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Daclatasvir plus asunaprevir for the treatment of HCV genotype 1b infection in Chinese patients with or without compensated cirrhosis

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BACKGROUND

- Two phase 3 studies evaluating efficacy and safety of daclatasvir plus asunaprevir (DCV/ASV) were conducted in HCV patients predominantly from mainland China.
- In AI447-036 study (NCT01995266), IFN±RBV-ineligible and/or intolerant patients with chronic HCV GT1b infection achieved a sustained virologic response (SVR) rate of 91% (99% without NS5A-L31M/V or Y93H)[1].
- In AI447-114 study (NCT02496078), treatment-naïve patients with chronic HCV GT1b infection achieved a SVR rate of 92% (96% without NS5A-L31M/V or Y93H)[2].

OBJECTIVES

- This analysis investigated the integrated efficacy and safety of DCV/ASV in Chinese patients with HCV GT1b infection in the Phase 3 studies AI447-036 (036) and AI447-114 (114).

METHODS

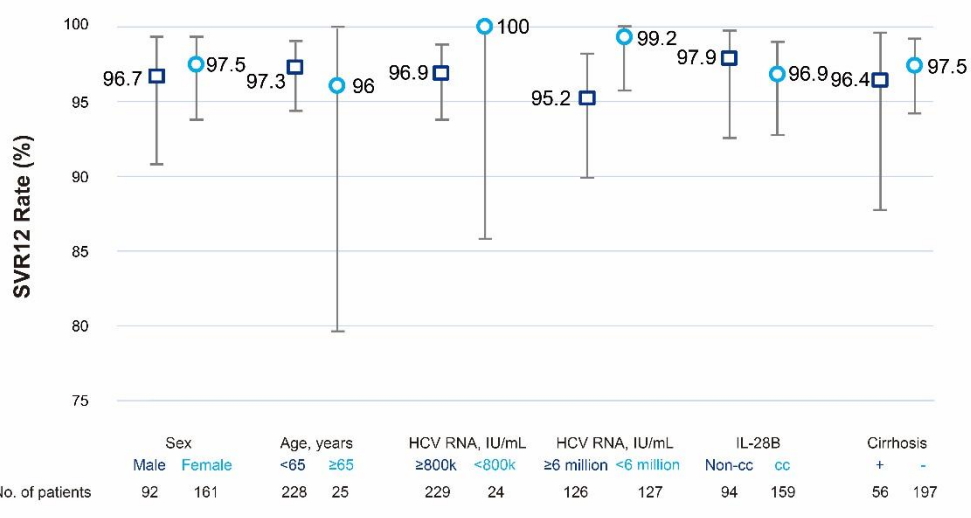
- Patients from mainland China with HCV GT1b infection treated with DCV/ASV were integrated across studies 036 and 114.
- In both studies, eligible patients were adults (≥18 years) with body mass index 18–35 kg/m^2, HCV RNA ≥10,000 IU/mL, seronegative for anti-HIV and hepatitis B surface antigen, with or without compensated cirrhosis.
- All patients received DCV 60 mg tablets once daily plus ASV 100 mg soft capsules twice daily for 24 weeks.
- Primary efficacy endpoint was SVR, defined as HCV RNA < lower limit of quantification, at follow-up Week 12 (SVR12).

Table 1. Baseline demographics and disease characteristics in patients treated with DCV/ASV

Parameter	AI447036 N=127	AI447114[a] N=161	Total N=288
Median age, years (min–max)	54 (20–74)	49 (19–70)	51 (18–74)
Age ≥65 years, n (%)	14 (11.0)	14 (8.7)	28 (9.7)
Females, n (%)	82 (64.6)	100 (62.1)	182 (63.2)
Median HCV RNA, $\log_{10}$ IU/mL (min–max)	6.75 (4.04–7.77)	6.85 (4.31–7.62)	6.79 (4.04–7.77)
HCV RNA ≥800,000 IU/mL, n (%) ≥6 x 10^6 IU/mL, n (%)	 117 (92.1) 61 (48.0)	 145 (90.1) 89 (55.3)	 262 (91.0) 150 (52.1)
IL28B non-CC, n (%)	56 (44.1)	42 (26.1)	98 (34.0)
Cirrhosis, n (%)	42 (33.1)	21 (13.0)[b]	63 (21.9)[b]
Without NS5A RAVs[c], n (%)	117 (92.1)	139 (86.3)	256 (88.9)

[a]One treatment-naïve patient was infected with GT1a;
[b]Cirrhosis status not reported for one treatment-naïve patient.
[c]NS5A RAVs include L31 and/or Y93H.
HCV, hepatitis C virus; IFN, interferon; R, ribavirin; RAVs, resistance-associated variants.

Figure 1. SVR12 and 95% confidence intervals by baseline subgroups in patients without baseline NS5A RAVs treated with DCV/ASV



RESULTS

- A total of 288 Chinese patients were treated with DCV/ASV; 127 from study 036 and 161 from study 114.
- At baseline, 52.1% of patients had high viral load (≥6 x 10^6 IU/mL), 34.0% had non-CC *IL28B* genotype, 21.9% had cirrhosis and 11.1% had NS5A resistance-associated variants (RAVs) at L31 and/or Y93H (Table 1).

Efficacy

- SVR12 was achieved by 90.2% (258/286) of patients overall, and by 97% (246/253) of patients without baseline NS5A RAVs.
- SVR12 rates were consistently high (≥95%) within baseline subgroups (sex, age, HCV RNA, *IL28B* genotype and cirrhosis status) in patients without baseline NS5A RAVs (Figure 1).

Safety

- DCV/ASV was generally well-tolerated and safe in both IFN±R ineligible/intolerant and treatment-naïve patients. Overall, 1.0% (3/287) of patients discontinued treatment due to an adverse event (AE).
- Serious AEs on treatment were reported by 3.1% (9/287) of patients, only 2 of which were considered to be treatment-related (both overdose). One patient died because of coronary artery disease, malignant arrhythmia, and Adams-Stokes syndrome, which was unrelated to study treatment.
- Grade 3–4 alanine aminotransferase (ALT) and aspartate transaminase (AST) abnormalities on treatment were reported in 3.1% (9/287) and 2.8% (8/287) of patients, respectively, most of which recovered within 4 weeks of the end of treatment (Table 2).

Table 2. Safety of IFN±R ineligible/intolerant and treatment-naïve HCV GT1b infected patients treated with DCV/ASV

Parameter	AI447036 N=127	AI447114 N=160	Total
Death[a], *n* (%)	1 (0.8)	0	1 (0.3)
AEs leading to discontinuation, *n* (%)	2 (1.6)	1 (0.6)	3 (1.0)
Serious AEs, *n* (%)	3 (2.4)	6 (3.8)	9 (3.1)
AEs (any Grade), ≥5%, *n* (%)	11 (8.7)	22 (13.8)	33 (11.5)
ALT elevation	8 (6.3)	16 (10.0)	24 (8.4)
AST elevation	4 (3.1)	12 (7.5)	16 (5.6)
Bilirubin increase	7 (5.5)	3 (1.9)	10 (3.5)
SCr	6 (4.7)	10 (6.3)	16 (5.6)
UA	4 (3.1)	9 (5.6)	13 (4.5)
Cough	7 (5.5)	2 (1.3)	9 (3.1)
Diarrhea	7 (5.5)	8 (5.0)	15 (5.2)
Dizziness	4 (3.1)	15 (9.4)	19 (6.6)
Hypertension	8 (6.3)	1 (0.6)	9 (3.1)
INR increase	5 (3.9)	13 (8.1)	18 (6.3)
Lipase increase	7 (5.5)	7 (4.4)	14 (4.9)
Monocyte count decrease	10 (7.9)	0	10 (3.5)
Neutrophil count decrease	11 (8.7)	3(1.9)	14 (4.9)
Platelet count decrease	14 (11.0)	10 (6.3)	24 (8.4)
Thrombocytopenia	10 (7.9)	3 (1.9)	13 (4.5)
Upper respiratory tract infection	7 (5.5)	21 (13.1)	28 (9.8)
WBC decrease	10 (7.9)	3 (1.9)	13 (4.5)
On-treatment Grade 3–4 laboratory abnormalities, *n* (%)			
ALT	2 (1.6)	7 (4.4)	9 (3.1)
AST	3 (2.4)	5 (3.1)	8 (2.8)
Hb	1 (0.8)	4 (2.5)	5 (1.7)
Lipase	2 (1.6)	3 (1.9)	5 (1.7)
LYMPA	2 (1.6)	1 (0.6)	3 (1.0)
Plt	15 (11.9)	1 (0.6)	16 (5.6)
PMNBA	1 (0.8)	0	1 (0.3)
Total bilirubin	1[b] (0.8)	1[c] (0.6)	2 (0.7)

3/10 patients with Grade 3–4 ALT/AST elevation return to normal range, 2.3±2.8 weeks (median±SD).
[a]One patient died because of coronary artery disease, malignant arrhythmia, and Adams-Stokes syndrome on day 25; the investigator considered this death to be unrelated to the study drugs; this patient did not receive concomitant amiodarone.
[b]Caused by acute cholecystitis. On Day 13, the patient was diagnosed with Grade 2 increased AST, increased ALT, increased GGT, and Grade 4 increased blood bilirubin. No treatment was provided and no action was taken with regard to the study therapy. Two days later (Day 15) the patient was hospitalized for a laparoscopic cholecystectomy. On Day 67 the event resolved. Acute cholecystitis was determined not related to the blinded study therapy by the investigator. The patient completed DUAL treatment and achieved SVR12.
[c]Experienced blood bilirubin increase, concomitant with Grade 2–3 ALT/AST elevation, considering treatment related.

CONCLUSIONS

- DCV/ASV was efficacious and well-tolerated in Chinese patients with HCV GT1b infection, with or without compensated cirrhosis, including those who were ineligible for or intolerant to interferon-based therapies, and treatment-naïve patients.

References:

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