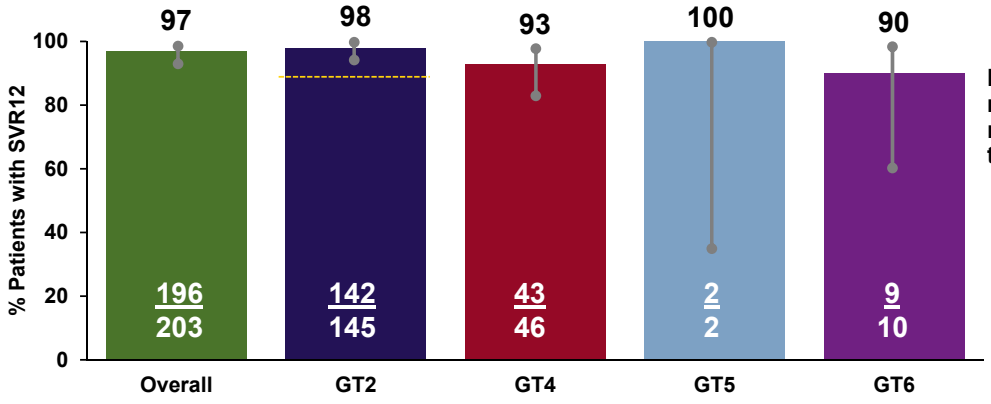
SURVEYOR-II, Part 4: Study Design



*Three 100 mg/40 mg pills taken once daily.

Hassanein T, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. LB-15.

SURVEYOR-II, Part 4: Results - SVR12, ITT Population



Dotted line (yellow) represents the non-inferiority threshold (89%)

		Overall	GT2	GT4	GT5	GT6
Breakthrough	0:	0	0	0	0	0
Relapse	2:	2	0	0	0	0
Discontinuation	2:	1*	1†	0	0	0
Missing SVR12 Data	3:	0	2	0	0	1

*Patient discontinued on Day 15 due to loss to follow-up.
†Patient discontinued on Day 36 due to non-compliance.

Hassanein T, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. LB-15.

SURVEYOR-II, Part 4: Characteristics of Patients with Virologic Failure

	Patient A*	Patient B
Time of Failure	Relapse post-treatment Day 29	Relapse, post-treatment Day 55
Age/Race/Gender	56-year-old white female	55-year-old white male
Genotype/Subtype	GT2a	GT2a
IL28B Genotype	C/C	C/T
Fibrosis Stage	F0–F1	F3
Baseline Viral Load	5 120 000 IU/mL	11 700 000 IU/mL
Prior Treatment Exposure	Experienced	Experienced
Treatment Compliant	Yes	Yes
Treatment Compliant[ł]	Yes	Yes
Treatment-emergent substitutions at time of failure		
NS3	None	None
NS5A	None	None

*Patient had a medical history of gastric bypass. Exposure of GLE on Day 1 and Week 4 was >75% lower than the men in patients in the same treatment arm; exposure of PIB was comparable to the other patients in the cohort.
ł Measured as the percentage of tables taken relative to the total tablets expected to be taken during the treatment period; compliance achieved if percentage was ≥80%.

Hassanein T, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. LB-15.

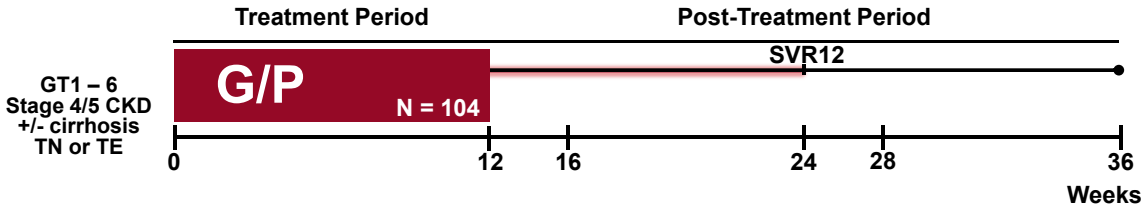
EXPEDITION-IV: Safety and Efficacy of GLE/PIB in Adults with Renal Impairment and Chronic Hepatitis C Virus Genotype 1 – 6 Infection

D. Pugatch, Y. Lei, M.P. Kosloski, F.J. Mensa, E. Lawitz, E.J. Gane, G.V. Papatheodoridis, N. Bräu, James J. Peters, A.S. Brown, S. Pol, V. Leroy, M. Persico, C. Moreno, M. Colombo, E.M. Yoshida, D.R. Nelson, G.V. Papatheodoridis, N. Bräu

Abstract LB-11

EXPEDITION-IV: Safety and Efficacy of GLE/PIB in Adults with Renal Impairment and Chronic Hepatitis C Virus Genotype 1 – 6 Infection

EXPEDITION-4: Objective and Study Design



- **Objective**
  - Determine the efficacy and safety of pangenotypic G/P for 12 weeks in patients with HCV GT1-6 and stage 4 or 5 chronic kidney disease (CKD)
- **Endpoints**
  - Efficacy: SVR12 defined as HCV RNA below the lower limit of quantification (LLOQ; 15 IU/mL)
  - Safety: Adverse events (AEs) and laboratory abnormalities

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

Gane E, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. LB-11.

EXPEDITION-IV: Baseline Characteristics

Characteristic	G/P N = 104
Male, n (%)	79 (76)
Black race, n (%)	26 (25)
Age, median years (range)	57 (28 – 83)
BMI, median kg/m^2 (range)	26 (18 – 45)
IL28B non-CC genotype, n (%)	80 (77)
HCV RNA, median $\log_{10}$ IU/mL (range)	5.9 (3.4 – 7.5)
Concomitant PPI use, n (%)	43 (41)

Patients were enrolled across 9 countries: Australia, Belgium, Canada, France, Greece, Italy, New Zealand, the United Kingdom, and United States

BMI, body mass index; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; G/P, coformulated glecaprevir/pibrentasvir; HCV, hepatitis C virus; IL28B, interleukin 288; PPI, proton pump inhibitor

Gane E, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. LB-11.

EXPEDITION-IV: Baseline Demographics and Clinical Characteristics

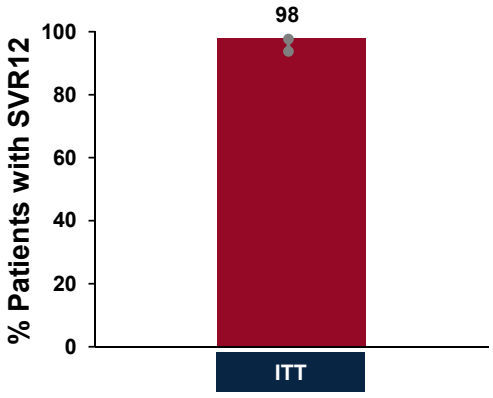
Characteristic	G/P N = 104
Male, n (%)	79 (76)
Black race, n (%)	26 (25)
Age, median years (range)	57 (28 – 83)
BMI, median kg/m^2 (range)	26 (18 – 45)
IL28B non-CC genotype, n (%)	80 (77)
HCV RNA, median $\log_{10}$ IU/mL (range)	5.9 (3.4 – 7.5)
Concomitant PPI use (%)	43 (41)

Characteristic, (n%)	G/P N = 104
HCV genotype	
1a / 1b / other	23 (22) / 29 (28) / 2 (2)
2	17 (16)
3	11 (11)
4 / 5 / 6	20 (19) / 1 (1) / 1 (1)
Prior treatment history	
Naïve	60 (58)
IFN/pegIFN ± RBV	42 (40)
SOF + RBV ± pegIFN	2 (2)
Compensated cirrhosis	
Yes	20 (19)
No	84 (81)
CKD stage	
Stage 4	13 (12)
Stage 5	91 (88)
Hemodialysis	85 (82)

Patients were enrolled across 9 countries: Australia, Belgium, Canada, France, Greece, Italy, New Zealand, the United Kingdom, and United States

Gane E, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. LB-11.

EXPEDITION-IV: Results – SVR12 by Intent-To-Treat (ITT) Analysis



Breakthrough	0
Relapse	0
Discontinuation	1
LTFU	1

mITT = 1--% SVR12

- 4 AEs leading to study drug discontinuation
- One death 2 weeks post-treatment due to cerebral hemorrhage non study drug related

Gane E, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. LB-11.

EXPEDITION-IV: Post-Baseline Laboratory Abnormalities

Event, n (%)	G/P N = 104
Hemoglobin Grade ≥3 (<8.0 – 6.5 g/dL)	5 (5)
AST Grade ≥2 (>3 – 20 x ULN)	0
ALT Grade ≥2 (>3 – 20 x ULN)	0
Total bilirubin Grade ≥3 (>3 – 10 x ULN)	1 (1)

Grade 3 or higher laboratory abnormalities were rare

Gane E, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. LB-11.