Efficacy and Safety of Glecaprevir / Pibrentasvir in Patients Infected with HCV GT1 – 3 by Renal Impairment Status: A Pooled Analysis of Two Phase 3 Japanese Trials

SAT1179

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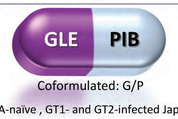
INTRODUCTION

- Glecaprevir (GLE, an NS3 / 4A protease inhibitor) and pibrentasvir (PIB, an NS5A inhibitor) are direct-acting antivirals (DAAs) approved in Japan as a once-daily, ribavirin (RBV)-free, fixed-dose combination regimen (G / P) to treat genotype (GT) 1 – 6 chronic HCV infection in patients with any degree of renal impairment, including those with end-stage renal disease requiring hemodialysis **(Figure 1)**
- 8-week G / P treatment duration approved in Japan for DAA-naive GT1 and GT2 patients without cirrhosis regardless of degree of renal impairment **(Figure 1)**
  - Of those infected with HCV in Japan, approximately 70% have GT1 infection and 30% have GT2 infection[1]
- There is an increased prevalence of chronic hepatitis C virus (HCV) infection in patients with chronic kidney disease (CKD)[2]
- There is an increased risk of CKD progression[3,4] and mortality from renal disease[5,6] in patient with HCV infection
- Minimal renal metabolism and negligible renal excretion of GLE and PIB makes this regimen a suitable treatment option for patients with all degrees of renal function[7]
- No G/P dose modification is required for patients with any degree of CKD, including those requiring hemodialysis; G/P can be dosed without regard to the timing of hemodialysis[8,9]
- No virologic failures in G / P-treated patients with advanced renal disease (Stage 4 or 5) in the EXPEDITION-4 study studies conducted outside of Japan[10]
- Here we report results of an integrated analysis of efficacy and safety of 332 Japanese patients with chronic HCV infection treated with G / P from phase 3 CERTAIN-1 and CERTAIN-2 studies with varying levels of renal dysfunction including those on hemodialysis

Figure 1

G/P is Approved for Patients with HCV GT1-6 Infection

Glecaprevir
pangenotypic NS3/4A protease inhibitor



Coformulated: G/P

Pibrentasvir
pangenotypic NS5A inhibitor

- 99% SVR12 rate across DAA-naïve , GT1- and GT2-infected Japanese patients without cirrhosis[1]
- 8 week duration approved for GT1- and GT2-infected, DAA-naïve Japanese patients without cirrhosis[1]* regardless of the presence of advanced CKD or prior IFN experience
- Favorable safety profile irrespective of baseline factors such as compensated liver cirrhosis or advanced renal disease
- Potent against common polymorphisms (eg, Y93H in NS5A and Q80K in NS3)

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

1. MAVIRET [Japan package insert]. AbbVie GK. 2017
*12 week option for patients infected with GT3-6

OBJECTIVE

- Evaluate efficacy and safety of G / P in Japanese patients with HCV infection and different degrees of renal impairment.

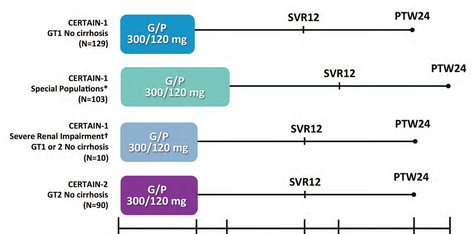
METHODS

- Data were pooled from the phase 3 studies CERTAIN-1 and CERTAIN-2, in which Japanese patients received treatment with co-formulated G / P (300 mg / 120 mg) without RBV for 8 or 12 weeks
  - CERTAIN-1 (NCT02707952): phase 3, partially randomized study to evaluate the efficacy and safety of G / P in Japanese adults with either chronic HCV GT1 infection without severe renal impairment administered G / P for 8 weeks (Substudy 1) or chronic HCV GT1-6 infection from predefined special populations who were administered G / P for 8 or 12 weeks (Substudy 2)
    - Special populations included patients with compensated cirrhosis, prior DAA experience, GT3-6, and severe renal impairment (both with or without compensated cirrhosis)
  - CERTAIN-2 (NCT02723084): phase 3, randomized study to evaluate the efficacy and safety of 8 weeks of G / P in Japanese adults with chronic HCV GT2 infection without severe renal impairment

METHODS (CONTINUED)

- Data from both studies were pooled and then grouped by patient baseline kidney function, defined by eGFR (mL / min / 1.73 m^2) according to the Modification of Diet in Renal Disease (MDRD) equation modified for Japanese population measured at screening:
  - CKD stage 1 = eGFR ≥90 (normal renal function)
  - CKD stage 2 = eGFR ≥60 - <90 (mild renal impairment)
  - CKD stage 3 = eGFR ≥30 - <60 (moderate renal impairment)
  - CKD stage 4 = eGFR ≥15 - <30 (severe renal impairment)
  - CKD stage 5 = eGFR <15 (severe renal impairment, including requirement for dialysis)

Figure 2. Phase 3 Multicenter Studies of GT1-6 HCV-infected Japanese Patients



BL, baseline; G/P, glecaprevir/pibrentasvir; PTW24, post-treatment week 24; SVR12, sustained virologic response at post-treatment week 12
*Special populations included patients with compensated cirrhosis, prior DAA experience, GT3-6, and renal impairment with compensated cirrhosis
†Severe renal impairment defined as an estimated glomerular filtration rate (eGFR) of < 30 mL/min/1.73 m^2

KEY ELIGIBILITY CRITERIA

- Japanese adults with chronic HCV GT 1, 2, 3, 4, 5 or 6 infection (HCV RNA > 1000 IU / mL)
- Age ≥ 18 years (no upper limit) and BMI ≥ 18 kg / m^2
- HCV treatment-naïve or treatment-experienced with interferon (IFN) or pegylated IFN ± ribavirin (RBV), or any approved, commercially available HCV DAA treatment in Japan
- Documented as either non-cirrhotic or having compensated cirrhosis (based on liver biopsy, Fibroscan®, Fibrotest® and APRI, or Discriminant Score)
  - Discrimination Score (z) < 0 according to the following formula: $Z = 0.124 \times [\text{gamma-globulin (\%)}] + 0.001 \times [\text{hyaluronate (}\mu\text{g} \times 1^{-1}\text{)}] - 0.075 \times [\text{platelet (x } 10^4 \text{ cells / mm}^3\text{)}] - 0.413 \times \text{gender (male, 1; female, 2)} - 2.005$
- Absence of co-infection with hepatitis B virus or HIV
- Any degree of renal function including severe renal impairment defined as eGFR <30 mL / min / 1.73 m^2 (patients requiring treatment with intermittent hemodialysis eligible)

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RESULTS

PATIENTS

- A total of 332 Japanese patients were enrolled and treated with G / P in CERTAIN-1 and CERTAIN-2, and are included in this integrated efficacy and safety analysis
- Baseline demographic and clinical characteristics are shown in Table 1 stratified by CKD stage defined by eGFR
- The majority of patients were over 65 years of age, HCV genotype 1 infected, treatment-naïve, non-cirrhotic, and CKD stage 2 (mild renal impairment)

Table 1. Baseline Demographics and Disease Characteristics

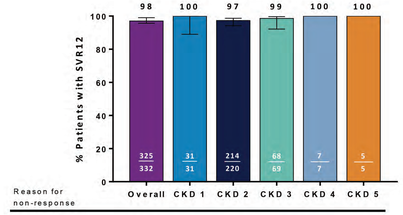
Characteristic	CKD 1 (n = 31)	CKD 2 (n = 220)	CKD 3 (n = 69)	CKD 4 (n = 7)	CKD 5 (n = 5)	Total N = 332
Male	16 (52)	82 (37)	34 (49)	2 (29)	4 (80)	194 (58)
Age < 65	24 (77)	113 (51)	23 (33)	2 (29)	2 (40)	164 (49)
Age ≥65 and <75 years	6 (19)	67 (30)	24 (35)	3 (43)	3 (60)	103 (31)
Age ≥75	1 (3)	40 (18)	22 (32)	2 (29)	0	65 (20)
BMI, median (range), kg / m^2	23.7 (14.2–33.6)	22.8 (16.0–33.4)	23.3 (15.2–38.0)	20.5 (18.9–23.3)	23.9 (20.6–30.9)	23.0 (14.2–38.0)
HCV genotype, n (%)*						
GT1	12 (39)	143 (65)	44 (64)	1 (14)	2 (40)	202 (61)
GT2	16 (52)	69 (31)	24 (35)	6 (86)	3 (60)	118 (36)
GT3	3 (10)	8 (4)	1 (1)	0	0	12 (4)
Treatment-naïve	20 (65)	148 (67)	45 (65)	6 (86)	3 (60)	222 (67)
Treatment Experienced						
IFN-experienced	10 (32)	46 (21)	18 (26)	1 (14)	2 (40)	77 (23)
DAA-experienced	1 (3)	26 (12)	6 (9)	0	0	33 (10)
Cirrhotic status						
Yes	2 (6)	36 (16)	24 (35)	0	2 (40)	64 (19)
No	29 (94)	184 (84)	45 (65)	7 (100)	3 (60)	268 (81)
Baseline HCV RNA level, $\log_{10}$ IU / mL, median (range)	6.2 (4.4–6.9)	6.2 (2.7–7.4)	6.2 (4.0–7.0)	6.1 (2.9–7.4)	5.7 (5.2–6.5)	6.2 (2.7–7.4)
Baseline FIB-4, median (range)	1.3 (0.4–7.7)	2.2 (0.6–17.0)	2.8 (1.0–12.4)	2.4 (1.2–4.6)	5.5 (0.4–6.2)	2.2 (0.4–17.0)

*No Japanese patients with GT4-6 were enrolled in the CERTAIN studies despite being eligible

EFFICACY

- High SVR12 rates were achieved irrespective of CKD stage **(Figure 3)**

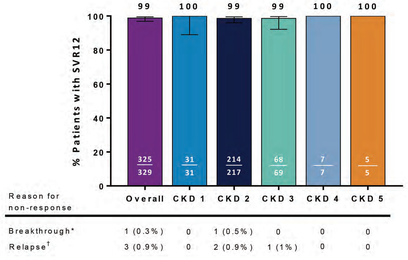
Figure 3a: Percentage of Patients Achieving SVR12 (ITT) by CKD stage



Reason for non-response	Overall	CKD 1	CKD 2	CKD 3	CKD 4	CKD 5
Breakthrough*	1 (0.3%)	0	1 (0.5%)	0	0	0
Relapse†	3 (0.9%)	0	2 (0.9%)	1 (1%)	0	0
Discontinuation	1 (0.3%)	0	1 (0.5%)	0	0	0
Lost to follow-up	2 (0.6%)	0	2 (0.9%)	0	0	0

ITT, intent-to-treat population
* One breakthrough was a DAA-experienced, GT1-infected patient with compensated cirrhosis that had the following signature amino acid variants at failure: A156D / V and D168V NS3 variants and P32del NS5A variant.
† Relapse patients were all non-cirrhotics with the following signature amino acid variants at failure: one DAA-experienced, GT3-infected patient with L28F, G92E, and Y93H NS5A variants, one DAA-experienced, GT1-infected patient with Y56F, Q80L, and V170I NS3 variants along with L31F and P32del NS5A variants, and one DAA-experienced, GT3-infected patient with V31M and Y93H NS5A variants.

Figure 3b: Percentage of Patients Achieving SVR12 (mITT) by CKD stage



Reason for non-response	Overall	CKD 1	CKD 2	CKD 3	CKD 4	CKD 5
Breakthrough*	1 (0.3%)	0	1 (0.5%)	0	0	0
Relapse†	3 (0.9%)	0	2 (0.9%)	1 (1%)	0	0

mITT, modified intent-to-treat. Analysis excluded all non-virologic failures.
* One breakthrough was a DAA-experienced GT1-infected patient with compensated cirrhosis that had the following signature amino acid variants at failure: A156D / V and D168V NS3 variants and P32del NS5A variant.
† Relapse patients were all non-cirrhotics with the following signature amino acid variants at failure: one DAA-experienced, GT3-infected patient with L28F, G92E, and Y93H NS5A variants, one DAA-experienced, GT1-infected patient with Y56F, Q80L, and V170I NS3 variants along with L31F and P32del NS5A variants, and one DAA-experienced, GT3-infected patient with V31M and Y93H NS5A variants.

SAFETY

- In total, 193 / 332 (58%) patients reported experiencing at least 1 treatment-emergent adverse event (TEAE) **(Table 2)**
- The majority of TEAEs were mild or moderate in severity
- The most commonly reported TEAEs occurring in ≥10% of patients (or >1 patient for CKD stages 4 and 5) were nasopharyngitis, pruritus, and blood creatinine increase (reported only in CKD stage 4 patients) **(Table 2)**
- 0.9% (3/332) of all patients experienced a serious adverse event (SAE); no SAE was judged to be DAA-related by the investigator
- Overall rates of AEs leading to discontinuation of study drug were low (3 / 332; 0.9%); all AEs leading to discontinuation of study drug were assessed by the investigator as being possibly related to DAA treatment

Table 2. Summary of Treatment Emergent Adverse Events

	CKD 1 (n = 31)	CKD 2 (n = 220)	CKD 3 (n = 69)	CKD 4 (n = 7)	CKD 5 (n = 5)	Total N = 332
Any AE	16 (52)	125 (57)	42 (61)	5 (71)	5 (100)	193 (58)
AE occurring in ≥10% patients*						
Nasopharyngitis	1 (3)	30 (13)	7 (10)	1 (14)	0	39 (12)
Pruritus	1 (3)	14 (6)	7 (10)	0	2 (40)	24 (7)
Blood creatinine increased	0	0	0	2 (29)	0	2 (0.6)
Any SAE†	0	2 (0.9)	0	0	1 (20)	3 (0.9)
DAA-related SAE	0	0	0	0	0	0
AE leading to discontinuation‡	0	2 (0.9)	1 (1)	0	0	3 (0.9)
Any Fatal AE	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

* AEs occurring in > 1 patient for CKD stage 4 or 5 due to small numbers.
† SAEs by patient were as follows: unstable angina at Day 86, spontaneous pneumothorax at Day 63, and fluid overload at Day 42.
‡ AEs leading to discontinuation were as follows listed by patient: GT1-infected patient with grade 2 drug eruption on Day 16, GT2-infected patient with grade 2 exanthematic drug eruption on Day 12, and GT2-infected patient with grade 2 nausea and vomiting on Day 18.

LABORATORY ABNORMALITIES*

- Post-baseline Grade ≥3 laboratory abnormalities were rare **(Table 3)**
- No patients experienced post-baseline grade 3 elevations in alanine aminotransferase (ALT)
- One (0.3%) patient with CKD stage 2 experienced a post-baseline grade 3 elevation in bilirubin
- No patient had laboratories values that were consistent with drug-induced liver injury

* Reported if worsened from baseline

Table 3. Summary of Laboratory Abnormalities*

Laboratory Abnormalities, n (%)	CKD 1 (n = 31)	CKD 2 (n = 220)	CKD 3 (n = 69)	CKD 4 (n = 7)	CKD 5 (n = 5)	Total N = 332
ALT ≥grade 3 (>5 x ULN)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AST ≥grade 3 (>5 x ULN)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hemoglobin ≥grade 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total bilirubin ≥grade 3 (>3 x ULN)	0 (0)	1 (0.5)†	0 (0)	0 (0)	0 (0)	1 (0.3)

* Reported if worsened from baseline
† Patient with compensated cirrhosis with a grade 2 level of total bilirubin at baseline; Blood bilirubin increased at Day 58 and resolved in 2 days.

MEAN CHANGE IN EGFR

- No clinically meaningful changes in eGFR were observed from baseline to end of treatment (EOT) or post-treatment week 4 (PTW4) for patients with any CKD stage

Table 4. Mean Change in eGFR (mL/min/1.73m²) From Baseline to End of Treatment (EOT) and Post-Treatment Week 4 (PTW4) Visit by CKD Stage*

	CKD 1 (n = 31)	CKD 2 (n = 220)	CKD 3 (n = 69)	CKD 4 (n = 7)	CKD 5 (n = 5)
Mean change eGFR at EOT, mean ± SD, mL/min/1.73m²	-2.7 ± 14.9	-2.4 ± 8.1	-2.6 ± 8.5	-1.2 ± 1.8	0.4 ± 2.3
Mean change eGFR at PTW4, mean ± SD, mL/min/1.73m²	-3.5 ± 15.0	-0.5 ± 9.0	-1.3 ± 8.7	-1.4 ± 1.4	-0.1 ± 1.5

GFR from creatinine adjusted for BSA (mL/min/1.73m²)
*A complete dataset was not available for post-treatment week 12 (PTW12)
BSA, body surface area; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EOT, end of treatment; PTW4, post-treatment week 4; SD, standard deviation

CONCLUSIONS

- G / P treatment demonstrated high SVR12 rates in Japanese patients with HCV GT1-3 regardless of degree of renal impairment or other baseline patient or viral characteristics
- G / P treatment was generally safe and well tolerated with <1% (3 / 332) SAEs in total population and <1% AEs leading to discontinuation regardless of degree of renal impairment
- Majority of AEs were mild or moderate in severity. No SAE was considered drug-related
- This integrated analysis demonstrates that, similar to the non-Japanese populations[11], renal function does not impact the high efficacy and favorable safety profile of G / P

DISCLOSURES

Masanori Atsukawa: participant in AbbVie-sponsored clinical trials.

Kazuaki Chayama: participant in AbbVie-sponsored clinical trials.

Fumitaka Suzuki: participant in AbbVie-sponsored clinical trials.

Ken Sato: received payment for lectures from MSD, AbbVie, BMS, Sumitomo Dainippon Pharma Co. Ltd., Gilead, Mitsubishi Tanabe Pharma, ASKA Pharmaceutical Co., Ltd, Eisai Co. Ltd., Takeda pharmaceutical Co. Ltd., Kowa Company Ltd., Shionogi & Co., Ltd.,Bayer Yakuhin, Ltd., Otsuka Pharmaceutical Co., Ltd.; Received reserch grant from MSD, AbbVie,Gilead, Mitsubishi Tanabe Pharma, Sumitomo Dainippon Pharma Co. Ltd.

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AbbVie sponsored the studies (NCT02707952 and NCT02723084), contributed to their design, collection, analysis, and interpretation of the data, and participated in the writing, review, and approval of the abstract. All authors had access to relevant data. This abstract contains information on the investigational products glecaprevir (ABT-493) and pibrentasvir (ABT-530).

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Safety and Efficacy of Glecaprevir/Pibrentasvir in Patients Aged 65 Years or Older With Chronic Hepatitis C: A Pooled Analysis of Phase 2 and 3 Clinical Trials

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BACKGROUND

- As the population infected with hepatitis C virus (HCV) continues to age, there is an increased need for safety and efficacy data on HCV direct-acting antiviral therapies for elderly patients
- However, in general, the numbers of patients aged 65 years and older enrolled into individual clinical trials have been insufficient to make meaningful conclusions for this demographic
- Glecaprevir/pibrentasvir (G/P) is a once-daily, all-oral, ribavirin-free, pangenotypic, direct-acting antiviral combination therapy that has shown high sustained virologic response (SVR) rates and a favorable safety profile in patients with chronic HCV infection[1–12]

Next Generation Direct-acting Antivirals

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

Pibrentasvir
(formerly ABT-530)
pangenotypic NS5A inhibitor

In vitro:
- 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)
- Synergistic antiviral activity

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

G/P 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.

OBJECTIVE

- To evaluate the safety and efficacy of G/P in a large data set of patients aged 65 years and older

METHODS

STUDY DESIGN AND PATIENTS

- Data were pooled for 2369 treatment-naïve and -experienced patients with chronic HCV genotype (GT) 1–6 infections who received G/P for 8, 12, or 16 weeks in nine Phase 2 and 3 trials **(Table 1)**

Table 1. Summary of G/P Phase 2 and Phase 3 Trials

Trial Name	HCV Genotype	Number of Patients	G/P Treatment Duration (Weeks)	Prior Treatment*	Cirrhosis Status
MAGELLAN-1[1]	GT1, GT4	113	12/16	DAA experienced	NC
SURVEYOR-I & -II[2–5]	GT1–6	590	8/12/16	TN/TE	NC/CC
ENDURANCE-1[6]	GT1	703	8/12	TN/TE	NC
ENDURANCE-2[7]	GT2	202	12	TN/TE	NC
ENDURANCE-3[8]	GT3	390	8/12	TN	NC
ENDURANCE-4[9]	GT4, GT5, GT6	121	12	TN/TE	NC
EXPEDITION-1[10]	GT1, GT2, GT4–6	146	12	TN/TE	CC
EXPEDITION-4 (CKD)[11]	GT1–6	104	12	TN/TE	NC/CC

*TE patients received prior interferon or pegylated interferon ± ribavirin; or sofosbuvir + ribavirin ± pegylated interferon.
CC, compensated cirrhosis; CKD, chronic kidney disease; DAA, direct-acting antiviral; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; NC, non-cirrhotic; TE, treatment experienced; TN, treatment naive.

- Patients enrolled in the trials received oral G/P 300/120 mg once daily (provided as three 100/40-mg tablets)
- A small number of patients enrolled in the Phase 2 trials also received a daily dose of ribavirin 800 mg, 1000 mg, or 1200 mg

STUDY OUTCOMES

- The percentages of patients aged ≥65 vs <65 years without any confirmed, quantifiable, post-treatment HCV RNA concentration for 12 weeks after the last dose of G/P (SVR12) were assessed
- SVR12 rates were also evaluated for patient subgroups stratified by HCV genotype (GT1–6), fibrosis stage (F0–F1, F2, F3, or F4), G/P treatment duration (8, 12, or 16 weeks), and G/P treatment compliance (yes or no)
- Adverse events (AEs) and changes in laboratory test values were monitored for safety

STATISTICAL ANALYSES

- All analyses were conducted for the intention-to-treat (ITT) population, which comprised all enrolled patients who received at least 1 dose of G/P
- Percentages of patients who achieved SVR12 were summarized and 2-sided 95% confidence intervals (CI) were calculated using the normal approximation to the binomial distribution

RESULTS

BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

- Of the 2369 patients enrolled, the majority were white (n = 1898, 80%), HCV treatment naïve (n = 1640, 69%), and did not have cirrhosis (n = 2061, 87%) **(Table 2)**
- A total of 328 patients (14%) were aged ≥65 years **(Table 2)**
  - Patients aged ≥65 years more commonly had HCV GT2 infections than those aged <65 years
  - HCV GT3 infections were more common in patients aged <65 years
- Prevalence of diabetes, hypertension, and cardiovascular disease was greater for elderly patients than younger patients **(Table 2)**
  - Concomitant antihypertensive, diuretic, and lipid-lowering medication use was more common for elderly patients than non-elderly patients **(Table 3)**
- Most patients received either 8 weeks (n = 850, 36%) or 12 weeks (n = 1399, 59%) of treatment with G/P **(Table 2)**

Table 2. Baseline Demographics and Clinical Characteristics

Characteristics	Patients Aged ≥65 Years (n = 328)	Patients Aged <65 Years (n = 2041)
Female	149 (45)	902 (44)
Race		
White	223 (68)	1675 (82)
Black	33 (10)	116 (6)
Hispanic or Latino ethnicity	31 (9)	180 (9)
Age, mean (SD), years	69.3 (4.3)	49.8 (10.4)
Body mass index, mean (SD), kg/m^2	26.5 (4.9)	26.7 (5.1)
HCV genotype		
GT1	139 (42)	848 (42)
GT2	111 (34)	366 (18)
GT3	37 (11)	606 (30)
GT4	24 (7)	158 (8)
GT5	12 (4)	20 (<1)
GT6	5 (2)	43 (2)
IL28B genotype*		
CC	113 (34)	653 (32)
CT	155 (47)	1069 (52)
TT	59 (18)	318 (16)
HCV RNA, mean (SD), $\log_{10}$ IU/mL	6.1 (0.9)	6.1 (0.8)
HCV RNA		
<1 000 000 IU/mL	128 (39)	834 (41)
≥1 000 000 IU/mL	200 (61)	1207 (59)
<6 000 000 IU/mL	268 (82)	1584 (78)
≥6 000 000 IU/mL	60 (18)	457 (22)
Treatment history		
Treatment naive	198 (60)	1442 (71)
Treatment experienced	130 (40)	599 (29)
PegIFN/RBV	115 (35)	501 (25)
NSSA ± PI	15 (5)	98 (5)
Fibrosis stage		
F0–F1	188 (57)	1463 (72)
F1	0	0
F2	33 (10)	132 (6)
F3	45 (14)	200 (10)
F4	62 (19)	241 (12)
Cirrhosis status		
Compensated cirrhosis	64 (20)	244 (12)
No cirrhosis	264 (80)	1797 (88)
Diabetes	57 (17)	147 (7)
Bipolar disorder or depression	52 (16)	456 (22)
Hypertension	177 (54)	478 (23)
Cardiovascular disease	204 (62)	572 (28)
G/P treatment duration		
8 weeks	94 (29)	756 (37)
12 weeks	214 (65)	1185 (58)
16 weeks	20 (6)	100 (5)

Data are n (%) unless stated otherwise.
*Data missing for 1 patient each from the elderly and non-elderly cohorts.
G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; *IL28B*, interleukin 28B; PegIFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; SD, standard deviation.

Table 3. Selected Concomitant Medications

Medication	Patients Aged ≥65 Years (n = 328)	Patients Aged <65 Years (n = 2041)
Any	302 (92)	1638 (80)
Antacids and proton pump inhibitors	63 (19)	299 (15)
Antidepressants	46 (14)	317 (16)
Antihypertensives*	263 (80)	677 (33)
Antipsychotics	10 (3)	88 (4)
Diuretics†	50 (15)	131 (6)
Lipid-lowering drugs	49 (15)	134 (7)

Data are n (%).
*Includes angiotensin II antagonists, beta-blocking drugs, calcium channel blockers, potassium-sparing drugs, and angiotensin-converting enzyme inhibitors (patients may have been receiving more than one of these medications and therefore may have been counted more than once).
†Includes combination diuretics and potassium-sparing drugs, high-ceiling diuretics, low-ceiling diuretics excluding thiazides, low-ceiling diuretics thiazides, and other diuretics.

EFFICACY

- The overall SVR12 rate for the ITT population was 97.4% (95% CI, 96.7–98.0; n/N = 2307/2369)
- The SVR12 rate for elderly patients was 97.9% (95% CI, 96.3–99.4; n/N = 321/328) compared with 97.3% (95% CI, 96.6–98.0; n/N = 1986/2041) for non-elderly patients **(Figure 1)**
  - Of the 7 elderly patients who did not achieve SVR12, 3 discontinued treatment, 2 had on-treatment virologic failure, and 2 had missing SVR12 data
- SVR12 rates were comparable between elderly and non-elderly patients across HCV genotypes, fibrosis stages, and G/P treatment durations **(Figure 1A–C)**
- SVR12 rates were not affected by treatment compliance **(Figure 1D)**

Figure 1A. Sustained Virologic Response at Post-treatment Week 12 by Genotype

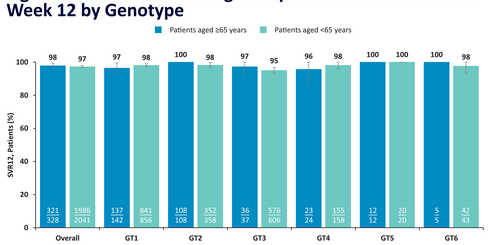


Figure 1B. Sustained Virologic Response at Post-treatment Week 12 by Fibrosis Stage

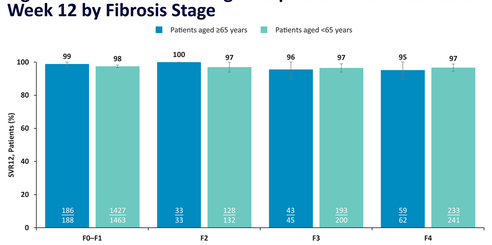
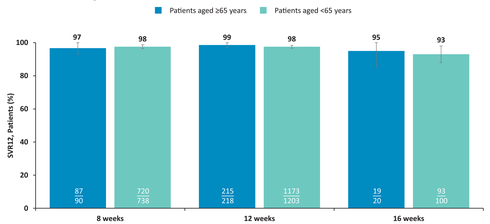
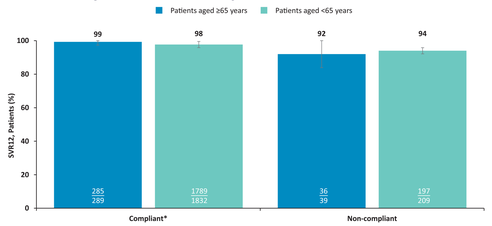


Figure 1C. Sustained Virologic Response at Post-treatment Week 12 by G/P Treatment Duration



*Compliant was defined as 80–120% compliance to G/P.
G/P, glecaprevir/pibrentasvir; GT, genotype; SVR12, sustained virologic response at post-treatment Week 12.

Figure 1D. Sustained Virologic Response at Post-treatment Week 12 by Treatment Compliance



SAFETY

- Overall, 211 patients (64%) aged ≥65 years and 1392 patients (68%) aged <65 years experienced AEs, most of which were mild or moderate in severity **(Table 4** and **Table 5)**
- The most common AEs experienced by elderly patients were headache and fatigue, similar to the non-elderly population
- Although serious AEs were more common in patients with severe renal impairment in both the elderly and non-elderly population, they were rarely associated with G/P
- Drug-related AEs leading to discontinuation were rare (<1% overall)
- Laboratory abnormalities were infrequent in the elderly and non-elderly populations; no patients experienced clinically relevant alanine aminotransferase elevations and Grade 3 bilirubin elevations occurred in <1% of patients **(Table 6)**

Table 4. Summary of Adverse Events for Patients Without Severe Renal Impairment

Event	Patients Aged ≥65 Years (n = 300)	Patients Aged <65 Years (n = 1965)
Any AE	189 (63)	1340 (68)
Any serious AE	13 (4)	35 (2)
Any AE with Grade 3 severity or greater	13 (4)	52 (3)
Any AE leading to treatment discontinuation	2 (<1)	6 (<1)
Any drug-related AE leading to treatment discontinuation	0	3 (<1)
Any DAA-related serious AE	0	1 (<1)
Common AEs		
Headache	36 (12)	374 (19)
Fatigue	32 (11)	298 (15)
Nausea	18 (6)	190 (10)
Diarrhea	14 (5)	132 (7)
Pruritus	22 (7)	81 (4)

Data are *n* (%).
AE, adverse event; DAA, direct-acting antiviral.

Table 5. Summary of Adverse Events for Patients With Severe Renal Impairment

Event	Patients Aged ≥65 Years (n = 28)	Patients Aged <65 Years (n = 76)
Any AE	22 (79)	52 (68)
Any serious AE	11 (39)	14 (18)
Any AE with Grade 3 severity or greater	11 (39)	14 (18)
Any AE leading to treatment discontinuation	2 (7)	2 (3)
Any drug-related AE leading to treatment discontinuation	1 (4)	1 (1)
Any DAA-related serious AE	0	0
Common AEs		
Headache	2 (7)	7 (9)
Fatigue	5 (18)	10 (13)
Nausea	5 (18)	7 (9)
Diarrhea	4 (14)	6 (8)
Pruritus	9 (32)	12 (16)

Data are n (%).
AE, adverse event; DAA, direct-acting antiviral.

Table 6. Summary of Post-baseline Clinical Laboratory Abnormalities

Laboratory Parameter, Maximum Grade	Patients Aged ≥65 Years (n = 328)	Patients Aged <65 Years (n = 2041)
Aspartate aminotransferase		
Grade 3	0	6/2039 (<1)
Grade 4	0	0
Alanine aminotransferase		
Grade 3	0	2/2039 (<1)*
Grade 4	0	0
Total bilirubin		
Grade 3	2 (<1)	7/2039 (<1)
Grade 4	0	0

Data are n (%).
*No cases were consistent with drug-induced liver injury, but were instead associated with fluctuations in alanine aminotransferase during the first 2 weeks of treatment and other causes, such as passage of a gallstone.

CONCLUSIONS

- G/P is a well tolerated and efficacious treatment option for elderly patients aged ≥65 years with chronic HCV infection
- Efficacy of G/P was unaffected by HCV genotype, liver fibrosis stage, and treatment duration
- Most AEs were mild or moderate and AEs leading to discontinuation were rarely observed among elderly patients

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Safety and Efficacy of Glecaprevir / Pibrentasvir in Patients with Chronic Hepatitis C Genotypes 1 – 6 and Recent Drug Use

P1182

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BACKGROUND

- Injection drug use is a primary mode of transmission for hepatitis C virus (HCV)[1]
- Anti-HCV seroprevalence is estimated at 60-80% in people who inject drugs (PWID)[2]
- HCV treatment guidelines recommend treating chronic HCV-infected PWID;[3] however, concerns about treatment adherence, poor treatment outcome, or risk of HCV reinfection have hindered widespread treatment uptake[4]
- Shorter duration, and more convenient, all-oral direct-acting antiviral (DAA) HCV treatment may increase treatment access for people who use drugs (PWUD)
- Prioritizing treatment of PWUD with such regimens may help to reduce the global HCV burden
- In phase 3 trials, the DAA combination of glecaprevir (NS5A inhibitor; identified by AbbVie and Enanta) and pibrentasvir (NS3/4A inhibitor) (coformulated: G/P) for 8 or 12 weeks was well-tolerated and demonstrated a 98% sustained virologic response at post-treatment week 12 (SVR12) in HCV GT1-6 infected patients without cirrhosis or with compensated cirrhosis. Glecaprevir identified by AbbVie and Enanta

ANALYSIS OBJECTIVES

- To evaluate efficacy, safety, adherence, and treatment completion among patients with chronic HCV genotype (GT) 1-6 infection, with or without a recent history of drug use, treated with G/P

METHODS

POOLED STUDIES

- Data were pooled across six phase 3 trials, encompassing 1666 patients treated with G/P for 8 or 12 weeks (including ENDURANCE-1, -2, -3, and -4, and EXPEDITION-1 and -4)

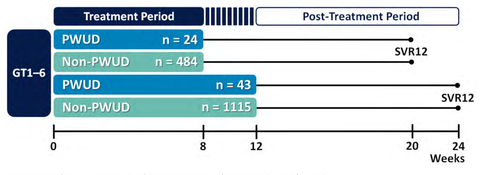
KEY ELIGIBILITY CRITERIA

- Age ≥18 years
- Chronic HCV GT1, 2, 3, 4, 5 or 6 infection (HCV RNA > 1000 IU/mL at screening)
- Absence of coinfection with hepatitis B virus
- Compensated liver disease, with or without cirrhosis
- HCV treatment-naïve or –experienced with interferon (IFN) or pegylated IFN ± ribavirin (RBV), or sofosbuvir (SOF) plus RBV ± pegIFN
- Ongoing drug use was not exclusionary unless it could preclude adherence to the protocol, per investigator assessment

DEFINITION OF PERSONS WHO RECENTLY USED DRUGS (PWUD)

- Self-reported recent injection drug use (≤12 months prior to screening)
- Positive urine drug screen results (for cocaine, amphetamines, phencyclidine, propoxyphene, heroin or other opiates) that could not be accounted for by prescribed concomitant medications (eg, opioid substitution therapy, opiates for pain, or amphetamines / dextroamphetamines for attention-deficit / hyperactivity disorder)
- Both recent injection drug use and positive urine drug screens, as defined above

METHODS (CONTINUED)



Patients treated for 8 or 12 weeks with coformulated glecaprevir / pibrentasvir (300 mg / 120 mg)

ASSESSMENTS

- Treatment adherence (≥90% compliance by pill count)
- Treatment completion
- SVR12, including breakdowns by drug use status, genotype, and treatment duration
- Safety, including adverse events and laboratory parameters

RESULTS

Table 1. Patient Demographics and Characteristics

Characteristic	PWUD N = 67	Non-PWUD N = 1599
Male, n (%)	51 (76)	849 (53)
Race, n (%)		
White	61 (91)	1258 (79)
Black or African American	2 (3)	85 (5)
Asian	1 (2)	221 (14)
Age, median years (range)	45 (22 – 66)	53 (19 – 88)
BMI, median kg/m^2 (range)	24 (18 – 48)	25 (17 – 55)
Category of recent drug use, n (%)		
Recent injection drug use	24 (36)	0
Positive urine drug screen*	39 (58)	0
Both	4 (6)	0
Class of positive UDS†, n (%)		
Opiates	19 (49)	0
Cocaine	9 (23)	0
Amphetamines	9 (23)	0
Heroin	6 (15)	0
HCV RNA, median $\log_{10}$ IU/mL (range)	6.0 (4.1 – 7.4)	6.1 (1.2 – 7.6)
Genotype, n (%)		
GT1	23 (34)	829 (52)
GT2	6 (9)	239 (15)
GT3	34 (51)	367 (23)
GT4 – 6	4 (6)	164 (10)
Baseline fibrosis stage, n (%)		
F0-F2	51 (76)	1285 (80)
F3	7 (10)	155 (10)
F4	9 (13)	154 (10)
Prior HCV treatment-naïve, n (%)	61 (91)	1158 (72)
History of depression or bipolar, n (%)	24 (36)	291 (18)
Opioid substitution therapy, n (%)	26 (39)	92‡ (6)
Current tobacco use, n (%)	42 (63)	561 (35)
Current alcohol use, n (%)	25 (37)	513 (32)

BMI, body-mass index; GT, genotype; HCV, hepatitis C virus; PWUD, person who uses drugs; UDS, urine drug screen
Recent injection drug use was defined as within 12 months of screening
* Positive urine screens for prescribed drugs (ie, methadone for opiate substitution therapy) were counted as negative
† Some patients had positive urine drug screen for more than one drug; percentages based on n = 39 patients with positive UDS
‡ Non-PWUD on OST could have reported former drug use (>12 months before screening)

- PWUDs had a higher percentage of HCV GT3, consistent with epidemiology,[5, 6] compared to non-PWUDs **(Table 1)**

RESULTS (CONTINUED)

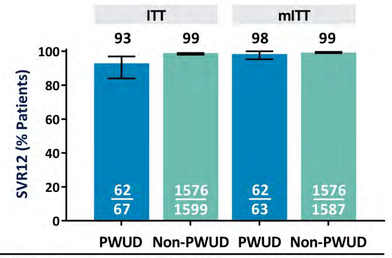
Table 2. Treatment Adherence and Compliance

	PWUD	Non-PWUD
	n/N (%)	
Treatment adherence	53/54 (98)	1441/1456 (99)
Treatment completion	65/67 (97)	1577/1599 (99)

Treatment adherence was considered ≥90% compliance based on pill counts; adherence data was not available for all patients
N = total number of patients in a given intention-to-treat subgroup; n = number of patients with treatment adherence or completion

- Treatment adherence and completion were similarly high (≥97%) regardless of drug use status **(Table 2)**

Figure 1. Overall SVR12 of PWUD versus non-PWUD



	ITT		mITT	
	PWUD	Non-PWUD	PWUD	Non-PWUD
Virologic failure	1* (1%)	11 (1%)	1 (1%)	11 (1%)
Premature d/c	2† (3%)	5 (<1%)		
Lost to follow-up	2 (3%)	7 (<1%)		

mITT, modified intent-to-treat analysis, excluding all patients that failed to achieve SVR12 for reasons other than virologic failure
* Patient with F0-F1 fibrosis and HCV GT3a had relapse at posttreatment week 12
† No patients discontinued due to adverse events

- Rates of premature discontinuation or loss to follow-up were low, regardless of drug use status
- One patient with history of injection drug use (>12 months prior to screening) had reinfection determined by phylogenetic analysis after post-treatment week 12

Table 3. SVR12 by Patient Subgroups

	ITT		mITT	
	PWUD	Non-PWUD	PWUD	Non-PWUD
SVR12, n/N (%)	N = 67	N = 1599	N = 63	N = 1587
Category of recent drug use				
Recent injection drug use	21/24 (88)	–	21/21 (100)	–
Positive urine drug screen	37/39 (95)	–	37/38 (97)	–
Both	4/4 (100)	–	4/4 (100)	–
None	–	1576/1599 (99)	–	1576/1587 (99)
Treatment duration				
8 weeks	23/24 (96)	474/484 (98)	23/23 (100)	474/481 (99)
12 weeks	39/43 (91)	1102/1115 (99)	39/40 (98)	1102/1106 (>99)
Genotype				
GT1	23/23 (100)	822/829 (99)	23/23 (100)	822/824 (>99)
GT2	6/6 (100)	238/239 (99)	6/6 (100)	238/238 (100)
GT3	29/34 (85)	353/367 (96)	29/30 (97)	353/362 (98)
GT4–6	4/4 (100)	163/164 (99)	4/4 (100)	163/163 (100)

GT, genotype; PWUD, people who use drugs; SVR12, sustained virologic response at post-treatment week 12
mITT, modified intent-to-treat analysis, excluding all patients that failed to achieve SVR12 for reasons other than virologic failure
N = total number of patients in a given subgroup; n = number of patients that achieved SVR12 within that subgroup
Recent injection drug use was defined as within 12 months of screening

- Lower ITT SVR12 rates among patients categorized with "Recent Injection Drug Use" or HCV GT3 infection were primarily due to reasons other than virologic failure

SAFETY

Table 4. Adverse Events and Laboratory Abnormalities

Adverse Event, n (%)	PWUD N = 67	Non-PWUD N = 1599
Any	55 (82)	1059 (66)
Serious AE	1 (1)	56 (4)
DAA-related* serious AE	0	1 (<1)
AE leading to drug discontinuation	0	11 (1)
DAA-related* AE leading to drug discontinuation	0	5 (<1)
AEs occurring in ≥10% of patients		
Headache	12 (18)	287 (18)
Fatigue	12 (18)	213 (13)
Nausea	9 (13)	142 (9)
Laboratory abnormalities, n (%)		
ALT Grade ≥3 (>5 ULN)†	0	1 (<1)‡
AST Grade ≥3 (>5 ULN)	1 (1)	3 (<1)
Total bilirubin, Grade ≥3 (≥3 ULN)§	1 (1)	5 (<1)
Hemoglobin, Grade ≥3 (<8 g/dL)	0	6 (<1)
Death¶	0	4 (<1)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAA; direct-acting antiviral; PWUD, person who uses drugs; ULN, upper limit of normal
* Relatedness of AEs to DAAs were determined by study investigator
† Post-nadir increase in grade to Grade ≥3
‡ Grade 3 ALT elevation associated with grade 2 bilirubin and grade 3 AST and alkaline phosphatase elevations at Week 12 in the context of cholelithiasis (multiple gallstones); patient achieved SVR12
§ All patients had bilirubin elevations at baseline; the grade 3 elevations were primarily indirect, with no associated post-nadir ALT elevations by grade
¶ All deaths occurred in the post-treatment period and all were considered not related to study drugs by investigator: acute toxicity to methadone and alcohol, heroin overdose, and 2 patients with cerebral hemorrhage

- The type and severity of adverse events (AEs) were similar between PWUD and non-PWUD
- There were no AEs leading to drug discontinuation among PWUD

CONCLUSIONS

- G/P demonstrated high efficacy in chronic HCV-infected PWUDs (93% ITT SVR12), with low rates of premature discontinuations and no HCV reinfections
  - Treatment adherence and compliance were similarly high (≥97%) regardless of drug use status
  - Higher rates of nonresponse due to non-virologic failure (eg, lost to follow-up) in PWUDS, compared to non-PWUDS, indicates close follow-up of this patient population may be needed
- G/P was well-tolerated, with a safety profile comparable between PWUDs and non-PWUDs
  - No AEs led to drug discontinuation in PWUDs
- Analysis is supportive of AASLD guidelines recommending treatment of chronic HCV infection in this population
- **G/P is a well-tolerated and efficacious pangenotypic regimen for chronic HCV infected patients with recent drug use**

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Exposure-Response Analyses of Virologic Response to Glecaprevir and Pibrentasvir in HCV Subjects from Phase 2 and 3 Studies

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BACKGROUND

- Glecaprevir (GLE, identified by AbbVie and Enanta)/pibrentasvir (PIB) 300 mg/ 120 mg QD regimen, has been approved for Hepatitis C (HCV) genotype (GT) 1-6 infection with a treatment duration as short as 8 weeks.
- The safety and efficacy of GLE/PIB were evaluated during clinical trials enrolling more than 2,300 adults with genotype 1-6 HCV infection without cirrhosis or with compensated cirrhosis.
- Results of the trials demonstrated that overall 98% cure rate (sustained viral response at 12 weeks post treatment, or SVR12) for patients who received GLE/PIB for 8, 12 or 16 weeks.
- The objective of this analysis was to describe the relationships between GLE and PIB steady-state exposure [area under the plasma time concentration curve (AUC) and SVR12, and identify variables predictive of SVR12.

METHODS

- The analysis dataset consists of subjects who have GLE and PIB exposure data with available SVR12 data from 2 Phase 2 and 6 Phase 3 studies.
- The pharmacokinetic (PK) parameters (steady-state GLE and PIB AUC values) estimated from the population-PK models were used in the exposure-response analyses.
- Data from subjects who did not achieve SVR12 for reasons other than virologic failure or who had missing GLE or PIB exposure data were excluded.
- The SVR12 rates were graphically evaluated by genotypes and previous treatment histories against GLE and PIB exposure quartiles to explore any potential subgroups with lower response rates.
- The logistic regression model was developed to study the relationships between SVR12 and log transformed steady-state GLE and PIB AUC values as well as the subject-specific covariates. These covariates were selected using step-wise procedure at the alpha level of 0.05.
- The following covariates were explored:
  - Demographics: age, sex, weight, and race
  - HCV genotypes baseline HCV RNA
  - IL28B genotype
  - Prior treatment history (pegylated interferon, ribavirin, and/or sofosbuvir experienced [TE_PRS]
  - Presence of compensated cirrhosis
  - Presence of renal impairment [CKD Stage 4 and 5]
  - Presence of HIV-coinfection
  - Inclusion or exclusion of RBV in the regimen
  - Treatment duration
- 2 separate analyses were conducted in:
  (1) treatment-naïve (TN) and treatment-experienced (TE-PRS) genotypes 1, 2, 4, 5, and 6 (non-GT3) subjects
  (2) TN GT3 subjects

RESULTS

Table 1. Demographic Summary

Demographic Characteristic	Trt-naïve (N=1830)	PRS-experienced[a] (N=666)
Genotype, N (%)		
GT1	627 (34.3%)	363 (54.5%)
GT2	408 (22.3%)	102 (15.3%)
GT3	608 (33.2%)	133 (20.0%)
GT4	121 (6.6%)	55 (8.3%)
GT5	26 (1.4%)	6 (0.9%)
GT6	40 (2.2%)	7 (1.1%)
Sex, N (%)		
Female	871 (47.6%)	252 (37.8%)
Race, N (%)		
Asian	170 (9.3%)	100 (15.0%)
Black	98 (5.4%)	36 (5.4%)
Other	43 (2.4%)	10 (1.5%)
White	1519 (83.0%)	520 (78.1%)
Baseline Viral Load (per log_{10} IU/mL)		
Median (Min-Max)	6.24 (0.75-7.75)	6.32 (3.06-7.63)
IL28B, N (%)		
C/C	657 (35.9%)	172 (25.8%)
Age, (years)		
Median (Min-Max)	53 (19-88)	57 (19-84)
Weight (kg)		
Median (Min-Max)	75 (39.6-179)	76 (43.8-147)
Renal function		
CKD stage <4	1772 (96.8%)	622 (93.4%)
CKD stage≥4	58 (3.2%)	44 (6.6%)
Cirrhosis Status		
With Cirrhosis	223 (12.2%)	108 (16.2%)

a: PRS-experienced population is referring to the subjects previously received pegylated interferon, ribavirin and sofosbuvir based regimens.

Table 2. Summary of Virologic Failure Rates for Treatment-Naïve and PRS Experienced GT1, 2, 4, 5, and 6 Subjects

GLE/PIB dose (mg)	Duration (Week)	Treatment-Naïve		PRS-Experienced[a]		Overall
		Without Cirrhosis	With Cirrhosis	Without Cirrhosis	With Cirrhosis	
GT1						
300/120	8	0% (0/245)	--	0.7% (1/139)	--	0.3% (1/384)
300/120	12	0% (0/241)	0% (0/69)	0% (0/159)	3.3% (1/30)	0.2% (1/499)
200/120	12	0% (0/27)	5% (1/20)	0% (0/15)	0% (0/6)	1.5% (1/68)
200/40	12	4% (1/25)	--	0% (0/14)		2.6% (1/39)
GT2						
300/120	8	0% (0/172)	--	8.7% (2/23)	--	1% (2/195)
300/120	12	0% (0/167)	0% (0/26)	0% (0/65)	0% (0/9)	0% (0/267)
200/120	12	0% (0/21)		0% (0/2)		0% (0/23)
200/120 +RBV	12	0% (0/22)		0% (0/3)		0% (0/25)
GT4						
300/120	8	0% (0/36)	--	0% (0/7)	--	0% (0/43)
300/120	12	0% (0/73)	0% (0/12)	0% (0/40)	0% (0/8)	0% (0/133)
GT5						
300/120	8	0% (0/2)				0% (0/2)
300/120	12	0% (0/22)	0% (0/2)	0% (0/6)		0% (0/30)
GT6						
300/120	8	0% (0/7)		0% (0/2)		0% (0/9)
300/120	12	0% (0/27)	0% (0/6)	0% (0/4)	0% (0/1)	0% (0/38)

a: PRS-experienced population is referring to the subjects previously received pegylated interferon, ribavirin and sofosbuvir based regimens.

Table 3. Summary of Virologic Failure Rates for Treatment-Naïve GT3 Subjects

GLE/PIB dose (mg)	Duration (Week)	Treatment-Naïve		Overall
		Without Cirrhosis	With Cirrhosis	
GT3				
300/120	8	3.4% (6/178)	--	3.4% (6/178)
300/120	12	1.5% (4/262)	0% (0/64)	1.2% (4/326)
300/120 + RBV	12		0% (0/24)	0% (0/24)
200/120	12	0% (0/27)	--	0% (0/27)
200/120 + RBV	12	3.7% (1/27)	--	3.7% (1/27)
200/40	12	3.9% (1/26)	--	3.9% (1/26)

Figure 1. SVR12 Rate versus AUC Quartiles for Treatment-Naïve and PRS Experienced GT1, 2, 4, 5, and 6 Subjects (N = 1755)

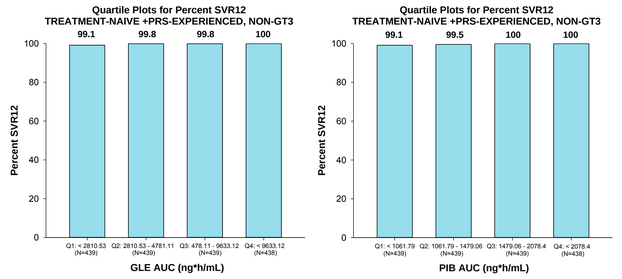
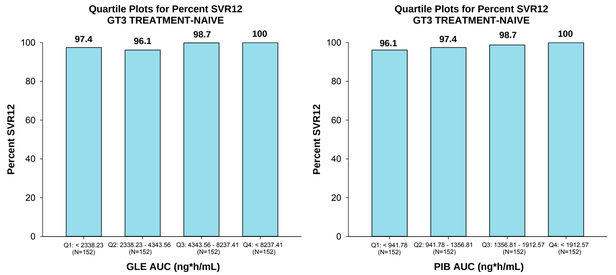
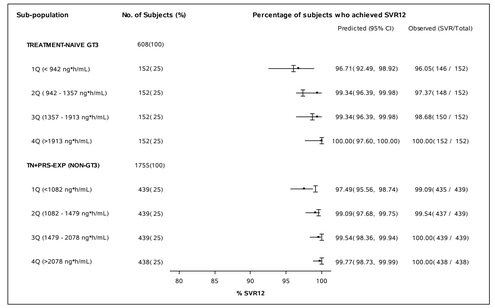


Figure 2. SVR12 Rate versus AUC Quartiles for Treatment-Naïve GT3 Subjects (N = 608)



- No apparent exposure-SVR12 correlation for treatment-naïve non-GT3 HCV-infected subjects was observed. Shallow trends were observed between GLE and PIB AUC and SVR12 rates in treatment-naïve GT3-infected subjects.

Figure 3. Model-predicted SVR Values are Comparable to the Observed SVR Rates Across Exposure Quartiles, Indicating the Model Describes the Data Well



Note: "|" represents observed SVR. The quartiles are based on PIB AUC.

Table 4. Summary of Predictor Variables for SVR12

Predictor Variable (unit)	Slope	SE	p-value
Treatment-naïve and PRS-experienced GT1, 2, 4, 5, and 6 (non-GT3) subjects			
Intercept	-7.1974	4.7936	0.1332
Ln PIB AUC (ng*hr/mL)	1.8276	0.7060	0.0096
Treatment-naïve GT3 subjects			
Intercept	-6.7969	3.2964	0.0392
Ln PIB AUC (ng*hr/mL)	1.5361	0.4879	0.0016

- PIB exposure was a statistically significant predictor of SVR12 ($p < 0.05$) in non-GT3 TN, TE_PRS subjects and GT3 TN subjects, but even the subjects in the lowest PIB exposure quartiles (Figure 3) had achieved SVR12 rates above 95%.
- No other variables tested including GLE exposures or treatment duration were significant predictors of response (p-values of > 0.05).

CONCLUSIONS

- **GLE/PIB regimen achieved high SVR rates of ~100% in treatment-naïve and PRS-experienced GT1, GT2, GT4, GT5, and GT6-infected (non-GT3) subjects, 96.6% in treatment-naïve GT3-infected subjects with a 8-week treatment duration.**
- **12 week treatment duration has no impact on SVR12 rates compared to the 8 week duration**
- **GLE exposure had no significant impact on SVR12 rates.**
- **PIB exposure showed a shallow relationship with SVR12 in treatment-naïve GT3 infected subjects. Although lower PIB exposure was a significant predictor for SVR12, its impact was not clinically significant as even those with low PIB exposures achieved high SVR rates.**
- **Covariates including demographic variables (age, sex, weight, and race), presence of cirrhosis, baseline HCV RNA viral load, IL28, GLE exposure, renal impairment status, co-infection with HIV and inclusion or exclusion of RBV in the regimen were evaluated and were not statistically significantly associated with SVR12.**

DISCLOSURES

- All authors are AbbVie employees and may hold AbbVie stocks or options.
- The studies were funded by AbbVie. AbbVie contributed to the design, research, and interpretation of data, writing, reviewing, and approving the publication.

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Glecaprevir and Pibrentasvir Exposures in Hepatitis C Virus-Infected Subjects in Phase 2 and 3 Studies

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Presented at the 2017 AASLD The Liver Meeting, October 20–24, 2017, Washington, DC

BACKGROUND

- Glecaprevir (GLE, identified by AbbVie and Enanta)/pibrentasvir (PIB) 300 mg/ 120 mg QD regimen, has been approved for Hepatitis C (HCV) genotype (GT) 1-6 infection with a treatment duration as short as 8 weeks.
- The safety and efficacy of GLE/PIB 300 mg/120 mg were evaluated during clinical trials enrolling more than 2,300 adults with genotype 1-6 HCV infection without cirrhosis or with mild cirrhosis.
- Results of the trials demonstrated that overall 98% cure rate (sustained viral response at 12 weeks post treatment, or SVR12) for patients who received GLE/PIB for 8, 12 or 16 weeks.
- The present analysis is to characterize the exposures of GLE and PIB in HCV-infected subjects and identify potential demographic, pathophysiologic and treatment factors that affect the exposures of GLE and PIB using a population pharmacokinetic (Pop PK) analysis approach

METHODS

- A total of 2708 subjects receiving GLE and 2702 subjects receiving PIB from four Phase 2 studies and six Phase 3 were included in the Pop PK analyses.
- Intensive PK data were collected in monotherapy study, frequent and spare PK samples were collected in GLE/PIB combination studies

Population Pharmacokinetic Analyses

- Population pharmacokinetic analysis was performed using nonlinear mixed-effects modeling approach in NONMEM 7.3.
- Compartment models were explored for structural model development.
- Nonlinearity of dose-exposure relationships for GLE and PIB were incorporated into the structural model.
- Specific intrinsic factor covariates include demographics (age, race, bodyweight, and sex), presence of cirrhosis, renal function by chronic kidney disease (CKD) stage, presence of dialysis, genotype, previous treatments, RBV co-administration and HIV-HCV coinfection, and extrinsic factor covariates include formulation (Phase 3 vs. Phase 2) and concomitant medications (Co-meds), Including 17 drug classes (e.g.: Proton pump inhibitors, anti-hypertensives and etc.) and drug categories by metabolic enzymes or transporters (CYP inhibitor/inducers, BCRP inhibitors, OATP1B1/B2 inhibitors and P-gp inhibitors or inducers).
- Covariate effects were included into the model in a multiplicative fashion and evaluated by a stepwise forward inclusion, backward elimination model building procedure.
- The final models were evaluated based on objective function value, visual predictive checks, and nonparametric bootstrap.

RESULTS

Table 1. Demographics Summary for the data included in the Population Pharmacokinetic Analyses

Characteristics		All Subjects GLE	All Subjects PIB
N		2708	2702
Age (years)	Mean (SD)	52.6 (11.7)	52.6 (11.7)
	Median	54.0	54.0
	Min – Max	19.0, 88.0	19.0, 88.0
Weight (kg)	Mean (SD)	77.8 (17.2)	77.8 (17.2)
	Median	76.0	76.0
	Min – Max	39.6, 179	39.6, 179
Race	White, N (%)	2203 (81%)	2196 (81%)
	Black, N (%)	176 (7%)	177 (7%)
	Asian, N (%)	276 (10%)	276 (10%)
	Others, N (%)	53 (2%)	53 (2%)
Sex	Male, N (%)	1531 (57%)	1528 (57%)
	Female, N (%)	1177 (43%)	1174 (43%)
Cirrhosis	Non-cirrhotic, N (%)	2316 (86%)	2311 (86%)
	Cirrhotic, N (%)	367 (14%)	366 (14%)
Renal Function	Normal, N (%)	1292 (48%)	1291 (48%)
	Mild impairment, N (%)	1261 (47%)	1256 (46%)
	Moderate impairment, N (%)	52 (2%)	52 (2%)
	Severe impairment, N (%)	16 (0.6%)	17 (0.6%)
	End stage impairment, N (%)	86 (3%)	86 (3%)

- A two-compartment model with first-order absorption and elimination adequately described the GLE and PIB plasma concentration-time data.

Co-meds evaluated and had shown no significant impacts on GLE/PIB Pharmacokinetics

Drug classes

- ✓ Acid reducing Agents (excluding PPIs and laxatives)
- ✓ Low/regular dose Proton pump inhibitors (PPIs)
- ✓ Anti-depressants/Anxiolytics/ Benzodiazepines/ Barbiturates
- ✓ Anti-hypertensives
- ✓ PDE5 inhibitors
- ✓ NSAIDs
- ✓ Statins and lipid-lowering agents
- ✓ Anti-psychotics
- ✓ Anti-epileptic drugs/ anti-convulsants
- ✓ Anti-diabetics
- ✓ Antihistamines/ anti-allergics/ respiratory agents
- ✓ Hormonal contraceptives
- ✓ Hormonal replacement therapies
- ✓ Steroids
- ✓ Anti-infectives

Drug categories by metabolic enzymes or transporters

- ✓ CYP3A inhibitors and inducers
- ✓ OATP1B1/B3 inhibitors
- ✓ P-gp inhibitors and inducers

- Subjects receiving high dose PPIs had slightly lower GLE exposure (↓5%) and subjects receiving opioids had higher GLE exposure (↑16%) compared to those who did not. Subjects receiving BCRP inhibitors had higher PIB exposure (↑27%) compared to those who did not.
- The differences in GLE/PIB exposures would not anticipated to have a meaningful impacts on efficacy and safety of GLE/PIB regimen

Figure 1. Observed and Model-Predicted GLE Concentration vs Time After Last Dose (GLE/PIB 300/120mg)

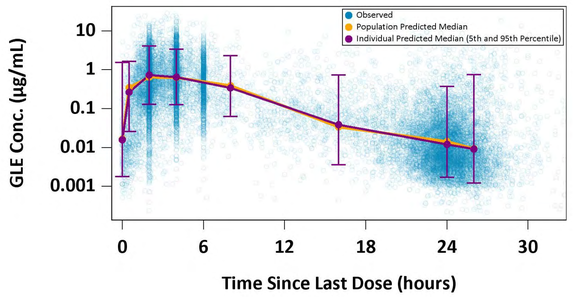
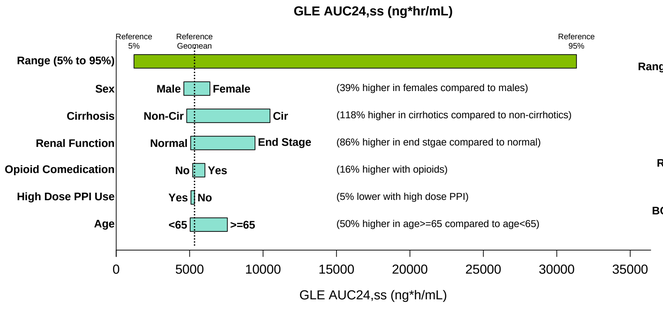


Figure 2. Distribution and geometric means of GLE AUC in covariate subgroups at GLE/PIB 300 mg/120 mg Dose



- Despite some covariates had shown to be associated with F1, CL/F or V2/F of GLE or PIB, the overall impacts on AUCss are relative small and less than the observed PK variability in GLE and PIB exposures.
- Presence of cirrhosis is the main factor increasing GLE exposure (118% higher) while no significant difference in PIB exposures was observed between HCV-infected subjects with or without cirrhosis

Table 2. Exposures of GLE and PIB in HCV-Infected Subjects without cirrhosis and with compensated cirrhosis (GLE/PIB 300/120mg)

Hepatic Function	Geometric Mean (%CV)			
	GLE		PIB	
	$AUC_{24,ss}$ ng•hr/mL	$C_{max,ss}$ ng/mL	$AUC_{24,ss}$ ng•hr/mL	$C_{max,ss}$ ng/mL
Non-Cirrhotics	4800 (198)	597 (150)	1430 (63)	110 (49)
Compensated Cirrhotics	10500 (93)	1110 (78)	1530 (54)	111 (44)
Ratio (cirrhotics/ non-cirrhotics)	2.18	1.86	1.07	1.01

Figure 3. Observed and Model-Predicted PIB Concentration vs Time After Last Dose (GLE/PIB 300/120mg)

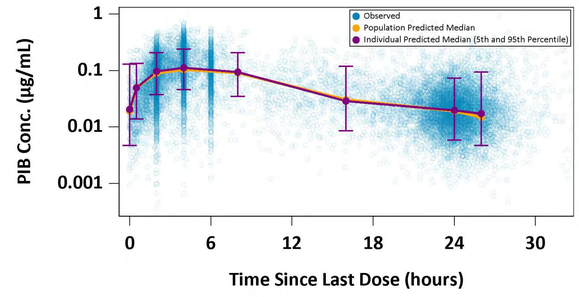
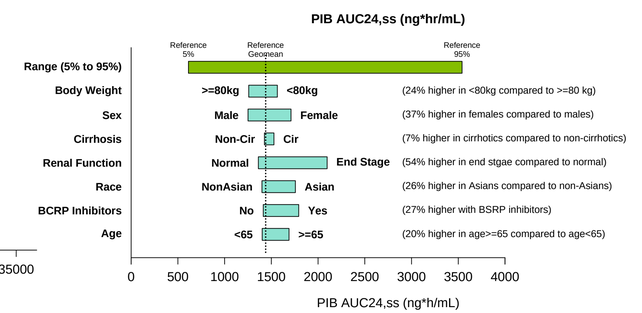


Figure 4. Distribution and geometric means of PIB AUC in covariate subgroups at GLE/PIB 300 mg/120 mg Dose



- On basis of the small impact of all of the tested covariates, no dose adjustments of GLE and PIB are warranted.

CONCLUSIONS

- Presence of cirrhosis is the main factor increasing GLE exposure
- With the favorable efficacy and safety profiles demonstrated over the wide GLE and PIB exposure ranges in Phase 2/3 studies, the evaluated covariates did not have clinically significant impacts on GLE or PIB exposure
- No GLE/PIB dose adjustment is recommended on the basis of age, weight, sex, race, presence of cirrhosis, renal function, or concomitant medications

DISCLOSURES

- All authors are AbbVie employees and may hold AbbVie stocks or options.
- The studies were funded by AbbVie. AbbVie contributed to the design, research, and interpretation of data, writing, reviewing, and approving the publication.

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Summary of the Incidence Rates in HCV Infected Subjects Who Have High GLE Exposures (Equal and 10-fold Higher Than the Geometric Mean Of GLE Exposure in Non-Cirrhotics)

Exposure-Safety Response Relationship for Glecapravir and Pibrentasvir in Hepatitis C Virus-Infected Subjects in Phase 2 and 3 Studies

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Presented at the 2017 AASLD The Liver Meeting, October 20–24, 2017, Washington, DC

BACKGROUND

- Glecaprevir (GLE, identified by AbbVie and Enanta)/pibrentasvir (PIB) 300 mg/ 120 mg QD regimen, has been approved for Hepatitis C (HCV) genotype (GT) 1-6 infection with a treatment duration as short as 8 weeks.
- The safety and efficacy of GLE/PIB were evaluated in clinical trials enrolling adult patients with genotype 1-6 HCV infection without cirrhosis or with compensated cirrhosis.
- Results of the trials demonstrated that overall 98% cure rate (sustained viral response at 12 weeks post treatment, or SVR12) for patients who received GLE/PIB for 8, 12 or 16 weeks.
- Other NS3/4A protease inhibitors have been associated with diarrhea, ALT and bilirubin elevations. Therefore, this analysis was focusing on these safety events.
- The objective of this analysis was to describe the relationships of GLE and PIB exposures and clinical safety parameters following administration of the DAAs, GLE and PIB as combinations, in Phase 2 and 3 clinical trials in HCV-infected subjects (N=2660).

METHODS

- All subjects who received GLE and PIB (without RBV) or placebo in the Phase 2 and 3 studies and had data for safety variables of interest and exposure values (except for subjects who received placebo) were included in the exposure-safety response analyses.

Table 1. Summary of GLE + PIB Combination Treatments evaluated in Phase 2 and 3 studies

Total Daily GLE/PIB Dose (mg)	Duration (Week)	Subjects (N)
0/0 (Placebo)	12	100
200/40	12	69
200/80	12	6
200/120	12	123
	8	844
300/120	12	1398
	16	120

- Exposure (steady-state AUC) of each drug was obtained using post-hoc estimates for individual subjects from population pharmacokinetic analyses for different doses and/or regimens. The response variables (ALT, total bilirubin, diarrhea) were the safety events of interest. Relationships between adverse event /laboratory abnormalities and drug exposures were evaluated by graphical analysis and logistic regression.
- Treatment-emergent adverse events were summarized by maximum severity of each preferred term. Each preferred term was assigned to a grade level based on severity and seriousness. Adverse events and laboratory observations for selected laboratory parameters were categorized according to the grades specified in Table 2, based on the CTCAE (Ver. 3.0) grading system.

METHODS (CONTINUED)

Table 2. Definitions of CTCAE Grades for Selected Safety Parameters

Test	Grade 1	Grade 2	Grade 3	Grade 4
ALT	> ULN – 3×ULN	> 3 – 5×ULN	> 5 – 20×ULN	> 20×ULN
Total Bilirubin	> ULN – 1.5×ULN	> 1.5 – 3×ULN	> 3 – 10×ULN	> 10×ULN
Diarrhea	Increase of < 4 stools per day over baseline	Increase of 4 – 6 stools per day over baseline	Increase of ≥ 7 stools per day over baseline	Life threatening consequences

RESULTS

Table 3. Demographic Data Summary

Patient Population		Non-Cirrhotics					Compensated Cirrhotics		Total
GLE/PIB Doses (mg)		Placebo	200/40	200/80	200/120	300/120	200/120	300/120	
Sex (N)	Male	45	33	3	53	1117	19	199	1469
	Female	55	36	3	44	937	7	109	1191
Race (N)	White	60	63	4	85	1633	24	261	2130
	Black	7	5	2	8	124	1	25	172
	Asian	32	0	0	2	253	0	17	304
	Other	1	1	0	2	44	1	5	54
Age (years)	Mean	57.6	50.4	53.5	51.9	51.7	59.1	58.4	52.8
Weight (kg)	Mean	73.6	79.5	82.4	81.5	76.2	83.2	84.3	77.4
Renal Impairment by CKD Stage (N)	CKD < 4	100	69	6	97	1970	26	288	2556
	CKD ≥ 4	0	0	0	0	84	0	20	104

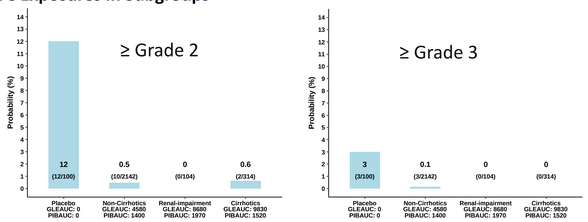
Table 4. Summary of Safety Events of Special Interest (≥Grade 2 only)

Safety Event	CTCAE Maximum Grade on Treatment	Treatment	
		Active N=2560	Placebo N=100
Post-nadir ALT elevation	G2	9 (0.4 %)	9 (9.0 %)
	G3	3 (0.1 %)	3 (3.0 %)
Post-baseline total bilirubin elevation	G2	52 (2.0 %)	0 (0 %)
	G3	9 (0.4 %)	0 (0 %)
Diarrhea	G2	12 (0.5 %)	0 (0 %)
	G3	1 (<0.1 %)	0 (0 %)

- Grade 3 ALT abnormalities observed (3/2560) were not clinically significant; either fluctuations from a baseline Grade 3 within the first 2 weeks (n=2) or associated to multiple cholelithiasis (n=1).

RESULTS (CONTINUED)

Figure 1. Percent of Subjects with Grade 2 or 3 Post Nadir ALT Elevations vs. AUC Exposures in Subgroups



- Subjects receiving active GLE/PIB regimens had significantly lower probability ALT elevation compared to subjects receiving placebo
- Subjects with renal impairment and/or compensated cirrhosis had similar rates of ALT abnormality, even with higher GLE exposures
- No exposure-ALT relationship was identified in the logistic regression analyses after controlling placebo effect

Figure 2. Percent of Subjects with Grade 2 or 3 Post-baseline Total Bilirubin Elevations vs. AUC Exposures in Subgroups

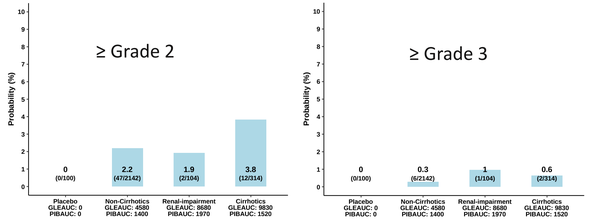
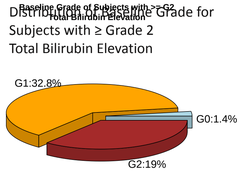


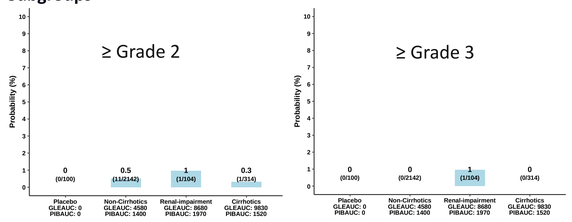
Table 5. Logistic Regression Analyses for Exposure-Response Relationship between GLE AUC and Grade 2/3 Total Bilirubin Elevation

Response Variable	Predictor Variable	Estimate of Slope	p-value
Maximum Post-baseline Total Bilirubin Elevation (≥ Grade 2)	log AUC of GLE	0.808	<.0001
	Baseline Bilirubin Value	0.168	<.0001
Maximum Post-baseline Total Bilirubin Elevation (≥ Grade 3)	Baseline Bilirubin Value	0.208	<.0001



- A shallow relationship was observed between GLE exposures and total bilirubin elevations ≥ Grade 2
- No significant exposure-response relationship for ≥ Grade 3 total bilirubin elevations was identified
- The observed GLE exposure-total bilirubin relationships were consistent with mild inhibition by GLE of bilirubin metabolism.
- The bilirubin abnormalities were mostly observed in patients with pre-existing high bilirubin level which is also identified as a predictor for total bilirubin elevation.

Figure 3. Percent of Subjects with Diarrhea vs. AUC Exposures in Subgroups



- No exposure-response relationship was identified for diarrhea

Table 6. Treatment-Emergent Diarrhea Events of Any Grade by GLE or PIB doses

	Doses	Diarrhea events[a] N (%)		Pearson Pr > ChiSq	Cochran-Armitage Pr > |Z|
		No	Yes		
GLE	300 mg (N = 2362)	2272 (96.2%)	90 (3.81%)	0.572	0.292
	200 mg (N = 196)	190 (96.9%)	6 (3.06%)		
	Placebo-0 mg (N = 100)	98 (98.0%)	2 (2.00%)		
PIB	120 mg (N = 2483)	2390 (96.3%)	93 (3.75%)	0.710	0.486
	80 mg (N = 6)	6 (100%)	0 (0%)		
	40 mg (N = 69)	66 (95.7%)	3 (4.35%)		
	Placebo-0 mg (N = 100)	98 (98.0%)	2 (2.00%)		

a: Treatment-emergent adverse event of diarrhea according to the MedDRA preferred term and considered have a reasonable possibility of being related to study drug by the investigator

- No significant dose-response relationship was identified for diarrhea by Pearson Chi-square test or Cochran Armitage test

CONCLUSIONS

- **Data from 2660 subjects were evaluated in this exposure-safety analysis. Overall, very few safety events of interest (ALT elevations, total bilirubin elevations, and diarrhea) were observed in subjects who received GLE/PIB regimens.**
- **Subjects with renal impairment and/or compensated cirrhosis had similar safety profiles, even with higher GLE exposures**
- **Grade 3 diarrhea events or ALT increases were rare (≤0.1%). No cases of consistent with hepatotoxicity were observed. No exposure-response relationship for ≥ Grade 3 post-nadir ALT elevations or diarrhea was identified.**
- **A shallow relationship was observed between GLE exposures and total bilirubin elevations ≥ Grade 2, consistent with mild inhibition of bilirubin metabolism.**
- **Covariates tested such as age, weight, sex, race, treatment duration, presence of cirrhosis or renal impairment were not associated with ALT or bilirubin elevations or diarrhea.**

DISCLOSURES

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