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

LB-15

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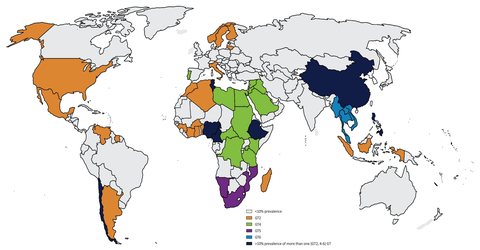
INTRODUCTION

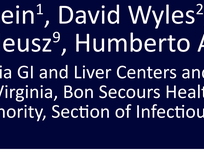
- Hepatitis C virus genotypes (HCV GT) 2, 4, 5, and 6 have diverse global distributions, accounting for approximately 9%, 8%, 1%, and 5% of HCV infections worldwide, respectively[1]

Global Prevalence of HCV Genotype 2, 4, 5, and 6 Infection



- A pangenotypic treatment that is safe and highly efficacious, with a treatment duration as short as possible, could improve patient adherence and access to care

Next Generation Direct-acting Antivirals



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

Pibrentasvir (formerly ABT-530) pangenotypic NS5A inhibitor

In vitro:[2,3]
- 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:
- Oral dosing of 3 pills once-daily
- 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.

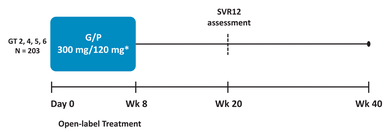
- In previous phase 2 studies, sustained virologic response at 12 weeks after treatment (SVR12) rates of 98% and 100% were achieved following treatment with GLE + PIB (G/P) for 8 weeks in GT2-infected patients or 12-weeks in GT 4–6 infected patients, respectively, with no virologic failures[4]

OBJECTIVE

- SURVEYOR-II, Part 4 is a phase 2, open-label, multicenter, single-arm study that evaluated the safety and efficacy of an 8-week G/P regimen in patients with GT4–6 infection and a larger cohort of GT2-infected patients

MATERIALS AND METHODS

STUDY DESIGN



*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.

KEY INCLUSION CRITERIA

- ≥18 years of age
- BMI ≥18 kg/m^2
- Chronic HCV GT2, 4, 5, or 6 infection with HCV RNA >1000 IU/mL
- Absence of cirrhosis documented by liver biopsy (eg, METAVIR <4 and ISHAK <5), transient elastography (FibroScan® ≤12.5 kPa) or serum markers (FibroTest® ≤0.48 + APRI <1)
- HCV treatment-naïve or
- Treatment-experienced with interferon (IFN) or pegIFN ± ribavirin (RBV), or sofosbuvir (SOF) + RBV ± pegIFN therapy

KEY EXCLUSION CRITERIA

- Prior HCV treatment experience with any direct-acting antiviral (DAA) other than SOF
- Co-infection with hepatitis B or HIV
- ALT >10 × ULN, AST >10 × ULN, direct bilirubin >ULN, albumin <LLN or platelets <90 000 cells/mm^3

ENDPOINTS AND ANALYSES

Primary Efficacy Endpoint	The percentage of patients with SVR12 (HCV RNA <25 IU/mL 12 weeks after the last dose of study drug)
	The percentage of GT2-infected DAA-naïve patients with SVR12 will be non-inferior to the historical 95% SVR12 rate (12 weeks SOF + RBV) if the lower confidence bound of the 2-sided 95% confidence interval is >89%
Secondary Efficacy Endpoints	The percentage of patients with on-treatment virologic failure, post-treatment relapse and SVR4
Safety Assessments	Adverse events (AEs) and laboratory abnormalities were assessed in all patients receiving at least 1 dose of study drug
Additional Assessments	Next generation sequencing (detection threshold = 15%) performed to identify baseline polymorphisms and, treatment-emergent substitutions in NS3 and NS5A

RESULTS

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	8 Week G/P N = 203
Male, n (%)	98 (48)
Race, n (%)*	
White	155 (76)
Black	21 (10)
Asian	23 (11)
Other	4 (2)
Age, median (range), years	55 (19-83)
BMI, median (range), kg/m^2	26.8 (17.3–65.7)
Genotype, n (%)†	
2	145 (71)
Subtype‡ a/b/c/q	21/103/3/1
4	46 (23)
Subtype‡ a/d/f/k/m/v/x–q	26/8/1/1/1/3/1
5	2 (1)§
6	10 (5)
Subtype‡ a/e/i	3/3/1
HCV Treatment-naïve, n (%)	176 (87)
Treatment-experienced, n (%)	27 (13)
IFN-based	21 (10)
SOF-based	6 (3)
HCV RNA, median (range), $\log_{10}$ IU/mL¶	6.45 (0.75–7.62)
Baseline Fibrosis Stage, n (%)	
F0–F1	170 (84)
F2	12 (6)
F3	21 (10)
Non-CC *IL28B* genotype, n (%)	115 (57)
PPI use	19 (9)

BMI, body mass index; IFN, interferon; SOF, sofosbuvir; HCV, hepatitis C virus; PPI, proton pump inhibitor.
*Race was self-reported. †Genotype determined by the Central Laboratory. ‡Subtype confirmed by phylogenetic analysis.
§One patient with confirmed GT5a subtype. ¶HCV RNA quantified using the Roche COBAS TaqMan RT-PCR assay, v2.0 or higher.

Table 2. Baseline Polymorphisms*

Sequence, n (%)	GT2 N = 123	GT4 N = 41	GT5 N = 1	GT6 N = 6
None	29 (24)	23 (56)	1 (100)	2 (33)
NS3 only	0	0	0	0
NS5A only	93 (76)	17 (42)	0	4 (67)
NS3 + NS5A	1 (0.8)	1 (2)	0	0

*Baseline polymorphisms detected at 15% next generation sequencing threshold in samples that had sequences available for both targets (N) at a key subset of amino acid positions (NS3: 155, 156, 168; NS5A: 24, 28, 30, 31, 58, 92, 93).

- 42% (53/126) of patients with GT2 infection had M at NS5A amino acid position 31 at baseline; 96% (51/53) of these patients achieved SVR12

Table 3. Adverse Events

Event, n (%)	8 Week G/P N = 203
Any AE*	128 (63)
AEs leading to discontinuation	0
Serious AE	2 (1)†
AEs occurring in ≥10% total patients	
Fatigue	37 (18)
Headache	28 (14)
Nausea	23 (11)

*Includes all AEs regardless of relation to study drug. †One patient experienced cholecystitis (Day 30 of treatment) and 1 patient experienced urosepsis (post-treatment Day 15), both assessed as not related to study drug.

Table 4. Laboratory Abnormalities

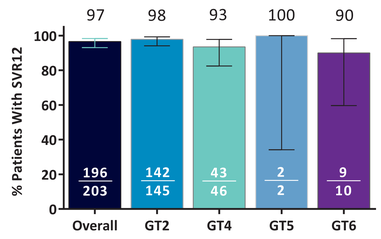
Event, n (%)	8 Week G/P N = 203
AST Grade 3 (>5–20 × ULN)*	1 (0.5)‡
ALT Grade 3 (>5–20 × ULN)†	0
Total Bilirubin Grade 3 (>3–10 × ULN)*	1 (0.5)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal. *Post-baseline increase in grade.
†Post-baseline and post-nadir increase in grade. ‡AST elevation associated with SAE of cholecystitis (described in **Table 3**) in same patient.

- The grade 3 bilirubin elevation occurred on Day 29 of treatment in a patient who had previously experienced grade 2 elevations
  - All total bilirubin elevations were predominately indirect
  - There were no associated post-nadir ALT elevations
- There were no grade 4 or higher lab abnormalities

Figure 1. Efficacy

A. SVR12, ITT Population

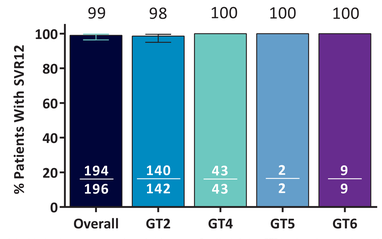


		Overall	GT2	GT4	GT5	GT6
Breakthrough	0:	0	0	0	0	0
Relapse	2:	2	0	0	0	0
Discontinuation	2:	1*	1†	0	0	0
Missing SVR12 data	3:	0	2	0	0	1

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

- Of the patients with missing SVR12 data, at the last study visit, 2 had achieved SVR4 and 1 had achieved SVR8

B. SVR12, mITT* Population



*mITT, modified intent-to-treat; excludes non-virologic failures and 2 patients in the GT2 treatment arm that were identified by phylogenetic analysis as having GT1 infection.

- 8-week treatment of DAA-naïve GT2-infected patients with G/P yielded a SVR12 rate of 99% (135/137) that was non-inferior to the historical 95% SVR12 rate (12 weeks SOF/RBV)

Table 5. 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	2 870 000 IU/mL	11 700 000 IU/mL
Prior Treatment Experience	Experienced	Experienced
Treatment compliant†	Yes	Yes
Baseline polymorphisms		
NS3	None	None
NS5A	L31M	L31M
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 mean in patients in the same treatment arm; exposure of PIB was comparable to the other patients in the cohort. †Measured as the percentage of tablets taken relative to the total tablets expected to be taken during the treatment period; compliance achieved if percentage was ≥80%.

CONCLUSIONS

- 97% (196/203, ITT) of GT2, 4, 5, or 6-infected patients without cirrhosis achieved SVR12 following 8 weeks of G/P
  - In DAA-naïve patients with GT2 infection, 8-week treatment was non-inferior to the historical 95% SVR12 rate achieved with 12 weeks SOF/RBV
  - There were no virologic failures in patients with GT4–6 infection
  - Baseline viral load, genotype/subtype, F0–F3 fibrosis stage, presence of baseline polymorphisms, and prior treatment experience with interferon- or SOF-based regimens did not impact achievement of SVR12
  - SVR rates were similar to observed rates following 12-week treatment with G/P
- G/P for 8 weeks was well-tolerated, with no discontinuations due to AEs, no DAA-related serious AEs, and rare grade 3 or higher lab abnormalities (0.5%)
- The all-oral, once-daily, IFN- and RBV-free regimen of G/P is highly efficacious for treatment of patients with HCV GT 2, 4, 5, or 6 infection without cirrhosis following an 8-week treatment duration

REFERENCES

1. Messina, et al. *Hepatology.* 2015.
2. Ng TI, et al. Abstract 636. CROI, 2014.
3. Ng TI, et al. Abstract 639. CROI, 2014.
4. Kwo, et al. *JHep.* 2016 (accepted manuscript under revision).

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Drug-Drug Interactions Between Direct Acting Antivirals Glecaprevir (ABT-493) and Pibrentasvir (ABT-530) with Angiotensin II Receptor Blockers Losartan or Valsartan

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INTRODUCTION

- The direct acting antiviral (DAA) combination of glecaprevir (GLE; formerly ABT-493), an NS3/4A protease inhibitor discovered by AbbVie and Enanta, and pibrentasvir (PIB; formerly ABT-530), an NS5A inhibitor, achieved high sustained virologic response rates across chronic hepatitis C virus (HCV) genotype 1-6 infection in Phase 2 studies with a favorable safety profile. The once daily fixed dose combination of GLE/PIB 300 mg/120 mg is currently being studied in Phase 3 clinical studies.
- Angiotensin II receptor blockers (ARBs) including losartan and valsartan are used in the treatment of hypertension and other cardiovascular conditions, and are commonly administered in HCV infected subjects with such comorbidities.
- Losartan is a competitive inhibitor of the angiotensin II receptor type 1 (AT1) and forms an active acid metabolite that is 10-40 times more potent of an AT1 inhibitor than the parent compound.
- Valsartan undergoes limited metabolism to form a largely inactive primary metabolite with 1/200th the potency of the parent compound.

OBJECTIVE

- This study was designed to assess the pharmacokinetics (PK), safety, and tolerability of GLE and PIB coadministered with losartan or valsartan and evaluate the drug-drug interaction potential of these agents.

METHODS

STUDY DESIGN

- Phase 1, single-center, non-fasting, open label study (**Figure 1**) in 12 healthy subjects.

Figure 1. Study Design

	Day 1	Day 2	Days 3 - 9	Day 10	Day 11
Arm 1 N=12	Losartan 50 mg, single dose (Day 1)		GLE 300 mg + PIB 120 mg QD (Days 3 – 11)	Losartan 50 mg, single dose (Day 10)	
Arm 2 N=12	Valsartan 80 mg, single dose (Day 1)		GLE 300 mg + PIB 120 mg QD (Days 3 – 11)	Valsartan 80 mg, single dose (Day 10)	

- Intensive PK samples for determination of losartan, losartan carboxylic acid, or valsartan plasma concentrations were collected on Days 1 and 10 of each arm. Intensive PK samples to evaluate GLE and PIB concentrations were collected on Days 9 and 10 of each Arm.

METHODS (continued)

- Non-compartmental analysis was performed with Phoenix WinNonlin v6.3 including estimation of maximum plasma concentration (C_{max}), area under the curve (AUC) from time zero to infinity (AUC_{inf}; losartan, losartan carboxylic acid, and valsartan), AUC from time zero to 24 hours (AUC_{24}; GLE and PIB), and trough concentrations (C_{24}; GLE and PIB).
- The ratio of central values and 90% confidence intervals (CI) were calculated for log-transformed pharmacokinetic parameters on Day 10 (test) versus Day 1 (reference) in each arm for losartan, losartan carboxylic acid, or valsartan, and for Day 10 (test) versus Day 9 (reference) in each arm for GLE and PIB.
- Safety metrics including monitoring of adverse events, vital signs, physical examinations, ECGs, and laboratory tests were assessed throughout the study.

MAIN INCLUSION CRITERIA

- Healthy male and female subjects between 18 and 55 years old.

RESULTS

Table 1. Subject Demographics and Disposition

	ARM 1 (N=12)		ARM 2 (N=12)	
	Mean ± SD	Min – Max	Mean ± SD	Min – Max
Age (years)	37 ± 11	22 – 52	32 ± 7	22 – 48
Weight (kg)	82 ± 12	57 – 97	80 ± 12	60 – 101
Height (cm)	174 ± 8	162 – 183	174 ± 8	160 – 185
Sex	2 Females (17%), 10 Males (83%)		3 Females (25%), 9 Males (75%)	
Race	5 White (42%), 6 Black (50%), 1 Multi-race (8%)		6 White (50%), 6 Black (50%)	

- All enrolled subjects completed the study and were included in pharmacokinetic and safety analyses.

SAFETY RESULTS

- No serious adverse events occurred in the study. In Arm 1, a single adverse event of Grade 2 viral infection was experienced by one subject following coadministration of GLE, PIB, and losartan. In Arm 2, a single adverse event of Grade 1 rhinorrhoea was experienced by one subject during administration of GLE and PIB. No other adverse events were reported.
- No clinically significant vital signs, ECGs, or laboratory abnormalities were observed in the study.

RESULTS (continued)

Figure 2. Arm 1: Losartan, Losartan Carboxylic Acid, GLE, and PIB Plasma Concentration-Time Profiles

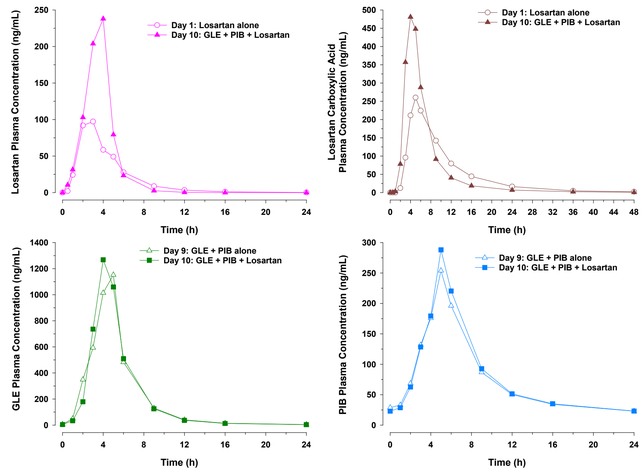
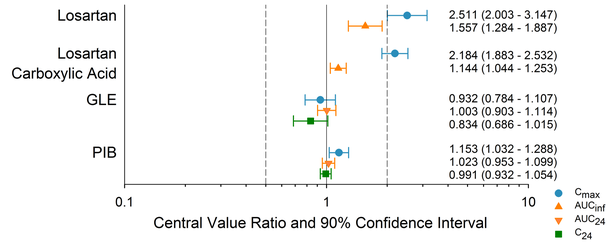


Figure 3. Interactions Between GLE and PIB with Losartan



- Exposures were higher for losartan (↑C_{max} 151% and ↑AUC_{inf} 56%) when administered with multiple doses of GLE + PIB, relative to losartan alone.
- Losartan active carboxylic metabolite C_{max} was 118% higher, while AUC_{inf} was similar (≤ 14% difference).
- Based on losartan prescribing information, similar magnitudes of exposure increases caused by other drugs or in special populations did not require dose adjustment.
- GLE and PIB exposures were similar with and without losartan (≤17% difference).

Figure 4. Arm 2: Valsartan, GLE, and PIB Plasma Concentration-Time Profiles

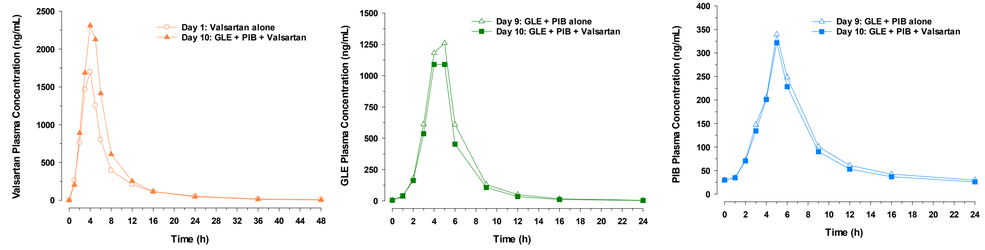
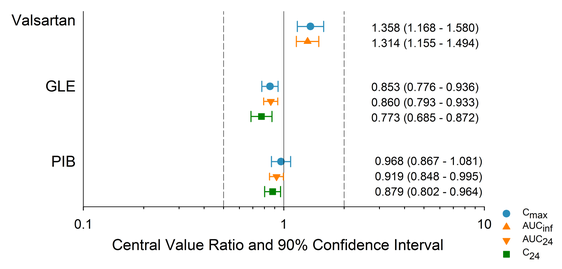


Figure 5. Interactions Between GLE and PIB with Valsartan



- Valsartan exposures were slightly higher (↑C_{max} 36% and ↑AUC_{inf} 31%) when administered with GLE and PIB.
- Based on valsartan prescribing information, similar magnitudes of exposure increases in special populations did not require dose adjustment.
- GLE and PIB exposures were similar with and without losartan (≤15% difference), except GLE C_{24} which was 23% lower.

CONCLUSIONS

- GLE and PIB increased losartan, losartan carboxylic acid, and valsartan exposures; however, the increases were not considered clinically significant and no dose adjustment is required when GLE + PIB are coadministered with losartan or valsartan.
- GLE or PIB exposures were not affected by losartan or valsartan.

DISCLOSURES

This study was funded by AbbVie. AbbVie contributed to the study design, research, and interpretation of data, writing, reviewing, and approving the publication. SD is a former AbbVie employee and may hold AbbVie stocks or options. All other authors are AbbVie employees and may hold AbbVie stocks or options.

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Hemodialysis Does Not Affect the Pharmacokinetics of Glecaprevir (ABT-493) or Pibrentasvir (ABT-530)

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855

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INTRODUCTION

- The direct acting antiviral (DAA) combination of glecaprevir (GLE; formerly ABT-493), an NS3/4A protease inhibitor discovered by AbbVie and Enanta, and pibrentasvir (PIB; formerly ABT-530), an NS5A inhibitor, achieved high sustained virologic response rates across chronic hepatitis C virus (HCV) genotype 1-6 infection in Phase 2 studies with a favorable safety profile, and a once daily fixed dose combination of GLE/PIB 300 mg/120 mg is currently being evaluated in Phase 3 studies.
- In a Phase 1 study conducted in non-HCV infected subjects, GLE and PIB exposure as determined by AUC_{inf} demonstrated a maximum increase of 56% and 46%, respectively, in subjects with end stage renal disease (ESRD) not on dialysis relative to normal subjects. C_{max} was similar across groups (≤ 25% difference).[1]
- Exposure changes in GLE and PIB in non-HCV infected subjects with renal impairment were not considered clinically significant and based on these findings, dose-adjustment of GLE or PIB is not required in subjects with any degree of renal impairment not on dialysis.

OBJECTIVE

- This study evaluated the impact of hemodialysis on the pharmacokinetics and safety of GLE and PIB in ESRD subjects requiring dialysis.

METHODS

STUDY DESIGN

- Phase 1, non-fasting, open label study (**Figure 1**) in N=8 subjects with ESRD requiring hemodialysis.

Figure 1 Study Design

Period 1			Period 2	
Day 1	Day 2	Washout ≥ 7 Days	Day 1	Day 2
DIALYSIS				DIALYSIS
GLE + PIB			GLE + PIB	

METHODS (CONTINUED)

- Subjects received single doses of the GLE 300 mg + PIB 120 mg combination in Period 1 three hours prior to the start of hemodialysis and in Period 2 on the day prior to a scheduled hemodialysis session.
- Intensive pharmacokinetic samples for determination of GLE and PIB plasma concentrations were collected up to 24 hours after dosing in each period. Additionally, arterial (predialyzer) and venous (postdialyzer) blood samples were collected during dialysis.
- Non-compartmental analysis was performed with Phoenix WinNonlin v6.3 including estimation of maximum plasma concentration (C_{max}) and area under the curve (AUC) from time zero to the last sampling point (AUC_t), AUC during dialysis for arterial ($AUC_{arterial}$) or venous (AUC_{venous}) samples, apparent oral clearance (CL/F), and clearance due to dialysis (CL_D). CL_D was derived from differences in arterial and venous exposures during dialysis.
- Unbound fractions of GLE and PIB were assessed ex vivo in plasma samples collected prior to the start of and immediately after dialysis.
- The ratio of central values and 90% confidence intervals (CI) were calculated for log-transformed pharmacokinetic parameters in Period 1 (Day of dialysis) versus Period 2 (Non-dialysis day) for GLE and PIB.
- Safety was evaluated throughout the study with assessment of adverse events, vital signs, ECGs and clinical laboratory tests.

MAIN INCLUSION CRITERIA

- Male and female subjects between 18 and 75 years old with ESRD receiving hemodialysis for at least 1 month.

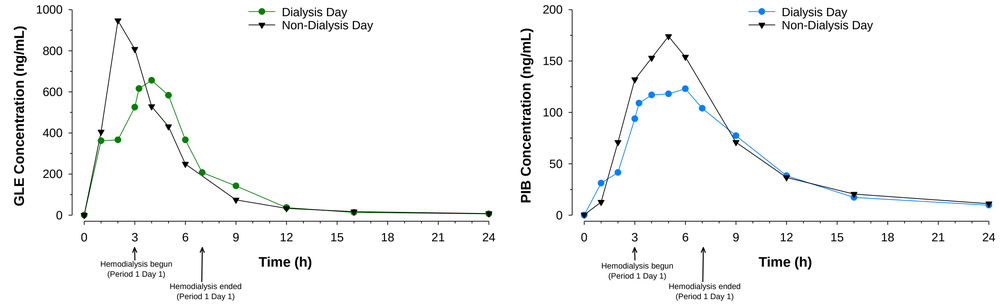
RESULTS

Table 1. Subject Demographics and Disposition

	Mean ± SD (N = 8)	Min – Max
Age (years)	57 ± 9	47 – 73
Weight (kg)	80 ± 23	52 – 122
Height (cm)	170 ± 9	156 – 183
Sex	2 Females (25%), 6 Males (75%)	
Race	8 Black (100%)	

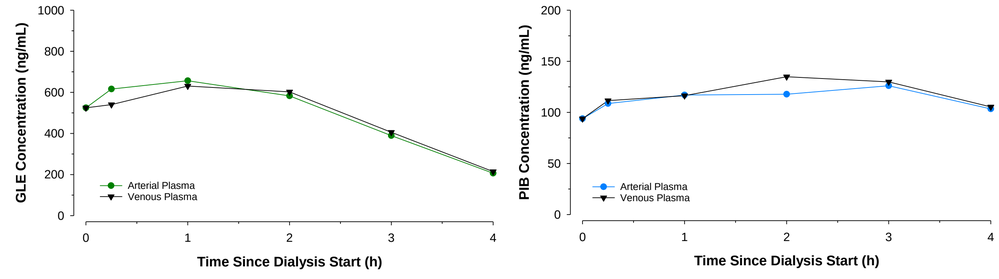
- All enrolled subjects completed the study and were included in pharmacokinetic and safety analyses.
- The typical hemodialysis session ended approximately 7 hours after dosing of study drug in Period 1, or 4 hours after the start of dialysis.

Figure 2. Mean GLE and PIB Plasma Concentration-Time Profiles



- Maximum concentrations of GLE and PIB reached by 2.5 and 5 hours post dose on non-dialysis day. Therefore, starting dialysis 3-hours post dose in Period 1 ensured the assessment of maximum dialysis effect on GLE and PIB exposure.

Figure 3. Mean GLE and PIB Arterial and Venous Plasma Concentrations During Hemodialysis



- Concentration-time profiles were similar for GLE and PIB in arterial and venous plasma samples collected during dialysis

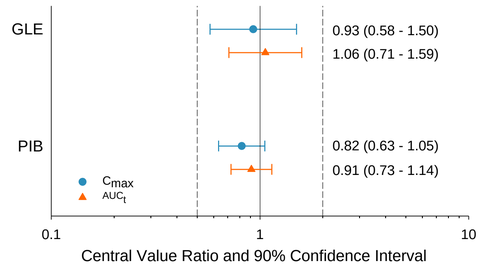
Table 2. Geometric Mean (Mean, CV%) GLE and PIB Pharmacokinetic Parameters

Pharmacokinetic Parameter (units)	GLE		PIB	
	Period 1, Day of Dialysis	Period 2, Non-Dialysis Day	Period 1, Day of Dialysis	Period 2, Non-Dialysis Day
C_{max} (ng/mL)	671 (883, 69)	723 (1050, 101)	128 (150, 48)	156 (193, 54)
T_{max} (h)[a]	3.6 (2.0 to 9.0)	2.5 (2.0 to 5.0)	5.5 (3.3 to 9.0)	5.0 (3.0 to 6.0)
AUC_t (ng·h/mL)	3010 (3820, 69)	2840 (4090, 102)	1020 (1180, 47)	1120 (1360, 54)
$AUC_{arterial}$ (ng·h/mL)	1580 (2000, 69)	--	358 (457, 54)	--
AUC_{venous} (ng·h/mL)	1560 (1980, 67)	--	377 (481, 52)	--
CL_D (L/h)[b]	(0.576, 119)	--	(0.00336, 283)	--
CL/F (L/h)[b,c]	(125, 74)	(144, 94)	(148, 90)	(152, 117)

a. Median (Minimum to Maximum); b. (Mean, CV%); c. Calculated as Dose/AUC_t

- Mean values of CL_D represented a minimal portion of CL/F for GLE (< 1%) and PIB (< 0.005%).
- Fraction of unbound drug pre- or post- dialysis was similar and ranged between 2.5 to 2.9% (GLE) or 0.019 to 0.029% (PIB).

Figure 4. The Effect of Hemodialysis on GLE and PIB Pharmacokinetics



- GLE and PIB exposures were similar (≤ 18% difference) when GLE + PIB were administered three hours prior to the start of hemodialysis or on a non-dialysis day.

SAFETY RESULTS

- Adverse events were rare; a single Grade 1 adverse event was reported.
- No clinically significant vital signs, ECGs, or laboratory abnormalities were observed in the study.

CONCLUSIONS

- GLE and PIB exposures were not affected by hemodialysis.
- No dose-adjustment is needed when GLE and PIB are administered in subjects with renal impairment, with or without dialysis.

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DISCLOSURES

This study was funded by AbbVie. AbbVie contributed to the study design, research, and interpretation of data, writing, reviewing, and approving the publication. SD is a former AbbVie employee and may hold AbbVie stocks or options. All other authors are AbbVie employees and may hold AbbVie stocks or options.

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Analysis of HCV Variants in the MAGELLAN-I Study (Part 1): ABT-493 and ABT-530 Combination Therapy of Genotype 1-Infected Patients Who Had Failed Prior Direct Acting Antiviral-Containing Regimens

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BACKGROUND

HCV DIRECT-ACTING ANTIVIRAL (DAA) TREATMENT FAILURE

- Although DAA therapies achieve high SVR rates in most HCV-infected patients, treatment failure may occur
- DAA-treatment failure is often associated with viral resistance due to
  - Baseline amino acid polymorphisms
  - Treatment-emergent amino acid substitutions
- Amino acid substitutions in different HCV targets persist for different periods of time
  - NS3 substitutions usually become undetectable within 1 year of post-treatment[1]
  - NS5A substitutions may persist beyond 2 years of post-treatment[1,2]
  - Some NS5B substitutions may persist beyond 1 year of post-treatment[1]
- Patients with baseline NS5A polymorphisms may achieve lower SVR rates when treated with NS5A-containing DAA regimens
  - LDV/SOF: 60% SVR12 in GT1a (33% if Y93H/N were present)[3,4]
  - GZR/EBR: 70% SVR12 in GT1a[5,6]
  - SOF/VEL: 88% SVR12 in GT3[7]

AbbVie's NEXT GENERATION HCV DAAs

- Glecaprevir[a] (GLE; ABT-493): NS3/4A protease inhibitor (PI)
- Pibrentasvir (PIB; ABT-530): NS5A inhibitor
- In vitro, GLE and PIB have each demonstrated[8,9]
  - Potent antiviral activity against major HCV genotypes
  - High barrier to development of resistance
  - Potent antiviral activity against common substitutions that confer resistance to previous generations of HCV PIs or NS5A inhibitors

Table 1. Antiviral Activity of GLE and PIB

	Stable HCV Replicon EC_{50}							
DAA	GT1a	GT1b	GT2a JFH-1	GT2b	GT3a	GT4a	GT5a	GT6a
GLE (nM)[a]	0.85	0.94	2.2	4.6	1.9	2.8	0.12[b]	0.86
PIB (pM)	1.8	4.3	5.0	1.9	2.1	1.9	1.4	2.8

[a]GLE was identified by AbbVie and Enanta.
[b]Transient replicon results.

OBJECTIVES

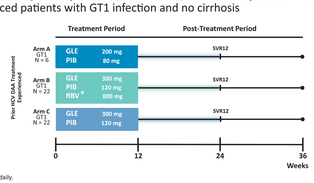
- MAGELLAN-I (Part 1) study: Retreatment of HCV GT1-infected patients who had failed prior DAA therapy
- Resistance analysis: Evaluation of viral sequences from HCV GT1-infected patients who were treated with the combination of GLE and PIB in MAGELLAN-I (Part 1) study
  - Assessed prevalence of NS3 and NS5A amino acid polymorphisms in baseline samples collected before GLE/PIB treatment
    - Since patients' HCV amino acid sequences prior to all previous DAA therapies were unknown, an amino acid detected in a patient baseline sample that was different than the reference sequence was defined as a polymorphism
  - Identified and characterized treatment-emergent substitutions

METHODS

- Clinical samples
  - Next generation sequencing (NGS) was performed on the HCV NS3/4A and NS5A genes from baseline and post-baseline patient samples
  - Amino acid polymorphisms/substitutions (NGS detection threshold of 2% or 15%) at the following signature resistance-associated positions for NS3/4A protease or NS5A inhibitor class were analyzed
    - NS3
      - GT1a: 36, 43, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, and 170
      - GT1b: 36, 54, 55, 56, 80, 107, 122, 155, 156, 158, 168, 170, and 175
    - NS5A
      - GT1a: 24, 28, 29, 30, 31, 32, 58, 62, 92, and 93
      - GT1b: 24, 28, 29, 30, 31, 32, 54, 58, 62, 92, and 93
- In vitro studies
  - Resistance analyses were performed by introducing NS3 or NS5A substitutions, as appropriate, into the corresponding wild-type replicons and testing their drug susceptibility in transient replicon assays
- Prior DAAs used:
  - NS3/4A PIs: Asunaprevir (ASV); boceprevir; (BOC); faldaprevir (FDV); paritaprevir (PTV); simeprevir (SMV); sovaprevir (SVP); telaprevir (TVR); vedroprevir (VDV)
  - NS5A inhibitors: Daclatasvir (DCV); ledipasvir (LDV); ombitasvir (OBV); odalasvir (ODV); ravidasvir (RDV); samatasvir (SAM)
  - NS5B polymerase inhibitors: Beclabuvir (BCV); dasabuvir (DSV); deleobuvir (DBV); sofosbuvir (SOF); VX-222; TMC-647055

MAGELLAN-I (Part 1) Study Design

- MAGELLAN-I (Part 1) is an open-label, multicenter, randomized phase 2 trial in DAA-experienced patients with GT1 infection and no cirrhosis

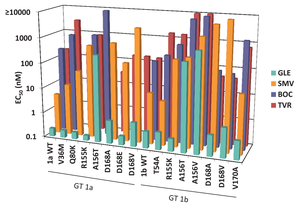


*RBV (ribavirin) dosed once-daily.

- Total GT1 patients = 50
  - GT1a patients = 42; GT1b patients = 8

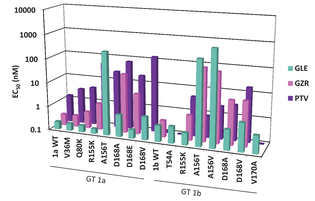
GLE IS ACTIVE AGAINST COMMON GT1 NS3 SUBSTITUTIONS

Figure 1A. GLE Demonstrates an Improved Resistance Profile Relative to 1st Generation NS3/4A PIs



GLE: Glecaprevir; SMV: Simeprevir[10,11]; BOC: Boceprevir[10,11,12]; TVR: Telaprevir[10,13]

Figure 1B. GLE Demonstrates an Improved Resistance Profile Relative to 2nd Generation NS3/4A PIs

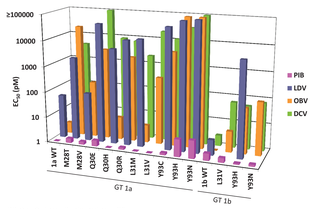


GLE: Glecaprevir; GZR: Grazoprevir[11,14,15]; PTV: Paritaprevir[16]

- GLE is potent against common GT1 NS3 substitutions at amino acid positions 80, 155, and 168
- A156T/V in GT1 confer resistance to GLE, but these substitutions have low viral fitness and are rarely detected clinically

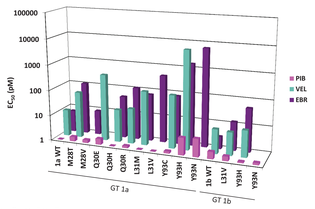
PIB IS ACTIVE AGAINST COMMON GT1 NS5A SUBSTITUTIONS

Figure 2A. PIB Demonstrates an Improved Resistance Profile Relative to 1st Generation NS5A Inhibitors



PIB: Pibrentasvir; LDV: Ledipasvir[17,18]; OBV: Ombitasvir[19]; DCV: Daclatasvir[20,21]

Figure 2B. PIB Demonstrates an Improved Resistance Profile Relative to 2nd Generation NS5A Inhibitors

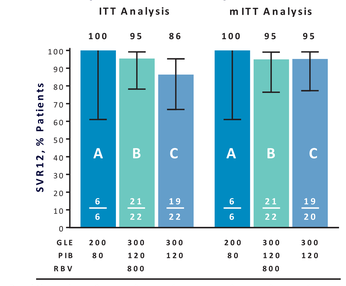


PIB: Pibrentasvir; VEL: Velpatasvir[22]; EBR: Elbasvir[23]

- PIB is highly active against common GT1 NS5A substitutions at amino acid positions 28, 30, 31, and 93 that confer resistance to 1st and 2nd generation NS5A inhibitors
- Of note, PIB retains activity against GT1 Y93 substitutions; many 1st and 2nd generation NS5A inhibitors have significantly lower activity against these substitutions

MAGELLAN-I (PART 1)

Figure 3. SVR12 Rate by ITT and mITT Analysis



*Two GT1a patients were lost to follow-up; both had undetectable HCV RNA at post-treatment Week 8.
ITT: intent-to-treat; mITT: modified intent-to-treat; SVR12: sustained virologic response at post-treatment Week 12; LTFU: lost-to-follow-up.

Table 2. Prior DAA Treatment Regimens

NS3/4A PI	NS5A Inhibitor	NS5B Inhibitor	Others	Total No. of Patients Treated
BOC			PR	10
TVR			PR	8
	LDV	SOF		8
SMV		SOF	± RBV	8
PTV/r	OBV	DSV	± RBV	4
FDV	RDV	DBV	± RBV	4
SMV	SAM	± TMC-647055	± RBV	3
	DCV		± PR	2
ASV	DCV	± BCV	± PR	2
Others *				6

*Other DAA-containing regimens with combinations/DAAs not listed above.
PR, peginterferon plus ribavirin; RBV, ribavirin; r, ritonavir.

- Most common prior DAA regimens
  - BOC + PR, TVR + PR, LDV + SOF (Harvoni), and SMV/SOF ± RBV
- All patients who failed LDV + SOF (Harvoni) or SMV/SOF ± RBV achieved SRV12 in this study
- 4 patients previously failed ≥2 different DAA-containing regimens
  - 75% (3/4) of them achieved SVR12 in this study

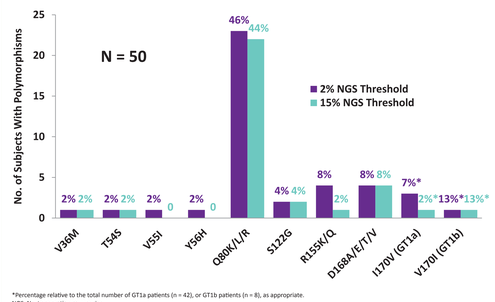
Table 3. Two Patients Experienced Virologic Failure

Patient ID	Prior Treatment	AbbVie Regimen	Subtype	Time Point	NS3 Polymorphism/ Substitution[a]	GLE EC_{50}[b] (-fold)	NS5A Polymorphism/ Substitution[a]	PIB EC_{50}[b] (-fold)
A[c]	DCV; TVR + PR	GLE/PIB + RBV (Arm B)	1a	Baseline	None	—	L31M, H58D	23
				Relapse	A156V	NA	Q30R, L31M, H58D	>1000
B[d]	OBV/PTV/r + DSV + RBV	GLE/PIB (Arm C)	1a	Baseline	Y56H, D168A/T	39[e]	M28V, Q30R, H58C	Pending
				Breakthrough	V36M, Y56H, D168A	162	M28G, Q30R, H58C	942

[a]Polymorphisms/substitutions detected at 2% NGS detection threshold.
[b]EC_{50} of single or linked polymorphism/substitution (if >1 polymorphism/substitution was detected in the same target).
[c]Patient received 2 different regimens previously: DCV as the first regimen, and TVR + PR as the second regimen.
[d]Patient had Crohn's disease, was on immunosuppressive therapy, and had a prior ileocolectomy.
[e]EC_{50} value shown is for Y56H + D168A; EC_{50} value for Y56H + D168T is pending.
NA: Not available due to low replication efficiency of the substitution in vitro.
DCV: Daclatasvir; TVR: telaprevir; PR: peginterferon plus ribavirin; OBV: ombitasvir; PTV: paritaprevir; r: ritonavir; DSV: dasabuvir; RBV: ribavirin.

RESULTS

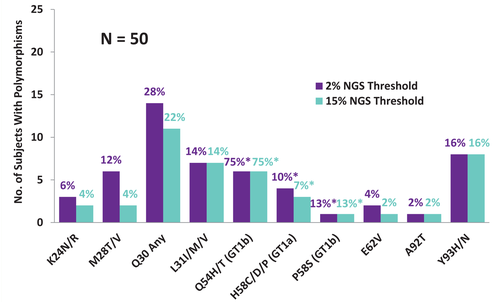
Figure 4. Baseline NS3 Polymorphisms



*Percentage relative to the total number of GT1a patients (n = 42), or GT1b patients (n = 8), as appropriate.
NGS: Next generation sequencing.

- At 2% NGS detection threshold, most common NS3 baseline amino acid polymorphisms were at positions
  - Q80 (46%), R155 (8%), and D168 (8%)

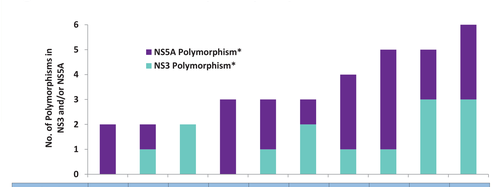
Figure 5. Baseline NS5A Polymorphisms



*Percentage relative to the total number of GT1a patients (n = 42), or GT1b patients (n = 8), as appropriate.
NGS: Next generation sequencing.

- At 2% NGS detection threshold, most common NS5A baseline amino acid polymorphisms were at positions
  - Q30 (28%), Y93 (16%), L31 (14%), M28 (12%), and GT1b Q54 (75%)*

Figure 6. Patients With Multiple Polymorphisms



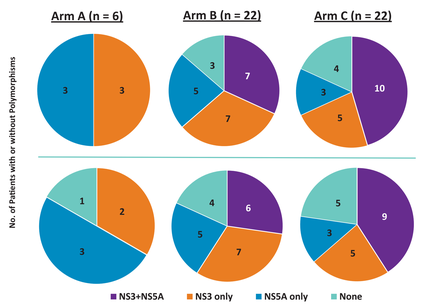
No. of Patients	7	4	3	1	6	1	2	1	2	1

*Polymorphisms detected at 2% NGS detection threshold.

Most patients had multiple (2 or more) baseline polymorphisms

- 14% (7/50) had no baseline polymorphism in NS3 or NS5A
- 30% (15/50) had 1 baseline polymorphism in NS3 or NS5A
- 56% (28/50) had multiple (2 or more) baseline polymorphisms in NS3 and/or NS5A
  - Most common baseline polymorphism combinations
    - 2 NS5A polymorphisms (14%, 7/50)
    - 1 NS3 + 2 NS5A polymorphisms (12%, 6/50)
- 6 patients had 4 or more baseline polymorphisms
  - 83% (5/6) of these patients achieved SVR12

Figure 7. Prevalence of Baseline Polymorphisms (N=50)



NGS: Next generation sequencing.

- No significant difference in the number of patients with at least 1 baseline polymorphism in NS3 or NS5A based on 2% or 15% NGS detection threshold
  - 86% (43/50 at 2% NGS detection threshold)
  - 80% (40/50 at 15% NGS detection threshold)
- More than 50% of patients had baseline polymorphisms in NS5A

SUMMARY

- High SVR12 rate among 50 DAA-experienced HCV GT1-infected patients without cirrhosis
  - 2 patients experienced virologic failure; 2 patients were lost-to-follow-up
  - RBV did not appear to increase SVR12 rate
- Resistance analysis of patient baseline samples
  - No significant difference in frequency of baseline polymorphisms in NS3 and/or NS5A based on 2% or 15% NGS detection threshold
  - Most patients (≥80%) had at least 1 baseline polymorphism in NS3 or NS5A
- High SVR12 rate was achieved (46/48 patients, mITT) despite the high prevalence of baseline polymorphisms, including in patients with NS5A polymorphisms
- MAGELLAN-I Part 2 is evaluating a RBV-free regimen of GLE/PIB in a larger group of DAA-experienced patients with GT1, 4, 5, or 6 infection, including compensated cirrhotics

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DISCLOSURES

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