IFN-free 3 DAA Regimen in HCV Genotype 1-infected Patients on Methadone or Buprenorphine

#662LB

Jacob Lalezari[1], J Greg Sullivan[2], Vinod Rustgi[3], Humberto Aguilar[4], Franco Felizarta[5], Daniel Cohen[6]

[1]Quest Clinical Research, San Francisco, California, United States; [2]Parkway Medical Center, Birmingham, Alabama, United States; [3]Metropolitan Research, Fairfax, Virginia, United States; [4]Louisiana Research Center, LLC, Shreveport, Louisiana, United States; [5]Private practice, Bakersfield, California, United States; [6]AbbVie Inc., North Chicago, Illinois, United States

Presented at the 21st Annual Conference on Retroviruses and Opportunistic Infections, March 3–6, 2014, Boston, Massachusetts

BACKGROUND

- ABT-450 is an NS3/4A protease inhibitor, identified by AbbVie and Enanta, with potent antiviral activity *in vitro* against HCV GT1a, 1b, 2a, 2b, 3a, 4a, and 6a[1,2]
  - Co-dosed with low-dose CYP3A4 inhibitor, ritonavir, to achieve therapeutic exposures at once-daily dosing frequency (combination is denoted ABT-450/r)
- ABT-267 is an HCV NS5A inhibitor with pangenotypic picomolar potency *in vitro* against HCV genotypes 1–6
  - Co-formulated with ABT-450 and ritonavir into a single tablet (ABT-450/r/ABT-267)
- ABT-333 is a non-nucleoside HCV NS5B RNA polymerase inhibitor with nanomolar potency *in vitro*
- This 3-DAA regimen, dosed with ribavirin (RBV) for 12 weeks, has demonstrated 24-week sustained virologic response (SVR_{24}) rates of 95% and 95.5% in treatment-naïve and -experienced HCV GT1-infected patients, respectively[3]
- Because HCV infection is common in patients with a history of intravenous drug use, further investigation of the efficacy and safety of this regimen in patients receiving opioid replacement therapy with methadone or buprenorphine is needed

OBJECTIVES

- To assess the SVR_{12} rate and safety among HCV GT1-infected adults who are on stable opioid replacement therapy with methadone or buprenorphine ± naloxone after receiving the 3-DAA + RBV regimen for 12 weeks.

METHODS

Figure 1. M14-103 Study Design



- M14-103 is a phase 2, open-label, single-arm study
- All patients received the 3-DAA regimen + RBV
  - ABT-450/r/ABT-267 (150/100/25 mg QD)
  - ABT-333 (250 mg BID)
  - RBV (1000 mg for body weight <75 kg, 1200 mg for body weight >75 kg, divided BID)

METHODS (CONTINUED)

KEY ELIGIBILITY CRITERIA

- Key inclusion criteria
  - 18 to 70 years of age
  - BMI ≥18 and <38 kg/m^2
  - Chronic HCV GT1 infection
  - Plasma HCV RNA >10 000 IU/mL
  - Absence of cirrhosis
  - Treatment-naïve or previous pegIFN/RBV-experienced
  - Stable opioid replacement therapy with methadone or buprenorphine ± naloxone
- Key exclusion criteria
  - HIV or hepatitis B co-infection
  - Liver disease due to causes other than hepatitis C

PRIMARY EFFICACY ENDPOINT

- Percentage of patients with SVR_{12} (HCV RNA below 25 IU/mL 12 weeks after the last dose of study drug)

RESULTS

Table 1. Baseline Demographics and Characteristics

Parameter	3-DAA + RBV (N = 38)
Sex, male	25 (65.8)
Race	
White	36 (94.7)
Black	2 (5.3)
Hispanic or Latino ethnicity	1 (2.6)
Age, years ± SD	48.2 ± 11.0
BMI, kg/m^2 ± SD	27.0 ± 3.9
HCV RNA level, $\log_{10}$ IU/mL ± SD	6.58 ± 0.70
IL28B genotype CT or TT	26 (68.4)
Fibrosis stage	
F0–F1	30 (78.9)
F2	6 (15.8)
F3	2 (5.3)
HCV subgenotype 1a	32 (84.2)
Treatment-naïve	36 (94.7)
Opioid replacement therapy	
Methadone	19 (50.0)
Buprenorphine	19 (50.0)

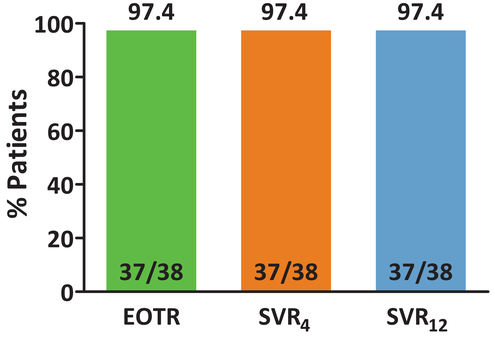
All values are n (%) unless otherwise noted.

- 38 patients were enrolled from 8 sites and received at least 1 dose of study drug (19 on methadone, 19 on buprenorphine)

RESULTS (CONTINUED)

EFFICACY

Figure 2. Intent-to-treat Virologic Response Rates



- 37 of 38 patients (97.4%; 95% CI, 92.3–100) achieved SVR_4 and SVR_{12} **(Figure 2)**
- One patient prematurely discontinued due to a serious adverse event (cerebrovascular accident) unrelated to study drug (see Serious Adverse Events)
- There were no virologic failures

SAFETY

Table 2. Safety Outcomes

Event, n (%)	3-DAA + RBV (N = 38)
Any AE	35 (92.1)
Severe AE	2 (5.3)
Serious AE	1 (2.6)
AE leading to early study discontinuation	1 (2.6)
Common AEs (>10% of patients)	
Nausea	19 (50.0)
Fatigue	18 (47.4)
Headache	12 (31.6)
Insomnia	7 (18.4)
Rash	6 (15.8)
Arthralgia	5 (13.2)
Anxiety	5 (13.2)
Anemia	4 (10.5)
Vomiting	4 (10.5)
Irritability	4 (10.5)

AE, adverse event.

- The most frequent adverse events were nausea, fatigue, and headache **(Table 2)**
- Two patients experienced serious adverse events that were not related to study drug
  - Cerebrovascular accident and high-grade sarcoma diagnosed at Week 2 on treatment (patient discontinued treatment)
  - Acute myeloid leukemia diagnosed after end of treatment (patient achieved SVR_{12})
- Eight patients experienced hemoglobin <10 g/dL while on treatment
  - RBV dose was reduced for anemia/decreased hemoglobin in 7 patients
- No patient required a change in the dosage of methadone or buprenorphine during study treatment

Table 3. Post-baseline Grade 3 or Grade 4 Laboratory Abnormalities, n (%)

	3-DAA + RBV (N = 38)
Total bilirubin	
Grade 3 (>3X–10 X ULN)	1 (2.6)
Grade 4 (>10 X ULN)	0
Hemoglobin	
Grade 3 (<8.0–6.5 g/dL)	2 (5.3)
Grade 4 (<6.5 g/dL)	0

- Treatment-emergent Grade 3/4 laboratory abnormalities are in **Table 3**
- Occasional bilirubin elevations were predominantly indirect bilirubin
  - Consistent with the known effect of ABT-450 on the bilirubin transporter OATP1B1
  - Maximum bilirubin level was 5.8 mg/dL
  - There were no discontinuations due to bilirubin elevation

DISCUSSION

- The 3-DAA + RBV regimen achieved an SVR_{12} rate of 97.4% among these 38 GT1-infected patients receiving opioid replacement therapy
- This result is comparable to those previously reported in both treatment-naïve and experienced GT1-infected patients[3]
- No viral breakthroughs or relapses were observed
- The 3-DAA + RBV regimen was well tolerated in this study, evidenced by the low rate of discontinuation and generally mild adverse events
- Numerous barriers to HCV treatment have been described among people who inject drugs, including those on opioid replacement therapy[4,5]
  - Many of these barriers are related to perceived poor tolerability of interferon-based treatment
- Adherence, compliance, and follow-up in this study were excellent
- No clinically evident treatment-emergent drug-drug interactions noted
- Patients on stable opioid replacement therapy may be well suited to all-oral treatment for HCV

CONCLUSIONS

- The 3-DAA + RBV regimen was well tolerated in GT1-infected patients receiving opioid replacement therapy, and achieved an SVR_{12} rate of 97.4% in this proof-of-concept study
- Safety in this population was comparable to that reported in previous studies
- A 12-week, highly efficacious, well-tolerated all-oral regimen may offer GT1-infected patients receiving opioid replacement therapy a more attractive option for treatment

REFERENCES

1. AbbVie. 2010. ABT-450 Investigator's Brochure.
2. Pilot-Matias T, Koev G, Krishnan P, Beyer J, Reisch TJ, et al. 2012. *In vitro combinatory effect of HCV NS3/4A protease inhibitor ABT-450, NS5A inhibitor ABT-267, and non-nucleoside NS5B polymerase inhibitor ABT-333.* Presented at 47th Annual Meeting of the European Association for the Study of the Liver, Barcelona, Spain.
3. Kowdley KV, Lawitz E, Poordad F, Cohen DE, Nelson DR, et al. 2014. *New England Journal of Medicine.* 370: 222–32.
4. Bruggmann P. 2012. *Journal of Viral Hepatitis.* 19: 829–35.
5. Treloar C, Rance J, Dore GJ, Grebely J. 2013. *Journal of Viral Hepatitis.*

DISCLOSURES AND ACKNOWLEDGEMENTS

J Lalezari: Nothing to disclose.

JG Sullivan: Grant/Research support: AbbVie.

V Rustgi: Research support: AbbVie.

H Aguilar: Grants: AbbVie. Speaker: Santarus, Ironwood.

F Felizarta: Speaker for Merck, Vertex, Boehringer-Ingelheim, and ViiV; research (as principal investigator) with AbbVie, Merck, Vertex, BI, Janssen, Gilead, Roche, BMS, and ViiV.

D Cohen: employee of AbbVie and may own AbbVie stock or options.

The design, study conduct, analysis, and financial support of the clinical trials 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.

This publication contains information on the investigational products ABT-450/r, ABT-267, and ABT-333 and investigational use of ribavirin.

The authors thank Laurinda Cooker, PhD, and Douglas E. Dylla, PhD, of AbbVie, for medical writing support.

To view an electronic version of this poster, scan QR code or visit **abbviescience.com/3143181591/1**

abbvie