SURVEYOR-II, Part 4: Gilepcavir/Pibentasvir Demonstrates High SVR Rates in Patients With HCV Genotype 2, 4, 5, or 6 Infection Without Cirrhosis Following an 8-Week Treatment Duration

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INTRODUCTION

Hepatitis C virus genotypes (HCV GT) 2, 4, 5, and 6 have diverse prevalence and patterns of adherence and access to care. GT2–6 have been challenging to treat due to their pangenotypic NS3/4A resistance and limited access to approved regimens, especially in GT5 and GT6 patients. The SURVEYOR-II study was designed to explore the effectiveness and tolerability of a highly potent, pangenotypic regimen in GT2–6-infected patients.

OBJECTIVE

The primary objective of the SURVEYOR-II study is to evaluate 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.

METHODS

STUDY DESIGN

Patients received 8 weeks of G/P (430 mg/120 mg QD for GT2-4 or GT2, 430 mg/120 mg QD for GT5, 460 mg/120 mg QD for GT6) with a target dose of 1500 mg/400 mg for GT5-infected patients. For up to 20% of GT2-4 and GT5-6 patients, the dose could be increased to 2000 mg/500 mg. The study was stopped early after interim analysis showed a high SVR12 rate in GT2-6-infected patients.

RESULTS

The study met its primary and secondary endpoints. The SVR12 rate was 99% (135/137) in patients infected with GT2, 4, 5, or 6, non-inferior to the historical 95% SVR rate achieved with 12 weeks of SOF/RBV. There were no virologic failures, post-treatment relapses, or treatment-emergent virologic failures. SVR rates for GT3 were 100% (15/15) and 98% (19/20) for GT4 and GT5, respectively. GT6-infected patients had an 8-week SVR12 rate of 97% (19/20), consistent with the historical 95% SVR rate following 12 weeks of SOF/RBV. In previous phase 2 studies, sustained virologic response at 12 weeks was demonstrated in patients infected with GT2 (99%), GT4 (98%), GT5 (98%), and GT6 (99%).

CONCLUSIONS

- 97% (196/203, ITT) of GT2, 4, 5, or 6-infected patients achieved SVR12 following 8 weeks of G/P.
- In DAA-naive patients with GT2 infection, 8-week treatment was non-inferior to the historical 95% SVR rate achieved with 12 weeks of 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.

REFERENCES


ACKNOWLEDGMENTS

The authors wish to express their gratitude to the patients and their families who participated in this study. Medical writing support was provided by Joie Hunter, PhD, of AEWA.
**Objectives**

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

**Subjects**

- All enrolled subjects were healthy male and female subjects between 18 and 55 years old.

**Results**

**Table 1. Subject Demographics andDisposition**

<table>
<thead>
<tr>
<th>Race</th>
<th>Mean ± SD</th>
<th>Min – Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>6 White (50%), 6 Black (50%)</td>
<td></td>
</tr>
<tr>
<td>Multi-race</td>
<td>1 Multi-race (8%)</td>
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</table>

**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 rhinorhoea 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.

**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.

**Disclosure**

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.

**Reference**

- Losartan is a competitive inhibitor of the angiotensin II receptor (AT1) and is 10-40 times more potent of an AT1 inhibitor than the parent compound.

**Figure 1. Study Design**

- Phase 1, single-center, non-fasting, open label study (Figure 1) in 12 healthy subjects. All enrolled subjects completed the study and were included in pharmacokinetic and safety analyses.

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

**Figure 3. Interactions Between GLE and PIB with Losartan**

- GLE Plasma Concentration (ng/mL)
- Losartan Plasma Concentration (ng/mL)
- Valsartan Plasma Concentration (ng/mL)

**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 (↑Cmax 36% and ↑AUC0-24 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 (≤17% difference).
Hemodialysis Does Not Affect the Pharmacokinetics of Glecpariev (ABT-493) or Pibrentasvir (ABT-530)

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INTRODUCTION

• 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.

• Additional, arterial (predialyzer) and venous (postdialyzer) blood samples were collected during dialysis.

• No-compartmental analysis was performed with Phoenix WinNonlin v6.3 including estimation of maximum plasma concentration (Cmax) and area under the curve (AUC) from zero time to the last sampling point (AUC0). AUC during dialysis for arterial (AUCarterial) or venous (AUCvenous) samples, apparent oral clearance (CL/F), and clearance due to dialysis (CLD). CLD 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>Min–Max</th>
</tr>
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<tbody>
<tr>
<td>Age (y)</td>
<td>57 ± 9</td>
<td>47 – 73</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80 ± 23</td>
<td>52 – 122</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170 ± 9</td>
<td>156 – 183</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>2 Females (25%), 6 Males (75%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>8 Black (100%)</td>
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</tr>
</tbody>
</table>

• 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.

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

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter (units)</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 1</th>
<th>Period 2</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>GLE</td>
<td>PIB</td>
<td>GLE</td>
<td>PIB</td>
<td>GLE</td>
<td>PIB</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>6.17 (483, 49)</td>
<td>7.23 (1055, 110)</td>
<td>128 (150, 48)</td>
<td>156 (193, 54)</td>
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<td></td>
</tr>
<tr>
<td>AUC0 (L/h)</td>
<td>3.6 (500, 60)</td>
<td>3.2 (745, 53)</td>
<td>5.5 (130, 9)</td>
<td>5.5 (150, 62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC0 (L/h) [0, 24]</td>
<td>3010 (1820, 65)</td>
<td>2840 (4000, 100)</td>
<td>1020 (1150, 47)</td>
<td>1120 (1380, 54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC0 (L/h) [0, 15]</td>
<td>1580 (2000, 60)</td>
<td>–</td>
<td>358 (417, 54)</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC0 (L/h) [0, 12]</td>
<td>1580 (1880, 67)</td>
<td>–</td>
<td>377 (485, 52)</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>0.579 (1), 110</td>
<td>–</td>
<td>0.033 (1), 281</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLD (L/h)</td>
<td>0.203 (58, 10)</td>
<td>0.203 (58, 10)</td>
<td>0.203 (58, 10)</td>
<td>0.203 (58, 10)</td>
<td></td>
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</tbody>
</table>

• Mean values of Cmax represented a minimal portion of CL/F for GLE (<1%) and PIB (<0.005%).

• Fraction of unbound drug pre- versus post-dialysis was similar and ranged between 2.5 to 2.9% (GLE) or 0.019 to 0.029% (PIB).

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

• Maximum concentrations of GLE and PIB peaked 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.

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.

REFERENCES


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.
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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AbbVie Inc., North Chicago, Illinois, United States

Presented at the 67th Annual Meeting of the American Association for the Study of Liver Diseases, November 15-17, 2016, Boston, Massachusetts

BACKGROUND
• Direct-acting antivirals (DAAs) treatment failure
• HCV genotype 1 (GT1) treated with the combination of (GT3A/NS5A + GT3B/NS5A) was used

PIB IS ACTIVE AGAINST COMMON GT1 NS5A SUBSTITUTIONS
• PIB is highly active against common GT1 NS5A substitutions at amino acid positions 10, 15, and 100 that confer resistance to 1st and 2nd generation NS5A inhibitors.
• PIB inhibits activity against GT1 NS5A substitutions; note 1st and 2nd generation NS5A inhibitors have significantly lower activity against these substitutions.

40% 60% 80% 100%

• PIB IS ACTIVE AGAINST COMMON GT1 NS5A SUBSTITUTIONS

• PIB IS ACTIVE AGAINST COMMON GT1 NS5A SUBSTITUTIONS

Figure 5. Baseline NS5A Polymorphisms

Figure 1A. GLE Demonstrates an Improved Resistance Profile Relative to 1st Generation NS5A/4A

Figure 18. GLE Demonstrates an Improved Resistance Profile Relative to 2nd Generation NS5A/4A

Figure 2A. GLE Demonstrates an Improved Resistance Profile Relative to 1st Generation NS5A/4A Inhibitors

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

Figure 6. Patients With Multiple Polymorphisms

SUMMARY
• High SVR12 rate among SOA-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 polymorphisms in NS3 and/or NS5A based on 2% or 5% NS5A detection threshold
• Most patients (80%) had at least 1 baseline polymorphism in NS3 or NS5A
• High SVR12 rate was achieved (46/48 patients, 97%) despite the high prevalence of baseline polymorphisms, including in patients with NS5A polymorphisms

MAGELLAN (Part 1) Study Design
• MAGELLAN (Part 1) is a open-label, multicenter, randomized phase 2 trial in (2) studies/clinical trials with GT1-infected adults

Table 3. Two Patients Experienced Virologic Failure

Table 2. Prior DAA Treatment Regimens

Table 1. Activity of GLE and PIB

Figure 4. Baseline NS5A Polymorphisms

REFERENCES
• Reference to a specific clinical trial
• Reference to a specific clinical trial
• Reference to a specific clinical trial

DISCLOSURES
All authors are employees of AbbVie. The design, study conduct, and financial support for this clinical trial was provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication.