SAFETY AND EFFICACY OF GLECAPREVIR/PIBRENTASVIR IN PATIENTS WITH CHRONIC HCV GENOTYPES 1–6 RECEIVING OPIOID SUBSTITUTION THERAPY

Jason Grebely[1], Gregory J Dore[1], N Niki Alami[2], Brian Conway[3], John Dillon[4], Michael Gschwantler[5], Franco Felizarta[6], Christophe Hézode[7], Krzysztof Tomasiewicz[8], Stanley Wang[2], Ran Liu[2], Emily O Dumas[2], Federico J Mensa[2]

[1]The Kirby Institute, UNSW Sydney, Sydney, Australia; [2]AbbVie, North Chicago, IL, USA; [3]Vancouver Infectious Diseases Centre, Vancouver, Canada; [4]Department of Gastroenterology, Ninewells Hospital and Medical School, Dundee, UK; [5]Department of Internal Medicine IV, Wilhelminenspital, Vienna, Austria; [6]Private Practice, Bakersfield, CA; [7]Department of Hepatology, Hôpital Henri Mondor, Université Paris-Est, Paris, France; [8]Medical University of Lublin, Lublin, Poland

International Network on Hepatitis in Substance Users (INHSU)
• New York, United States •
08 September 2017

abbvie

Disclosures

J Grebely: Advisor/Research Support: AbbVie, Bristol-Myers Squibb, Cepheid, Gilead Sciences, Merck, MSD.

GJ Dore: Research support: AbbVie, Gilead, Merck, Bristol-Myers Squibb; Advisor: AbbVie, Gilead, Merck, Bristol-Myers Squibb.

B Conway: Research Support/Advisor: AbbVie, Bristol-Myers Squibb, Gilead, Janssen, Merck.

J Dillon: Research support/Speaker: Gilead, Merck, Janssen, Roche, AbbVie.

M Gschwantler: Advisor/Speaker for Janssen, MSD, Bristol-Myers Squibb, Gilead, AbbVie; Research Support: Gilead, AbbVie, MSD.

F Felizarta: Research support: AbbVie, Janssen, Merck. Speaker: AbbVie, Gilead, Merck.

C Hezode: Personal fees from AbbVie, Bristol-Myers Squibb, Gilead, Janssen, Merck.

K Tomasiewicz: Consultancy/Advisory Board/Speaker: AbbVie, Alfa Wasserman, BMS, Gilead, Janssen, MSD, Roche; Grant/Research: AbbVie, BMS, Gilead, Janssen, MSD, Roche.

NN Alami, S Wang, R Liu, EO Dumas, and **FJ Mensa:** Employees of AbbVie; may hold AbbVie stock or options.

The design, study conduct, analysis, and financial support of the NCT02243280 (SURVEYOR-1), NCT02243293 (SURVEYOR-2), NCT02604017 (ENDURANCE-1), NCT02640157 (ENDURANCE-3), NCT02640482 (ENDURANCE-2), NCT02636595 (ENDURANCE-4), NCT02642432 (EXPEDITION-1), NCT02651194 (EXPEDITION-4) studies were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the content. All authors had access to all relevant data and participated in writing, review, and approval of this presentation.

Medical writing was provided by **Ryan J Bourgo, PhD**, of AbbVie.

Acknowledgement

The authors would like to express their gratitude to the patients who participated in these studies and their families, as well as the investigators and coordinators of the studies

HCV Treatment in Patients receiving OST

Injection drug use is the primary mode of transmission for HCV,[1] and anti-HCV seroprevalence is estimated at 60–80% in people who inject drugs (PWID)[2]

Among people receiving OST, DAA treatment for HCV is effective[3-5]

Guidelines for HCV recommend treatment of those receiving OST; however, treatment uptake remains suboptimal due to concerns about treatment adherence, poor outcomes, or risk of HCV reinfection[6]

Availability of shorter and more convenient HCV treatment regimens may increase treatment access in PWID or people who are on OST, decreasing transmission and reducing the global HCV burden

1. Hajarizadeh et al. *Nat Rev Gastroenterol Hepatol.* 2013;10(9):553-562.
2. Nelson et al. *Lancet.* 2011;378(9791):571-583.
3. Dore et al. *Ann Intern Med.* 2016;165(9):625-634.
4. Grebely et al. *Clin Infect Dis.* 2016;63(11):1479-1481.
5. Grebely et al. *Clin Infect Dis.* 2016;63(11):1405-1411.
6. Grebely et al. *Int J Drug Policy.* 2015;26(10):893-898.

Next Generation Direct-Acting Antivirals

Glecaprevir
pangenotypic NS3/4A protease inhibitor

Coformulated: G/P

Pibrentasvir
pangenotypic NS5A inhibitor

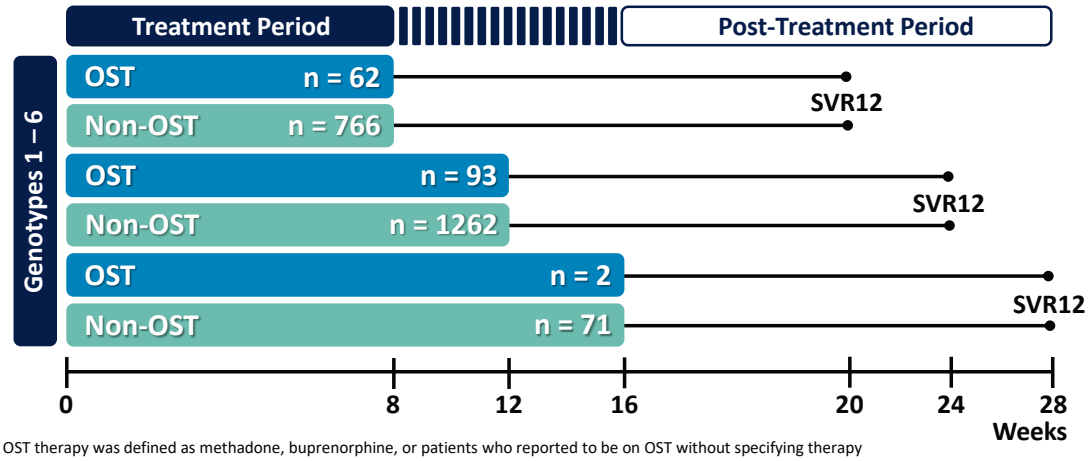
In vitro and PK:[1,2]
- High barrier to resistance; potent against most NS3 and NS5A polymorphisms
- Once-daily oral dosing with food
- Minimal metabolism and negligible renal excretion (<1%)

Clinical :
- Overall SVR12 rate of 98% in over 2000 patients in Phase 3 studies
- Favorable safety profile irrespective of baseline factors such as compensated liver cirrhosis and advance renal disease
- No clinically significant drug-drug interactions between G/P and OST drugs expected

G/P is co-formulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg
Glecaprevir was identified by AbbVie and Enanta. 1. Ng TI, et al. *Antimicrobial Agents and Chemotherapy;* 2017 . 2. Ng TI, et al. Abstract 636. CROI, 2014

Integrated Efficacy and Safety: 8 Phase II and III Studies

Objective: Determine the adherence, treatment completion, efficacy and safety of G/P in HCV genotype 1-6 infected patients on OST, compared to those not on OST



OST therapy was defined as methadone, buprenorphine, or patients who reported to be on OST without specifying therapy

Key Patient 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
- Recent (≤6 months prior to study drug administration) drug use was not exclusionary unless it could preclude adherence to the protocol, per investigator assessment

Assessments

Primary efficacy was assessed in the intent-to-treat population (ITT), including all patients that received ≥1 dose of study drug

- Sustained virologic response at post-treatment week 12 (SVR12; HCV RNA below the lower limit of quantification)
- OST versus Non-OST populations

Additional assessments included:

- Treatment adherence (defined as ≥90% compliance by pill count)
- Treatment completion (defined as ≥52, 77 and 105 days for 8, 12, and 16 weeks of treatment, respectively)
- SVR12 by genotype and treatment duration
- Safety and adverse events

Baseline Demographics and Clinical Characteristics

Characteristic	OST N = 157	Non-OST N = 2099
Male, n (%)	109 (69)	1127 (54)
Race, n (%)		
White	146 (93)	1671 (80)
Black or African American	3 (2)	116 (6)
Asian	4 (3)	266 (13)
Age, median years (range)	47 (23 – 76)	54 (19 – 88)
BMI, median kg/m^2 (range)	26 (17 – 51)	26 (17 – 66)
HCV RNA, median $\log_{10}$ IU/mL (range)	6.2 (3.4 – 7.6)	6.2 (0.7 – 7.8)
History of depression or bipolar, n (%)	67 (43)	409 (19)
Current tobacco use, n (%)	113 (72)	725 (35)
Current alcohol use, n (%)	44 (28)	699 (33)

BMI, body mass index; OST, opioid substitution therapy

Baseline Demographics and Clinical Characteristics

Characteristic	OST N = 157	Non-OST N = 2099
Genotype, n (%)		
GT1	41 (26)	848 (40)
GT2	17 (11)	449 (21)
GT3	94 (60)	549 (26)
GT4 – 6	5 (3)	253 (12)
Baseline fibrosis stage, n (%)		
F0-F1	104 (66)	1487 (71)
F2	11 (7)	144 (7)
F3	14 (9)	214 (10)
F4	28 (18)	249 (12)
Prior HCV treatment-naïve, n (%)	135 (86)	1505 (72)

OST, opioid substitution therapy; GT, genotype

Baseline Demographics and Clinical Characteristics

Characteristic	OST N = 157	Non-OST N = 2099
Genotype, n (%)		
GT1	41 (26)	848 (40)
GT2	17 (11)	449 (21)
GT3	94 (60)	549 (26)
GT4 – 6	5 (3)	253 (12)
Baseline fibrosis stage, n (%)		
F0-F1	104 (66)	1487 (71)
F2	11 (7)	144 (7)
F3	14 (9)	214 (10)
F4	28 (18)	249 (12)
Prior HCV treatment-naïve, n (%)	135 (86)	1505 (72)

OST, opioid substitution therapy; GT, genotype

The majority of patients on OST had HCV genotype 3, consistent with epidemiology[1,2]

1. Cunningham et al. *Nat Rev Gastroenterol Hepatol.* 2015;12(4):218-230. 2. Morice et al. *J Med Virol.* 2006;78(10):1296-1303.

Type of OST

Type of OST, n (%)	OST N = 157	Non-OST N = 2099
Methadone	119 (76)	–
Buprenorphine	19 (12)	–
Morphine sulfate	5 (3)	
Not reported	14 (9)	–

Patients that reported being on stable opioid substitution therapy, but did not report a specific therapy (ie, methadone or buprenorphine) were listed under Not Reported

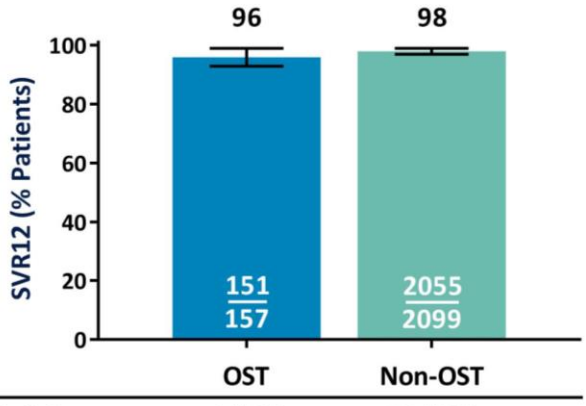
Treatment Adherence and Completion

	OST N = 157	Non-OST N = 2099
	n/N (%)	
Treatment adherence	121/123 (98)	1884/1905 (99)
Treatment completion	154/157 (98)	2070/2099 (99)

Treatment adherence was considered ≥90% compliance based on pill counts
Patients with missing drug accountability records were not assessed for adherence; thus, total adherence N is lower than total patients enrolled
N = total number of patients in a given subgroup; n = number of patients with treatment adherence or completion

Adherence to, and proportion of patients completing, HCV treatment was similarly high (≥98%) for those receiving OST and those not receiving OST

SVR12 by Intent-to-treat (ITT) Analysis



	OST	Non-OST
Virologic failure	1 (1%)	22 (1%)
Premature d/c	1 (1%)	11 (1%)
Lost to follow-up	4 (3%)	11 (1%)
HCV Reinfection	0	0

Summary of Adverse Events (AE)

Adverse Event, n (%)	OST N = 157	Non-OST N = 2099
Any	117 (75)	1403 (67)
Serious AE	8 (5)	62 (3)
DAA-related* serious AE	0	1 (<1)†
AE leading to drug discontinuation	0	12 (1)
DAA-related* drug discontinuation	0	5 (<1)
AEs occurring in ≥10% of patients		
Headache	32 (20)	362 (17)
Fatigue	28 (18)	305 (15)
Nausea	21 (13)	189 (9)
Death‡	1 (1)	5 (<1)

AE, adverse event; DAA; direct-acting antiviral; OST, opioid substitution therapy
* Relatedness of AEs to DAAs were determined by study investigator
† Transient ischemic attack
‡ All deaths occurred in the post-treatment period and all were considered unrelated to study drugs by investigator

Post-baseline Laboratory Abnormalities

Event, n (%)	OST N = 157	Non-OST N = 2097
Alanine aminotransferase*		
Grade ≥3 (>5 × ULN)	0	2 (<1)
Aspartate aminotransferase		
Grade ≥3 (>5 × ULN)	1 (1)	5 (<1)
Total bilirubin		
Grade ≥3 (>3 × ULN)	0	9 (<1)
Hemoglobin		
Grade ≥3 (<8 g/dL)	1 (1)	6 (<1)

OST, opioid substitution therapy; ULN, upper limit of normal
* Post-nadir increase in grade to Grade ≥3

Summary

G/P achieved high efficacy, regardless of OST:

- 96% SVR12 in patients with OST, compared to 98% without OST

Treatment completion and adherence was similarly high for patients receiving OST and not receiving OST

G/P was well-tolerated with a safety profile comparable in patients receiving or not receiving OST

No HCV reinfections observed

Conclusion

G/P is a well-tolerated and efficacious pangenotypic regimen for chronic HCV-infected people receiving opioid substitution therapy

SVR12 by Genotype and Treatment Duration

SVR12, n/N (%)	OST N = 157	Non-OST N = 2099
Treatment duration		
8 weeks	61/62 (98)	752/766 (98)
12 weeks	89/93 (96)	1248/1262 (99)
16 weeks	2/2 (100)	67/71 (94)
Genotype		
GT1	41/41 (100)	845/848 (99)
GT2	17/17 (100)	444/449 (99)
GT3	89/94 (95)	527/549 (96)
GT4 – 6	5/5 (100)	251/253 (99)

OST, opioid substitution therapy; GT, genotype; SVR12, sustained virologic response at post-treatment week 12
N = total number of patients in a given subgroup; n = number of patients that achieved SVR12 within that subgroup

SVR12 rates were similarly high across all GTs and treatment durations, regardless of OST status