Supplementary Material

Real-world safety and effectiveness of an 8-week regimen of glecaprevir/ pibrentasvir in cirrhotic hepatitis C patients

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Table S1: Summary of Adverse events/ serious adverse events (AE/ SAE) by planned treatment duration.

		All (N=166)	8 Wks (N=43)	12 Wks (N=116)	Oth (N=7)
Anemia	AE	-	-	-	-
	SAE	-	-	-	-
Appetite, decreased	AE	-	-	-	-
	SAE	-	-	-	-
Bradycardia	AE	-	-	-	-
	SAE	-	-	-	-
Cardiac arrest	AE	-	-	-	-
	SAE	-	-	-	-
Chills	AE	-	-	-	-
	SAE	-	-	-	-
Depression	AE	-	-	-	-
	SAE	-	-	-	-
Diarrhea	AE	1 (1%)	-	1 (1%)	-
	SAE	-	-	-	-
Dyspnea	AE	1 (1%)	-	1 (1%)	-
	SAE	1 (1%)	-	1 (1%)	-
Fatigue	AE	-	-	-	-
	SAE	-	-	-	-
Fever	AE	-	-	-	-
	SAE	-	-	-	-
Flu	AE	2 (1%)	-	2 (2%)	-
	SAE	-	-	-	-
Headache	AE	1 (1%)	-	1 (1%)	-
	SAE	1 (1%)	-	1 (1%)	-
Hepatic decompensation	AE	1 (1%)*	-	1 (1%)	-
	SAE	-	-	-	-
Hepatic failure	AE	-	-	-	-
	SAE	-	-	-	-
Insomnia	AE	-	-	-	-
	SAE	-	-	-	-
Irritability	AE	-	-	-	-
	SAE	-	-	-	-
Jaundice	AE	2 (1%)	-	2 (2%)	-
	SAE	1 (1%)	-	1 (1%)	-
Muscle pain	AE	1 (1%)	1 (2%)	0 (0%)	-
	SAE	-	-	-	-
Myocardial infarction	AE	-	-	-	-
	SAE	-	-	-	-
Nausea	AE	4 (2%)	1 (2%)	3 (3%)	-
	SAE	-	-	-	-
Neutropenia	AE	-	-	-	-
	SAE	-	-	-	-
Other	AE	5 (3%)	0 (0%)	3 (3%)	2 (29%)
	SAE	4 (2%)	0 (0%)	2 (2%)	2 (29%)
Pancreatitis	AE	-	-	-	-
	SAE	-	-	-	-
Pancytopenia	AE	1 (1%)	-	1 (1%)	-
	SAE	1 (1%)	-	1 (1%)	-
Photosensitivity	AE	-	-	-	-
	SAE	-	-	-	-
Pneumonia	AE	-	-	-	-
	SAE	-	-	-	-
Pneumonitis	AE	-	-	-	-
	SAE	-	-	-	-
Pruritis	AE	1 (1%)	-	1 (1%)	-
	SAE	-	-	-	-
Pulmonary sarcoidosis	AE	-	-	-	-
	SAE	-	-	-	-
Skin reaction	AE	5 (3%)	-	4 (3%)	1 (14%)

	SAE	1 (1%)	-	-	1 (14%)
Stool, black/ bloody	AE	-	-	-	-
	SAE	-	-	-	-
Suicide attempt	AE	1 (1%)	1 (2%)	-	-
	SAE	1 (1%)	1 (2%)	-	-
Vomiting	AE	1 (1%)	-	-	1 (14%)
	SAE	1 (1%)	-	-	1 (14%)

Table S2: Summary of Serious Adverse Events (SAEs) and hepatic events including one death during treatment

<table>
<tr><th>Obs rRecord #</th><th>Planned course length (weeks)</th><th>SAE</th><th>Comments</th><th>Related to G/P therapy?</th><th>Completed full course of G/P?</th><th>Achieved SVR?</th></tr>
<tr><td>15</td><td>12</td><td>Hyperbilirubinemia</td><td>ER visit for jaundice/hyperbilirubinemia w/ potential alcohol ETOH use (. (Ppatient had history of relapsing alcohol misuse but stated they had discontinued use 4 weeks prior to GLE/PIB treatment initiation ETOH abuse.). Planned 12 wk course of G/P was discontinued early (after 3 weeks); patient still achieved SVR. Patient had concomitant use of OTC H2 blocker during G/P therapy.

Total bilirubin .Bili peaked at 6.1 mg/dL about approximately 2 weeks after initiation of GLE/PIB. Levels began to decline while on starting G/P, but started to decline even before G/P therapy was terminatedtreatment, and then continued to decline after treatment ended and had fully normalized by 2 months after end of treatment.2 mos. later. However, both total & direct bilirubin were elevated again 6 mos 6 months later, after that, then normalized, for a while, then became elevated again about 5 months after that. Patient has history of ETOH abuse, although stated had d/c'd use 4 weeks prior to starting G/P. Patient Wwas reported to be misusing alcoholabusing ETOH 1 year after G/P therapy ended. Planned 12 wk course of G/P was discontinued early after 3 weeks; patient still achieved SVR. Patient had concomitant use of OTC H2 blocker during G/P therapy.

<table><tr><th>Total bilirubin levels</th><th>Relative to Treatment Period</th></tr><tr><td>Ranged from 1.1-1.5 mg/dL</td><td>Before</td></tr><tr><td>Ranged from 6.1 mg/dL two weeks after starting treatment to 3.8 mg/dL the day before stopping treatment at 3 weeks.</td><td>During</td></tr><tr><td>Declined from 2.3 to 0.9 mg/dL during the first 73 days after EOT. However, during the following 18 months, fluctuated between normal (<1.0 mg/dL) and prolonged raised levels (up to 3.5 mg/dL)</td><td>After</td></tr></table></td><td>Possible (also possible ETOH use)</td><td>No</td><td>Yes</td></tr>
<tr><td>31</td><td>12</td><td>Pancytopenia</td><td>Hospitalization while on G/P therapy due to ongoing rapidly progressive glomerulonephritis in setting of ESRD and who presented with anemia post outpatient plasmapheresis session and</td><td>Unlikely (Ongoing</td><td>Yes</td><td>Yes</td></tr>
</table>

			ongoing pancytopenia multifactorial from CKD, autoimmune process, and plasmapheresis. This has been a recurring problem resulting in recurring hospitalizations both before and after GLE/PIB	problem before and after)		
49	12	Death while on treatment	Patient had recurrent GT1a HCV post-liver transplant with liver stiffness=21.6kPA. Patient had no evidence of decompensation and denied any past or recent history of jaundice, generalized pruritis, right upper quadrant pain, lower extremity edema, or symptoms suggestive of GI bleeding. Patient also had chronic kidney disease (eGFR=36), was receiving immunosuppressant medication for transplant, gabapentin for neuropathy in lower extremity, and Chantix for smoking cessation. Treating physician was notified that patient Patient's son called to notify treating hepatologist that patient passed away at [9 weeks + and 5 days after GLE/ PIB treatment initiation. starting G/P treatment]. Had a planned 12 week G/P course. Patient was found by his visiting nurse unresponsive in his house. Patient was He was declared deceased at home, and was taken directly to the funeral home. Son ; family reporteds that death was due to "natural causes", but stated cause of death is otherwise unclear. Hepatologist reply: "I indicated that based on rrecent laboratory tests were unremarkable and that patient did not have new complaints 3 days prior to their death, but did have unchanged fatigue since the start of G/P initiation.s the patient appeared to be doing well, and when I spoke with him [3 days before his death]..., he did not have any new complaints at that time, but noted unchanged fatigue which began when he started taking Mavyret." Patient had recurrent HCV post-liver OLT in 1999, was treatment naive, genotype 1a, and LS=21.6 kPa before starting treatment, without prior evidence of decompensation (denied any past or recent history of jaundice, generalized pruritis, right upper quadrant pain, lower extremity edema, or symptoms suggestive of GI bleeding such as hematemesis, melena, or hematochezia). Patient had CKD (eGFR-36, and was on immunosuppressants due to OLT as well as gabapentin for neuropathy in left leg and Chantix for smoking cessation (the latter prescribed by an outside provider about a month after G/P treatment started). Chart review showed revealed that patient complained of consistent fatigue prior to initiating G/P therapy.	Unknown	No	Unk
52	12	Other – Facial swelling	Developed facial/lip swelling about 2 weeks after starting G/P. It was determined to be an allergic reaction to lisinopril, even though patient had been taking lisinopril prior to G/P initiation. Reaction resolved after ER treatment and lisinopril was d/c'd and replaced with a different anti-hypertensive .	Unlikely	Yes	Yes
60	16	Skin issue & edema	ER visit w/ Rx for skin issue with edema (penoscrotal edema and serous fluid output from penis and scrotum) during G/P therapy.	Unknown	Yes	Yes
64	12	Headache	Patient hospitalized for headache (and received Rx) during G/P therapy. Concomitant OTC PPI during G/P therapy.	Unknown	Yes	Yes
78	16	Vomiting & homicide ideation	ER visit (with rx) for vomiting. Hospitalization for homicide ideation.	Unknown	Yes	Yes
105	12	Other – Contusions & abrasions	ER visit for multiple contusions and abrasions resulting from bicycle accident.	No	Yes	Yes

158	12	Dyspnea	ER visit & rx for dyspnea	Unknown	Yes	Yes
163	8	Suicide ideation	Patient experienced suicide ideation/attempt while on therapy and was hospitalized.	Unknown	Yes	Yes

Table S3: Additional liver-related events identified using data from the electronic medical record (i.e., ICD codes, total bilirubin and albumin levels, and lactulose/rifaximin prescriptions) for the period during GLE/PIB treatment

<table>
<tr><th>Obs record #</th><th>Planned course length (weeks)</th><th>Hepatic event</th><th>Comments</th><th>Related to G/P therapy?</th><th>Completed full course of G/P?</th><th>Achieved SVR?</th></tr>
<tr><td>2</td><td>12</td><td>Transient, self-limited hyperbilirubinemia</td><td>T.Bili was elevated throughout treatment but treatment continued unaltered, and T.Bili returned to normal after treatment ended. Hyperbilirubinemia was not documented in CRF as an AE because there were no hospitalizations, ER visits, RX's, or changes in G/P therapy due to the hyperbilirubnemia.
<table>
<tr><th>Total bilirubin levels</th><th>Relative to Treatment Period</th></tr>
<tr><td>Ranged from 1.3-1.7 mg/dL during the 12 months prior to starting G/P.</td><td>Before</td></tr>
<tr><td>Increased to 4.3-4.9 mg/dL during the first two weeks of G/P, then dropped to 2.3 mg/dL by week 5, then 1.7 mg/dL by week 10 of treatment.</td><td>During</td></tr>
<tr><td>0.8-0.9 mg/dL starting at day 11 after EOT through 2 years after EOT.</td><td>After</td></tr>
</table></td><td>Probable</td><td>Yes</td><td>Yes</td></tr>
<tr><td>12</td><td>12</td><td>Hyperbilirubinemia</td><td>Hyperbilirunemia detected 6 weeks after G/P was initiated; resolved around the time G/P therapy ended. However, two weeks after initiating G/P, patient underwent HCC ablation and was subsequently hospitalized multiple times for V-tach (recurrent due to severe LV systolic dysfunction and CHF) in which pacemaker was adjusted and amiodarone bolus/infusion was administered to resolve it. The hyperbilirubinemia began shortly after the HCC ablation. Hyperbilirubinemia was not documented in CRF as an AE because there were no hospitalizations, ER visits, RX's, or changes in G/P therapy due to the hyperbilirubnemia.
<table>
<tr><th>Total bilirubin levels</th><th>Relative to Treatment Period</th></tr>
<tr><td>Ranged from 0.5-0.7 mg/dL for the two years prior to starting treatment</td><td>Before</td></tr>
<tr><td>Increased slightly to 1.1 mg/dL during first 30 days, but jumped to 2.8 by day 45 and stayed in the 2.0-2.8 mg/dL range until 7 weeks, at which point began to decline, reaching to 1.4 mg/dL by EOT.</td><td>During</td></tr>
<tr><td>Declined to 0.7 mg/dL by 40 days after EOT. Thereafter fluctuated between 0.8-1.2 mg/dL for the next year.</td><td>After</td></tr>
</table></td><td>Unknown

(possibly related to HCC ablation)</td><td>Yes</td><td>Yes</td></tr>
</table>

<table>
<tr>
<td>74</td>
<td>12</td>
<td>Hyperbilrubinemia - without overt other signs of decompensation</td>
<td>T.bili was normal prior to starting G/P therapy. However 9 days after starting G/P, T.bili started to rise into abnormal range and kept increasing until peaked at 6.2 at around week 7 ½, at which point planned G/P course was discontinued early. T.bili normalized 4 mo after stopping G/P. No overt other signs of decompensation. Recorded as an AE in the CRF because planned 12 week course of G/P was stopped early. But there was no associated hospitalization or ER visit so it was not classified as an SAE.
<table>
<tr><th>Total bilirubin levels</th><th>Relative to Treatment Period</th></tr>
<tr><td>Fluctuated between 0.2-0.7 mg/dL.</td><td>Before</td></tr>
<tr><td>Increased to 1.8 mg/dL by day 9 of treatment, then to 3.1 mg/dL by day 31, declined slightly to 2.1 mg/dL by day 44, then increased to 6.2 mg/dL the day before EOT.</td><td>During</td></tr>
<tr><td>Decreased to 0.9 mg/dL by 13 days after EOT, and thereafter fluctuated between 0.2-0.6 mg/dL over the next year.</td><td>After</td></tr>
</table>
</td>
<td>Probable</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>129</td>
<td>12</td>
<td>Hepatic encephalopathy</td>
<td>Patient prescribed rifaximin for HE about 30 days after commencing G/P therapy. No related hospitalization/ER visit.</td>
<td>Probable</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</table>

Table S4: Details regarding patients who did not have confirmed sustained virological response at 12 weeks post-end of treatment

Obs record #	Planned G/P course (weeks)	Full course completed?	SVR	ITT / mITT Population	EOT viral load	Comments
17	**16**	Yes	**Unknown**	ITT only	**Undetectable**	Patient became viral negative on day 57 of treatment (Week 8) and remained negative through EOT. Patient did not return for requested post-treatment viral load testing. Lost to follow-up.
38	**12**	Yes	**Unknown**	ITT only	**N/A** (but Week 4 viral load = 136 IU/mL)	Week 4 viral load was 136 IU/mL (down from pre-treatment viral load of 5.8M IU/mL). Patient did not comply with requested Week 8, EOT, and post-treatment viral load testing, although the course of treatment was completed. Lost to follow-up.
49	**12**	No	**Unknown**	ITT only	**N/A** (but Week 4 viral load = 47 IU/mL)	Patient died unexpectedly of unknown causes while on G/P therapy, 9 weeks and 5 days after starting treatment. Week 4 viral load had declined to 47 IU/mL (from pre-treatment viral load of 3.1M IU/mL). No viral load measurements after that.
83	**12**	No	**No**	ITT & mITT	**N/A**	Patient stopped G/P treatment after 1 week due to skin reaction. Switched 10 days later to elbasvir/grazoprevir for 12 wks, which was completed and SVR was achieved.
136	**12**	Yes	**Unknown**	ITT only	**Undetectable**	Week 5 and EOT viral loads were negative. Patient died 9 weeks after EOT, so SVR12 could not be assessed.
141	**8**	Yes	**Unknown**	ITT only	**Undetectable**	Week 4 and EOT viral loads were negative. Patient died 5 weeks after EOT, so SVR12 could not be assessed.
149	**12**	Yes	**Unknown**	ITT only	**Undetectable**	Week 5 viral load negative. Still negative when tested again 4 weeks after EOT. No test results available after that.

Table S5: Distribution and rates of sustained virological response (SVR) by planned treatment duration for subsample of patients with genotyping/ subtyping data available by Intention to Treat (ITT) and modified ITT samples.

	ITT						mITT					
	All with subtyping			SVR			All with subtyping			SVR		
	8 Wks	12 Wks	Oth	8 Wks	12 Wks	Oth	8 Wks	12 Wks	Oth	8 Wks	12 Wks	Oth
All	42	109	7	40 (95.2%)	104 (95.4%)	6 (85.7%)	40	105	6	40 (100%)	104 (99%)	6 (100%)
GT 1A	25	63	3	24 (96%)	59 (93.7%)	3 (100%)	24	59	3	24 (100%)	59 (100%)	3 (100%)
GT 1B	7	20	1	7 (100%)	19 (95%)	0 (0%)	7	20	0	7 (100%)	19 (95%)	-
GT 2A	0	1	0	-	1 (100%)	-	0	1	0	-	1 (100%)	-
GT 2B	2	12	0	2 (100%)	12 (100%)	-	2	12	0	2 (100%)	12 (100%)	-
GT 3A	0	2	2	-	2 (100%)	2 (100%)	0	2	2	-	2 (100%)	2 (100%)
GT 3O	8	11	1	7 (87.5%)	11 (100%)	1 (100%)	7	11	1	7 (100%)	11 (100%)	1 (100%)

Wks, weeks; Oth, other planned treatment duration; GT, genotype; subtype “O”, other (non-A).