Integrated Efficacy and Safety of Glecaprevir/Pibrentasvir in Patients With Psychiatric Disorders

THU-338

David Back[1], Pamela Belperio[2], Mark Bondin[3], Francesco Negro[4], Andrew H Talal[5], Caroline Park[3], Yang Lei[3], Brett Pinksy[3], Eric Crown[3], Federico Mensa[3], Fiona Marra[1]

[1]University of Liverpool, Liverpool, United Kingdom; [2]US Department of Veterans Affairs, VA Palo Alto Healthcare System, Palo Alto, California, United States; [3]AbbVie Inc., North Chicago, Illinois, United States; [4]University of Geneva, Geneva, Switzerland; [5]Jacobs School of Medicine and Biomedical Sciences, University of Buffalo, Buffalo, New York, United States

Presented at the European Association for the Study of the Liver's 53rd Annual International Liver Congress, 11–15 April 2018, Paris, France

INTRODUCTION

- Chronic hepatitis C (HCV) has been reported to be associated with neurological and psychiatric disorders in up to 50% of cases[1]
- Patients with psychiatric co-morbidities are less likely to receive HCV treatment with direct-acting antivirals (DAA)[2,3]
- Interferon-free, DAA regimens achieve high (~90%) sustained virologic response at post-treatment Week 12 (SVR12) regardless of psychiatric co-morbidities and without interferon associated depression and cognitive disorders[3,4]
- Achievement of SVR is associated with improvements in neurocognitive symptoms in patients with chronic HCV infection with comorbid neuropsychiatric disorders[5]

G/P is Approved for Patients With HCV GT1–6 Infection

Glecaprevir
pangenotypic NS3/4A protease inhibitor

Coformulated: G/P

Pibrentasvir
pangenotypic NS5A inhibitor

- Overall SVR rate of 98% across GT1–6 in more than 2200 patients[6]
- 8 week duration approved for all treatment naïve patients without cirrhosis[7]
- 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 orally dosed as 3 pills taken once daily with food for a total dose of 300 mg/120 mg. Glecaprevir was identified by AbbVie and Enanta.

- Here, we report the efficacy and safety of G/P in patients with psychiatric disorders compared to those without a psychiatric disorder in order to inform clinical practice on administering G/P in this patient population

OBJECTIVE

- Evaluate the efficacy and safety of G/P in patients with chronic HCV infection and comorbid psychiatric disorders

METHODS

- Data were pooled for 2522 treatment-naïve and -experienced patients with chronic HCV genotype (GT) 1–6 infections who received G/P once-daily (QD) for 8, 12, or 16 weeks in ten Phase 2 and 3 trials
  - Data were included for all patients who received at least 1 dose of study drug in an intent-to-treat analysis
- Patients were classified as having a psychiatric disorder if they had:
  - Medical history of psychiatric or neurological disorder including anxiety, bipolar disorder, cognitive or psychiatric disorder, depression, Parkinson's disease, seizure disorder/convulsion, OR
  - Concomitant medication use of antidepressants or antipsychotics as defined by Anatomical Therapeutic Chemical (ATC) Classification System[8]

METHODS (CONTINUED)

- Concomitant neurological drugs were allowed in G/P clinical trials except for carbamazepine, phenytoin, pentobarbital, phenobarbital, and primidone
  - These 5 neurological drugs are contraindicated for concomitant use with G/P in EU, but not in US

KEY ELIGIBILITY CRITERIA

- Adults with chronic HCV GT 1, 2, 3, 4, 5, or 6 infection (HCV RNA >1000 IU/mL)
- Age ≥18 years and BMI ≥18 kg/m^2
- Compensated liver disease with or without cirrhosis. The presence of cirrhosis was based on liver biopsy, Fibroscan®, or Fibrotest® and APRI
- Absence of co-infection with hepatitis B virus
- Normal renal function or any degree of renal function including severe renal impairment and end-stage renal disease (one Phase 3 study)

ENDPOINTS AND ANALYSES

- Percentage of patients with SVR12 (HCV RNA <LLOQ 12 weeks after the last dose of study drug) in intent-to-treat (ITT) analyses
- Treatment compliance defined as taking ≥80% and ≤120% of the total of tablets expected to be taken during G/P treatment
- Adverse events (AEs), including AEs leading to treatment discontinuations, AEs occurring in ≥5% of patients, serious AEs, and laboratory abnormalities
- Patient Reported Outcomes (PROs) related to mental quality-of-life (Short Form-36; SF-36) and fatigue (Fatigue Severity Scale; FSS)

RESULTS

PATIENTS

- Of the 2522 patients, 789 (31%) were classified as having a psychiatric disorder based on a previous medical history of ≥1 psychiatric disorder (90%; 708/789) and/or concomitant psychiatric medication use (58%; 455/789)
- Overall, patients with psychiatric disorders were more often female, white, GT3-infected, had more severe fibrosis (F4), and had a medical history of injection drug use
- Patients with psychiatric disorders were also more often taking concomitant opioids, anxiolytics, antiepileptic drugs, hypnotics and sedatives, and drugs used in addictive disorders **(Table 1)**
- The most common psychiatric drugs by class (n, %) taken by patients with psychiatric disorders (N = 789) were trazodone (n = 62; 8%) as an antidepressant and quetiapine (n = 47; 6%) as an antipsychotic
- The most common neurological drugs taken by patients with psychiatric disorders were alprazolam (n = 65; 8%) as an anxiolytic, gabapentin (n = 68; 9%) as an antiepileptic, zolpidem (n = 43; 5%) as a hypnotic and sedative, and methadone (n = 60; 8%) for treatment of addictive disorders

RESULTS (CONTINUED)

Table 1. Baseline Demographics and Disease Characteristics

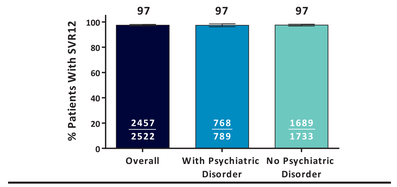
Characteristic	Patients With Psychiatric Disorders N = 789	Patients Without a Psychiatric Disorder N = 1733
Male, n (%)	403 (51)	1043 (60)
Age, median (range), years	53 (21–82)	54 (19–88)
Race, n (%)		
White	685 (87)	1334 (77)
Black or African American	53 (7)	121 (7)
Asian	36 (5)	242 (14)
Other	13 (2)	35 (2)
Missing	2	1
BMI, median (range), kg/m^2	26.4 (17.3–55.4)	25.6 (17.4–65.7)
Baseline HCV RNA level, median (range), $\log_{10}$ IU/mL	6.3 (1.2–7.6)	6.2 (0.7 .8)
HCV genotype, n (%)		
GT1	331 (42)	764 (44)
GT2	144 (18)	332 (19)
GT3	251 (32)	418 (24)
GT4–6	63 (8)	219 (13)
HCV Treatment-naïve, n (%)	568 (72)	1197 (69)
Fibrosis Status, n (%)		
F0–F1	541 (69)	1230 (71)
F2	41 (5)	126 (7)
F3	83 (11)	177 (10)
F4	123 (16)	196 (11)
Missing	1	4
G/P treatment duration, n (%)		
8 weeks	312 (40)	653 (38)
12 weeks	433 (55)	1004 (58)
16 weeks	44 (6)	76 (4)
History of Injection Drug Use*	439 (56)	595 (34)
History of Psychiatric Disorders ≥5% of patients, n (%)		
Depression	506 (64)	N/A[†]
Anxiety	216 (27)	N/A[†]
Cognitive or Psychiatric Disorder	97 (12)	N/A[†]
Bipolar Disorder	57 (7)	N/A[†]
Concomitant CNS drug use in ≥10% of patients by class, n (%)[‡]		
Antidepressants	396 (50)	N/A[†]
Opioids	272 (34)	221 (13)
Anxiolytics	244 (31)	74 (4)
Antiepileptic	217 (28)	69 (4)
Hypnotics and sedatives	159 (20)	98 (6)
Antipsychotics	117 (15)	N/A[†]
Drugs used in addictive disorders[§]	116 (15)	98 (6)

BMI, body-mass index; HCV, Hepatitis C virus; GT, genotype; N/A, not applicable; CNS, central nervous system.
*Includes all patients who previously injected drugs regardless of how recent the patient injected drugs.
†Not applicable to patients without psychiatric disorders since this parameter was used to define the population with psychiatric disorders.
‡Concomitant medications grouped by Anatomical Therapeutic Chemical (ATC) Classification System[8].
§Includes the following drugs: methadone, buprenorphine (with or without naloxone), nicotine, diamorphine, levomethodone, disulfiram, naltrexone, varenicline, acamprosate, and naloxone.

EFFICACY

- Overall SVR12 rate for the ITT population was ≥97% in patients with or without psychiatric disorders **(Figure 2)**
  - Of the 21 (3%) patients with psychiatric disorders not achieving SVR12, 4 (<1%) had on-treatment virologic failure and 4 (<1%) had relapse; all but 1 was ≥80% compliant
  - 7 (<1%) were lost-to-follow-up and 6 (<1%) discontinued G/P due to adverse events (n = 2), non-compliance (n = 3) or withdrawing consent (n = 1)
- The percentage of patients deemed treatment compliant tended to decrease as the number of psychiatric disorders and concomitant psychiatric drugs increased **(Table 2)**
- Subgroup analyses in patients with psychiatric disorders revealed ITT SVR12 rates ≥94% regardless of patient characteristics including treatment duration, fibrosis status, the presence of a psychiatric disorder, and concomitant CNS medications **(Figures 3 and 4)**

Figure 2. Efficacy of G/P in Patients With or Without Psychiatric Disorders by ITT Analysis



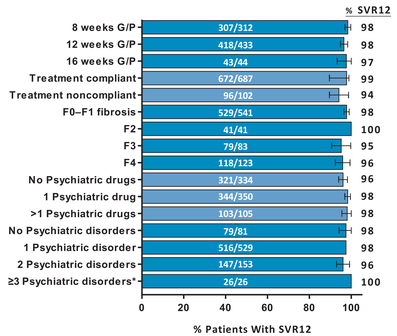
	Overall	With Psychiatric Disorder	No Psychiatric Disorder
Breakthrough	12 (<1%)	4 (<1%)	8 (<1%)
Relapse	22 (<1%)	4 (<1%)	18 (1%)
Discontinuation	13 (<1%)	6 (<1%)	7 (<1%)
Lost to follow-up	18 (<1%)	7 (<1%)	11 (<1%)

Table 2. Overall Treatment Compliance by Patient Characteristics and Treatment Duration

Characteristic, % (n/N)	G/P Treatment Compliance
Psychiatric Disorder	
Without a Psychiatric Disorder	90.0 (1560/1733)
With Psychiatric Disorder	87.1 (687/789)
Number of Psychiatric Medications	
0	89.6 (1853/2067)*
1	86.6 (303/350)
2	86.7 (91/105)
Number of Psychiatric Disorders	
0	89.7 (1628/1814)[†]
1	87.7 (464/529)
2	86.9 (133/153)
≥3	84.6 (22/26)[‡]
Treatment duration	
8 weeks	87.9 (848/965)
12 weeks	90.5 (1300/1437)
16 weeks	82.5 (99/120)

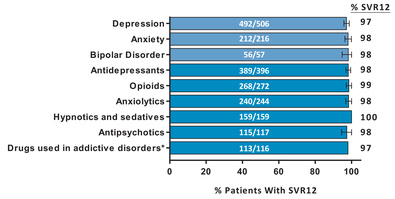
*Includes 334 patients who were not taking a psychiatric medication, but were classified as having a history of psychiatric disorders based on 1 or more diagnoses.
†Includes 81 patients who were not previously diagnosed with a psychiatric disorder, but were classified as having a psychiatric disorder based on concomitant use of psychiatric medication(s).
‡One patient with 4 diagnosed psychiatric disorders in medical history included and was G/P treatment compliant.

Figure 3. Subgroup Efficacy Analysis for Patients With Psychiatric Disorders by Patient Characteristics Using an ITT Analysis



G/P, glecaprevir/pibrentasvir; ITT, intent-to-treat.
*One patient with 4 diagnosed psychiatric disorders in medical history included; all others had 3 diagnoses.

Figure 4. Subgroup Efficacy Analysis by Psychiatric Disorders or CNS Mediations Using an ITT Analysis



ITT, intent-to-treat.
*89/116 (76.7%) had ≥80% treatment compliance; all other subgroups had more than 84% of patients with ≥80% treatment compliance.

SAFETY

- Overall, 610 patients (77%) with psychiatric disorders and 1087 patients (63%) without a psychiatric disorder experienced AEs, most of which were mild to moderate in severity **(Table 3)**
- The most common AEs were headache, fatigue, and nausea, tending to occur more often in patients with psychiatric disorders
- Laboratory abnormalities, AEs leading to discontinuation, and G/P-related serious AEs were rare (<1%) in both patients with and without psychiatric disorders

Table 3. Adverse Events and Laboratory Abnormalities

Event, n (%)	Patients With Psychiatric Disorder N = 789	Patients Without a Psychiatric Disorder N = 1733
Any AE	610 (77)	1087 (63)
Serious AE	30 (4)	47 (3)
DAA-related serious AE	0	1 (<1)*
AEs leading to discontinuation	5 (<1)	8 (<1)
AEs occurring in ≥10% of patients		
Headache	158 (20)	273 (16)
Fatigue	140 (18)	223 (13)
Nausea	102 (13)	131 (8)
Laboratory Abnormalities		
ALT, grade ≥3	1 (<1)	1 (<1)
AST, grade ≥3	3 (<1)	3 (<1)
Total bilirubin, grade ≥3	6 (<1)	4 (<1)

DAA, direct-acting antiviral; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
*Grade 3 ALT at the end of treatment (Week 12 visit) in the context of multiple gallstones.

PATIENT-REPORTED OUTCOMES

- Patients with and without psychiatric disorders reported a trend toward a mean increase from baseline in the mental health component of the SF-36
- Both populations reported a trend toward a mean decrease from baseline in FSS

Table 4. Mean Change From Baseline to PTW12 in PROs Related to Mental Health and Fatigue

Quality of Life Measure, mean change (± SD)	Patients With Psychiatric Disorders N = 542*	Patients Without a Psychiatric Disorder N = 1080*
SF-36 (MCS)	3.6 (±11.7)[†]	1.5 (±7.4)[†]
FSS	-0.5 (±1.6)	-0.3 (±1.6)

SD, standard deviation; SF-36 (MCS), Short Form-35 Mental Health Component Summary; FSS, Fatigue Severity Scale.
*Patients with both baseline and PTW12 data available are included for patients enrolled in SURVEYOR-I and -II, ENDURANCE-2, -3, and -4, and EXPEDITION-1, -2, and -4.
†Data only available for n = 538 patient with psychiatric disorders and n = 1077 patients without a psychiatric disorder from SURVEYOR-I and -II, ENDURANCE-2, -3, and -4, and EXPEDITION-1, -2, and -4 clinical trials.

LIMITATIONS

- This post-hoc analysis integrated data from G/P Phase 2 and 3 registrational studies that did not select patients based on medical history of psychiatric disorders or associated medication use
- Patients who participated in these registrational studies with G/P may be biased in terms of treatment adherence compared to patients in a real world clinical setting. Despite this, overall SVR12 rates in a post hoc analysis were shown to be >98% in patients with non-compliance (<80%)[9]
- As many as 10% (81/789) of patients with psychiatric disorders were characterized by concomitant medication use. These medications could have been prescribed to treat co-morbidities other than psychiatric disorders
- No long-term follow-up was performed for the PROs data in these registrational studies thereby limiting interpretation of the changes from baseline beyond PTW12

CONCLUSIONS

- G/P demonstrated high efficacy and a favorable safety profile in patients with psychiatric disorders regardless of the type and number of psychiatric disorders or concomitant use of psychiatric drugs
- Despite a trend toward slightly decreased G/P treatment compliance, there was no corresponding difference in efficacy observed in patients taking drugs for addictive disorders, diagnosed with more psychiatric disorders or taking more psychiatric medications
- Serious AEs and laboratory abnormalities were not common in either population despite higher rates of mild-to-moderate AEs in patients with psychiatric disorders
- Patient-reported outcomes demonstrated a trend toward improved mental health scores and decreased fatigue from baseline to PTW12 in both patient populations

REFERENCES

1. Adinolfi, LE, et al. Chronic hepatitis C virus infection and neurological and psychiatric disorders: An overview. *World J Gastroenterol.* 2015;21(8):2269–80.
2. Lin M, et al. Barriers to hepatitis C treatment in the era of direct-acting anti-viral agents. *Aliment Pharmacol Ther.* 2017;46:992–1000.
3. Ford MM, et al. From care to cure: Demonstrating a model of clinical patient navigation for hepatitis C care and treatment in high-need patients. *CID.* 2017;64:685–91.
4. Yek C, et al. Effectiveness of direct-acting antiviral therapy for hepatitis C in difficult-to-treat patients in a safety-net health system: a retrospective cohort study. *BMC Medicine.* 2017;15:204.
5. Kraus MR, et al. Improvements of neurocognitive function in responders to an antiviral therapy for chronic hepatitis C. *Hepatology.* 2013;58:497–504.
6. Grebely J, et al. Safety and efficacy of glecaprevir/pibrentasvir in patients with chronic HCV genotypes 1–6 receiving opioid substitution therapy. INHSU, 2017 (oral presentation).
7. MAVYRET/MAVIRET [US Package insert/EU SmPC]. AbbVie. 2017.
8. WHO. The anatomical therapeutic chemical classification system with defined daily doses (ATC/DDD). Geneva: World Health Organization; 2014.
9. Brown A, et al. Adherence to pangenotypic glecaprevir/pibrentasvir treatment and SVR12 in HCV-infected patients: an integrated analysis of Phase 2/3 clinical trial program. *Hepatology.* 2017;66:Suppl 1:198.

ACKNOWLEDGEMENTS

- The authors would like to express their gratitude to the patients and their families, investigators, and coordinators who made these studies possible
- Medical writing support was provided by Dan O'Brien, PhD, of AbbVie

DISCLOSURES

David Back: Advisory board member/speakers bureau and receives honorarium from: Gilead, Merck, AbbVie, Bristol-Myers Squibb, Janssen; received research grant funding from: Gilead, Merck, AbbVie, Bristol-Myers Squibb, Janssen; received travel sponsorship from: AbbVie.
Pamela Belperio: Nothing to disclose.
Fiona Marra: Consulting or grants from AbbVie, Gilead, MSD, Janssen, BMS.
Francesco Negro: Advisor: Gilead, AbbVie, Merck. Unrestricted research grant from AbbVie. Investigator initiated study supported by Gilead.
Andrew H Talal: Research grants: AbbVie, Merck, Gilead, Intercept, Conatus, Abbott Laboratories; Advisor: AbbVie, Merck, Abbott Laboratories.
Mark Bondin, Caroline Park, Yang Lei, Brett Pinsky, Federico Mensa, Eric Crown: Employees of AbbVie Inc. and may hold stock or stock options.
AbbVie sponsored the studies (NCT02243280, NCT02243293, NCT02604017, NCT02640482, NCT02640157, NCT02636595, NCT02642432, NCT02651194, NCT02446717, and NCT02738138), 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. Glecaprevir was identified by AbbVie and Enanta.