Efficacy and Safety of All-Oral, 12-Week Ravidasvir Plus Ritonavir-Boosted Danoprevir and Ribavirin in Treatment-Naïve Non-Cirrhotic HCV Genotype 1 Patients : Results from a Phase 2/3 Clinical Trial in China

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INTRODUCTION

- In China, more than 10 million people may be chronically infected with the hepatitis C virus (HCV)， HCV genotype 1b (GT1b) is the most prevalent sub-genotype. [1]
- Ravidasvir (RDV) is a potent pan-genotypic NS5A inhibitor, chemically classified as a benzimidazole-naphthylene –imidazole core containing compound with high barrier to resistance . [2]
- In a phase I clinical study, Ravidasvir was proved to be well tolerated, with no reported treatment discontinuation in both healthy volunteers and patient groups. [3]
- As reported in the phase 2 EVEREST study, all-oral RDV and Danoprevir (DNVr) plus ribavirin(RBV) regimen achieved 100% SVR12 rate (38/38) in the treatment-naïve non-cirrhotic Taiwan patients with HCV GT1 infection. [4]
- The EVEREST study demonstrated that RDV and DNVr plus RBV regimen was safe and well tolerated by treatment-naïve, non-cirrhosis HCV GT1 patients. There was no death, treatment-related serious adverse events, or discontinued cases due to AE. [4]

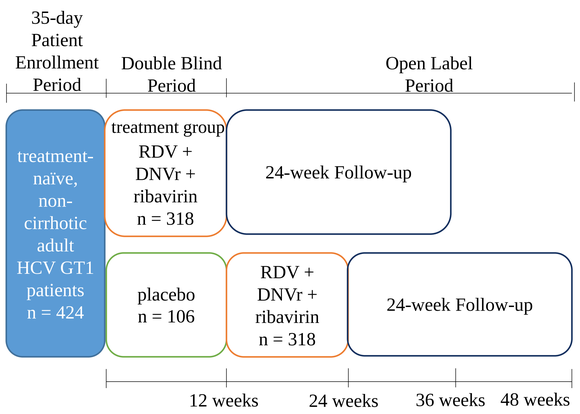
OBJECTIVE

- This phase 2/3 study is carried out to confirm the efficacy and safety of RDV and DNVr in combination with RBV regimen for treatment-naïve HCV genotype 1 (GT1) patients without cirrhosis in a large population from the Mainland of China.

METHODS

- This is a multi-center, randomized, double-blind, placebo-controlled phase 2/3 trial (NCT03362814).
- Four hundred and twenty four treatment-naïve, non-cirrhotic adult HCV GT1 patients were enrolled and randomized 3:1 to receive a combination of RDV 200 mg once daily plus DNVr 100 mg/100 mg twice daily and oral RBV 1000/1200 mg/day (body weight<75/≥75 kg) (n = 318) or placebo (n = 106) for 12 weeks (Figure 2). Patients were recruited from 42 sites in different provinces.

Figure 2. Study Design



- Dosage：RDV 200 mg once daily, DNVr 100 mg/100 mg twice daily, RBV 1000/1200 mg/day.

Inclusion Criteria:

- Chronic GT1b HCV-infection;
- Anti-HCV positive;
- HCV RNA ≥1 × 10000 IU / mL;
- Not treated with interferon and / or any other direct-acting antiviral (DAA) drug;
- Absence of Cirrhosis using 1 of the following criteria;
  - Determined as non-cirrhotic by Liver biopsy 1 year prior to the baseline (metavir ≤ 3);
  - Fibroscan value ≤ 9.6 kpa during the enrollment period
  - 9.6 kpa < Fibroscan value ≤12.9 kpa, and determined as non-cirrhotic by liver biopsy (metavir ≤ 3). (If the liver biopsy results are inconsistent with the Fibroscan value, use the liver biopsy results.)

Exclusion Criteria:

- HCV genotypes 2 to 7 or undetectable HCV genotype or mixed HCV genotype;
- Fibroscan value > 12.9 kPa ,or determined as cirrhotic by histopathological examination;
- Previous or current evidence shows the presence of non-HCV-induced chronic liver disease;
- Previous history of hepatocellular carcinoma, or suspected of hepatocellular carcinoma prior to or during the enrollment period , or AFP > 100 ng/mL when being screened;
- Anti-HAV (IgM), HBsAg, anti-HEV (IgM) or anti-HIV is positive;
- BMI < 18 or ≥ 30 kg/m^2;
- ANC < 1.5×10^9/L, PLT< 100×10^9/L, HB < 110 g/L(female) or < 120 g/L (male) ; INR>1.5; ALT or AST ≥ 5*ULN; TBIL ≥ 2*ULN (DBIL ≥ 35%TBIL); Cr ≥ 1.5*ULN;
- Others are as specified in the study protocol.

End Points:

•The Primary Efficacy Endpoint

- Percentage of patients achieved sustained virologic response 12 weeks after the end of treatment (SVR12) accessed by the CAP/CTMHCV 2.0 assay (LLOQ =15 IU/mL).

•Safety Assessment

- Percentage of patients with treatment emergent adverse events (AEs) or laboratory abnormalities during the double-blind phase of the study.

RESULTS

- A total of 424 patients were enrolled and treated in 41 centers across China.

Figure 3. Regional Distribution of the Patients

Table 1. Baseline Characteristics （FAS）

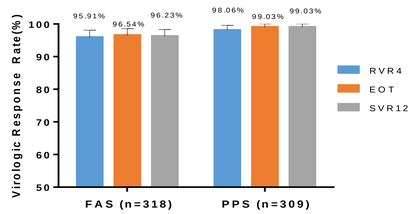
Characteristic	Treatment group (n=318)	Placebo group (n=106)
Female, n (%)	165(52%)	58(55%)
Age, median (range), years	48(21-73)	45(23-72)
BMI, mean ± SD, kg/m2	23.2±2.8	22.8±2.8
HCV RNA, median (range), log10 IU/mL	6.3(4.1-7.3)	6.2(4.1-7.4)
IL28B CC genotype, n (%)	259(81%)	89(84%)
HCV genotype 1a, n(%)	6(1.9%)	2(1.9%)
HCV genotype 1b, n(%)	312(98.1%)	104(98.1%)

Table 2. Prevalence of NS5A RAS in the Treatment Group (PPS)

- In the treatment group, NS5A resistance-associated substitution (RAS) was detected in 76 patients (24.6%, 76/309) at baseline.

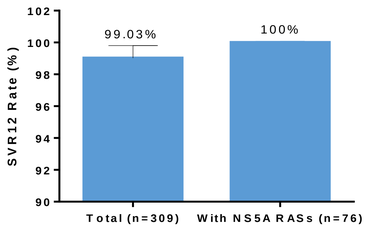
Baseline with NS5A RASs	Treatment group (n=309)
R30Q, n (%)	38(12.3%)
Y93H,n (%)	21(6.8%)
R30Q/Y93H,n (%)	8(2.6%)
L28M,n (%)	3(1.0%)
R30H,n (%)	1(0.3%)
Y93C,n (%)	1(0.3%)
R30Q/L31M,n (%)	1(0.3%)
L28M/Y93C,n (%)	1(0.3%)
L28M/Y93H,n (%)	1(0.3%)
L28Q,n (%)	1(0.3%)
Total, n (%)	76(24.6%)

Figure 4. Virologic Response Following Treatment



- The overall SVR12 rate was 96.23% (306/318, 95%CI:93.50% ~ 98.04%, FAS) and 99.03% (306/309，95%CI:97.19% ~ 99.80%, PPS) respectively.

Figure 5. SVR12 Rate of Patients with NS5A RASs (PPS)



- All patients with baseline NS5A RASs achieved SVR12 (76/76, 95%CI: 95.26% ~ 100.00%, PPS).

Table 3. Safety Summary

Any AE	SAE	Drug-Related Serious AE	AEs Leading to Drug d/c	Death
68% （216/318）	2% (7/318)	0% （0/318）	1.6% （5/318）#	1 (0.23%)*

#One patient discontinued due to drug allergy, others was not considered to be related to the study drugs

*One death due to traffic accident was not considered to be related to the study drugs.

- Most of the liver function abnormalities were mild or moderate (grade 1 ~ 2).

Table 4. Prevalence of AE Frequency > 10%

AE	Treatment group n (%)	Control group n (%)
anemia	128 (40%)	5 (5%)
upper respiratory tract infection	67 (21%)	22 (21%)
elevated bilirubin	52 (16%)	6 (6%)
hyperuricemia	34 (11%)	4 (4%)

CONCLUSIONS

- Treatment with all-oral RDV and DNVr in combination with RBV for 12 weeks resulted in SVR 12 of 96.23%(FAS) and 99%(PPS).
- All-oral RDV and DNVr in combination with RBV for 12 weeks treatment was well tolerated in treatment-naïve non-cirrhotic HCV genotype 1 Chinese patients.

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DISCLOSURE

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