ABT-450/r/Ombitasvir + Dasabuvir With or Without Ribavirin in HCV Genotype 1–Infected Patients Receiving Stable Opioid Substitution Treatment: Pooled Analysis of Efficacy and Safety in Phase 2 and Phase 3 Trials

Massimo Puoti[1], Curtis Cooper[2], Mark Sulkowski[3], Graham R Foster[4], Thomas Berg[5], Erica Villa[6], Federico Rodriguez-Perez[7], Vinod Rustgi[8], David Wyles[9], Martin King[10], Barbara McGovern[10], Heiner Wedemeyer[11]

[1]Ospedale Niguarda Ca Granda, Milan, Italy; [2]University of Ottawa, Ottawa, Ontario, Canada; [3]Johns Hopkins University, Baltimore, Maryland, United States; [4]Queen Mary University of London, Barts Health, London, United Kingdom; [5]Universitätsklinikum Leipzig, Leipzig, Germany; [6]AOU Policlinico di Modena, Modena, Italy; [7]Gastroenterology and Hepatic Wellness Center, Santurce, Puerto Rico; [8]University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, United States; [9]University of California at San Diego, La Jolla, California, United States; [10]AbbVie Inc., North Chicago, Illinois, United States; [11]Medizinische Hochschule Hannover, Hannover, Germany

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INTRODUCTION

- Injection drug use is currently the primary mode of hepatitis C virus (HCV) transmission in developed countries, and people who inject drugs (PWIDs) represent the majority of new cases of HCV infection[1,2]
- Treatment uptake for HCV infection remains low in PWIDs, largely because of barriers to care at the level of the healthcare system, clinician, and patient[2]
  - Patients are reluctant to undergo therapy because of concerns about side effects or because they do not understand the implications of chronic HCV infection on liver-related health
  - Physicians may be reticent about treating PWIDs because of concerns about reinfection
  - Adequate healthcare support systems for opioid replacement clinics remain limited
- Among the small portion of PWIDs who initiate treatment for HCV infection, high discontinuation rates related to interferon (IFN) toxicity limit the efficacy of therapy.[3,4] Thus, IFN-free regimens of direct-acting antivirals with improved efficacy and tolerability[5–7] may be critical in achieving higher rates of treatment success in this patient population
- Mathematical models suggest that increased uptake of treatment in this patient population could substantially reduce the incidence and prevalence of HCV infection, leading to tangible benefits for overall public health[8]
- Currently, there is limited information to help guide clinical management regarding HCV treatment outcomes among PWIDS who receive new therapies
- A novel IFN-free all-oral treatment regimen consisting of ABT-450 (an HCV NS3/4A protease inhibitor identified by AbbVie and Enanta, dosed with ritonavir 100 mg [ABT-450/r]), ombitasvir (an NS5A inhibitor), and dasabuvir (an NS5B RNA polymerase inhibitor) has demonstrated high sustained virologic response (SVR) rates in patients with and without cirrhosis[6,7,9–11]

OBJECTIVE

- The objective of this study was to evaluate the efficacy and safety of coformulated ABT-450/r/ombitasvir and dasabuvir (3D) with or without ribavirin (RBV) in patients with HCV genotype (GT) 1 infection who were on stable opioid substitution therapy (OST) with either methadone or buprenorphine in phase 2 and 3 clinical trials

METHODS

STUDY DESIGN

- The 2 phase 2 clinical trials included in the analysis were AVIATOR (NCT01464827)[9] and M14-103 (NCT01911845). Both were multicenter, open-label, 12-week (M14-103) and up to 24-week (AVIATOR) studies
  - M14-103 was conducted at 8 sites in the United States, and AVIATOR was conducted at 97 sites in 9 countries, including the United States
  - Before patient enrollment in M14-103, a drug–drug interaction study was performed to evaluate the effect of ABT-450/r/ombitasvir and dasabuvir in 24 healthy volunteers taking chronic methadone and 24 healthy volunteers taking buprenorphine/naloxone. In addition, volunteers completed questionnaires that evaluated opioid withdrawal symptoms (Subjective Opiate Withdrawal Scale) and the desire for drugs (Desire for Drugs Questionnaire). The pharmacokinetic studies did not demonstrate any significant drug–drug interactions with methadone, buprenorphine, or naloxone, and there were no significant interactions with the 3D regimen[12]
- The 6 phase 3 studies were PEARL-II (NCT01674725),[5] PEARL-III (NCT01767116),[7] and PEARL-IV (NCT01833533),[7] and SAPPHIRE-I (NCT01716585),[6] SAPPHIRE-II (NCT01715415),[10] and TURQUOISE-II (NCT01704755).[11] All trials were, multicenter, international, randomized trials that included 12 weeks of treatment with the study drug
  - Studies were conducted at sites in Australia, North America, Europe, and Russia

METHODS (CONTINUED)

- Patients in all studies received ABT-450/r and ombitasvir once daily (at doses of ≥100 mg/100 mg and ≥25 mg, respectively) and dasabuvir twice daily (BID; 250 mg)[5–7,10,11]
  - Some patients also received RBV BID according to body weight (1000 mg daily if <75 kg; 1200 mg daily if ≥75 kg)

PATIENTS

- Men and women 18–70 years of age with chronic HCV GT1 infection (HCV RNA levels >10 000 IU/mL) with or without cirrhosis were included in this analysis; patients could have been treatment-naïve or treatment experienced with prior pegylated interferon (pegIFN)/RBV therapy[5–7]
  - Patients were also classified as either OST users or nonusers
  - OST included methadone or buprenorphine ± naloxone
- Patients were excluded if they had HIV or hepatitis B virus coinfection

EFFICACY ASSESSMENT

- SVR12 was defined as HCV RNA below the lower limit of quantitation 12 weeks after the last dose of study drug
- Virologic failure was defined as failure to suppress HCV RNA by week 6, viral breakthrough while on treatment, or post-treatment relapse

SAFETY ASSESSMENTS

- Information on adverse events (AEs) was collected at baseline and at each study visit from the first time the study drug was administered until 30 days after the last dose; serious AEs (SAEs) were monitored throughout the study
- Laboratory tests, including liver function and hematology, were conducted at screening, baseline, and each study visit

STATISTICAL ANALYSES

- All patients receiving OST who received ≥1 dose of 3D with or without RBV during the treatment period were included in the analysis
  - SVR12 was summarized for all patients receiving OST and for patients with HCV GT1a and GT1b infection
- The incidence of AEs and laboratory abnormalities was summarized

RESULTS

PATIENTS

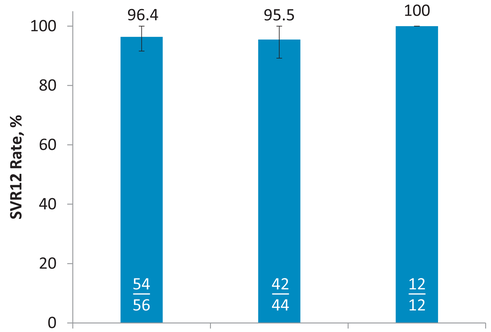
- Across the 8 clinical trials, 2292 patients were randomized and received at least 1 dose of study drug; 56 patients were receiving OST
  - 2 patients (3.6%) in the OST group discontinued treatment; 1 patient (1.8%) discontinued because of an AE, and 1 patient (1.8%) discontinued because of noncompliance
  - The majority of patients receiving stable OST were male (66.1%), white (94.6%), and treatment-naïve (83.9%). Demographic and baseline characteristics are summarized in **Table 1**

EFFICACY

- 54 of 56 patients (96.4% [95% CI, 91.6%–96.4%]) receiving OST achieved SVR12
- SVR12 rates were 95.5% for patients with HCV GT1a infection and 100% for patients with HCV GT1b infection **(Figure 1)**
- No patient receiving OST experienced virologic failure

RESULTS (CONTINUED)

Figure 1. SVR12 Rates in Patients Receiving OST With HCV GT1a and GT1b Infection



SVR12, sustained virologic response 12 wk after the last dose of study drug.
Error bars represent 95% CIs.

Table 1. Baseline Demographics and Disease Characteristics (ITT Population)

Parameter	Patients Receiving OST (n = 56)
Sex, n (%)	
Female	19 (33.9)
Male	37 (66.1)
Age, y (mean ± SD)	47.9 ± 10.4
<55, n (%)	36 (64.3)
≥55, n (%)	20 (35.7)
BMI, kg/m^2, n (%)	
<30	41 (73.2)
≥30	15 (26.8)
Race, n (%)	
White	53 (94.6)
Black/African American	3 (5.4)
Geographic region, n (%)	
United States	51 (91.1)
European Union	5 (8.9)
HCV GT1 subtype, n (%)	
1a	44 (78.6)
1b	12 (21.4)
HCV RNA, $\log_{10}$ IU/mL (mean ± SD)	6.7 ± 0.7
History of diabetes, n (%)	
Yes	2 (3.6)
No	54 (96.4)
Previous HCV treatment, n (%)	
None	47 (83.9)
PegIFN/RBV	9 (16.1)
Liver cirrhosis, n (%)	
Yes	1 (1.8)
No	55 (98.2)
Former injection drug user, n (%)	
Yes	35 (81.4)
No	8 (18.6)
Unknown	13

BMI, body mass index; GT, genotype; HCV, hepatitis C virus; ITT, intent-to-treat; OST, opioid substitution therapy; pegIFN, pegylated interferon; RBV, ribavirin.
Percentages calculated on non-missing and non-unknown values.

SAFETY

- 89.3% of patients (50/56) in the OST group experienced at least 1 AE; the most common AE was nausea **(Table 2)**
  - Most common AEs were mild in intensity
  - 2 patients experienced an SAE (acute myeloid leukemia, n = 1; cerebrovascular accident and sarcoma, n = 1)
  - 1 patient discontinued study drug because of an AE (sarcoma and cerebrovascular accident) on day 26
  - No patient required a dose adjustment of OST during the treatment period

Table 2. Common Treatment-emergent Adverse Events Occurring in ≥10% of Patients

Event, n (%)	Patients Receiving OST (n = 56)
Nausea	24 (42.9)
Fatigue	23 (41.1)
Headache	15 (26.8)
Rash	9 (16.1)
Insomnia	8 (14.3)
Anxiety	8 (14.3)
Anemia	6 (10.7)
Arthralgia	6 (10.7)
Diarrhea	6 (10.7)
Vomiting	6 (10.7)

LABORATORY ABNORMALITIES: AEs OF SPECIAL INTEREST

- Grade 3 bilirubin elevation occurred in 1 patient (1.8%) receiving OST **(Table 3)**
- There were no grade 2 or higher elevations in alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase
- Grade 2 (<10–8 g/dL) and grade 3 (<8–6.5 g/dL) hemoglobin decreases were reported in 8 patients (14.3%) and 2 patients (3.6%), respectively

Table 3. Laboratory Abnormalities

Abnormality, n (%)	Patients Receiving OST (n = 56)
Hemoglobin	
<10–8 g/dL	8 (14.3)
<8–6.5 g/dL	2 (3.6)
<6.5 g/dL	0
ALT, grade 2 or higher (>3 × ULN)	0
AST, grade 2 or higher (>3 × ULN)	0
Alkaline phosphatase, grade 2 or higher (>2.5 × ULN)	0
Total bilirubin	
Grade 1 (>1.0–1.5 × ULN)	12 (21.4)
Grade 2 (>1.5–3 × ULN)	9 (16.1)
Grade 3 (>3–5 × ULN)	1 (1.8)
Grade 4 (>5 × ULN)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

CONCLUSIONS

- In agreement with previous reports, a pooled analysis of 2 phase 2 trials and 6 phase 3 trials showed that the 3D regimen with or without RBV was well tolerated in patients on stable OST, with an SVR12 rate of 96.4%
- These data suggest that this IFN-free regimen may be a suitable treatment option for patients receiving OST and may increase treatment uptake in this patient population
- Improved treatment uptake and completion rates could significantly decrease the burden of liver disease in this underserved patient population and could decrease the risk of HCV transmission. OST clinics may be an ideal setting to offer IFN-free therapies

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