



## Efficacy and Safety of All-oral, 12-week Ravidasvir Plus Ritonavir-boosted Danoprevir and Ribavirin in Treatment-naïve Noncirrhotic HCV Genotype 1 Patients: Results from a Phase 2/3 Clinical Trial in China

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### Abstract

**Background and Aims:** Ravidasvir (RDV) is a new generation pangenotypic hepatitis C virus (HCV) NS5A inhibitor, with high barrier to baseline resistance-associated species. This is the first phase 2/3 study conducted in Mainland China

**Keywords:** Ravidasvir; Danoprevir; HCV; SVR; Treatment-naïve; Noncirrhotic; GT1.

**Abbreviations:** AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DAA, direct acting antiviral therapy; DNVr, ritonavir-boosted danoprevir; GT1, genotype 1; HCV, hepatitis C virus; RBV, ribavirin; RDV, ravidasvir; SAE, serious adverse event; SVR12, sustained virological response at 12 weeks after treatment.

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confirming the efficacy and safety of RDV + ritonavir-boosted danoprevir + ribavirin for 12 weeks in treatment-naïve noncirrhotic patients with genotype 1 infection in a large population. **Methods:** In this multicenter, randomized, double-blinded, placebo-controlled phase 2/3 trial (NCT03362814), we enrolled 424 treatment-naïve, noncirrhotic adult HCV genotype 1 patients. All patients were randomized at 3:1 ratio to receive a combination of RDV 200mg once daily plus ritonavir-boosted danoprevir 100mg/100mg twice daily and oral ribavirin 1000/1200mg/day (body weight <75/≥75 kg) ( $n = 318$ ) or placebo ( $n = 106$ ) for 12 weeks. The primary end-point was the rate of sustained virologic response 12 weeks after the end of treatment, and the safety was evaluated and compared between treatment and placebo groups. **Results:** The overall rate of sustained virologic response at 12 weeks after treatment is 99% (306/309, 95%, CI: 97%–100%) under per protocol set analysis.

All patients harboring baseline NS5A resistance-associated species in the treatment group (76/76, per protocol set) achieved sustained virological response at 12 weeks after treatment. No treatment-related serious adverse events were reported. Laboratory abnormalities showed mild or moderate severity (grade 1 and grade 2) in liver function tests. **Conclusions:** In treatment-naïve, noncirrhotic HCV Chinese patients infected with HCV genotype 1, all-oral regimen of RDV + ritonavir-boosted danoprevir + ribavirin for 12 weeks was highly efficacious, safe, and well tolerated.

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## Introduction

In China, more than 10 million people are estimated to be chronically infected with hepatitis C virus (HCV),<sup>1</sup> with genotype 1 (GT1) b as the most prevalent sub-genotype (56.8%).<sup>2</sup> Currently, approximately 50–75% of the patients infected with GT1 HCV are able to achieve a sustained virological response (SVR) after treatment with a combination of pegylated-interferon plus ribavirin (RBV) for 48 weeks, the current standard of care for chronic HCV infection in China,<sup>3</sup> leaving strong needs for new direct acting anti-viral therapy (DAA) with higher efficacy as warranted.

Ravidasvir (RDV), a potent pangenotypic NS5A inhibitor, has a favorable pharmacokinetic profile, with rapid absorption, stable plasma distribution and high plasma trough concentration, allowing for continuous HCV inhibition with once-daily oral dosing.<sup>4</sup> Danoprevir (DNV) is a potent, macrocyclic inhibitor of the HCV NS3/4A serine protease<sup>5,6</sup> that can be co-administered with low-dose ritonavir to achieve therapeutic trough concentrations throughout the dosing interval. Combination of RDV and DNV may serve as a potent regimen against HCV infection.

As reported in the phase 2 EVEREST study, all-oral RDV + ritonavir-boosted danoprevir (DNVr) + RBV regimen has demonstrated sustained virological response at 12 weeks after treatment (SVR12) at 100% (38/38) in treatment-naïve noncirrhotic Taiwanese patients with HCV GT1 infection, and was safe and well tolerated.<sup>7</sup> This phase 2/3 study was designed to investigate the safety and efficacy of this combination regimen in treatment-naïve HCV GT1 patients without cirrhosis in a larger population from Mainland China.

## Methods

### Patients

Patients with confirmed chronic HCV infection were screened and recruited from 42 sites in different provinces across China, and eligible subjects were enrolled in the study according to the inclusion and exclusion criteria as below:

### Inclusion criteria

Chinese adult of  $\geq 18$  years-old with chronic GT1 HCV-infection; absence of cirrhosis (defined as a liver stiffness measurement  $< 9.6$  kPa by Fibroscan<sup>®</sup> or a screening liver

biopsy indicating no cirrhosis [metavir score  $\leq 3$ ]); plasma HCV RNA  $\geq 1 \times 10,000$  IU/mL; and never received antiviral treatment for HCV infection.

### Exclusion criteria

Mixed HCV genotypes; HCV genotypes other than GT-1; HBV or HIV co-infection; alpha-fetoprotein  $> 100$  ng/mL; presence or suspected of other chronic liver illness or hepatocellular carcinoma; presence of cirrhosis as assessed by Fibroscan<sup>®</sup> ( $> 12.9$  kPa) or liver biopsy (metavir score at 4); body mass index  $< 18$  or  $\geq 30$  kg/m<sup>2</sup>; anti-HAV (IgM), HBsAg, anti-HEV (IgM) or anti-HIV positivity; ANC  $< 1.5 \times 10^9$ /L; platelet  $< 100 \times 10^9$ /L; hemobilirubin  $< 110$  g/L (female) or  $< 120$  g/L (male); international normalized ratio  $> 1.5$ ; alanine aminotransferase (ALT) or aspartate aminotransferase (AST)  $\geq 5 \times$ ULN; total bilirubin  $\geq 2 \times$ ULN (direct bilirubin  $\geq 35\%$  total bilirubin); or creatinine  $\geq 1.5 \times$ ULN.

### Study design

Eligible subjects were enrolled and randomly assigned at a 3:1 ratio to active treatment (the treatment group) or placebo (the placebo group) arms (Fig. 1). During the double-blinded phase, subjects in the treatment arm received a combination of RDV at 200 mg once daily plus DNVr at 100 mg/100 mg twice daily and oral RBV at 1000/1200 mg/day (1000 mg daily if the body weight was  $< 75$  kg and 1200 mg daily if the body weight was  $\geq 75$  kg) for 12 weeks. Subjects in the placebo arm received placebo during the double-blinded phase and entered into a deferred open-labelled active treatment arm for another 12 weeks. All subjected were followed up for 24 weeks after the end of active treatment (Fig. 1).

The study is currently completed. Efficacy and safety outcomes for both study arms are presented herein.

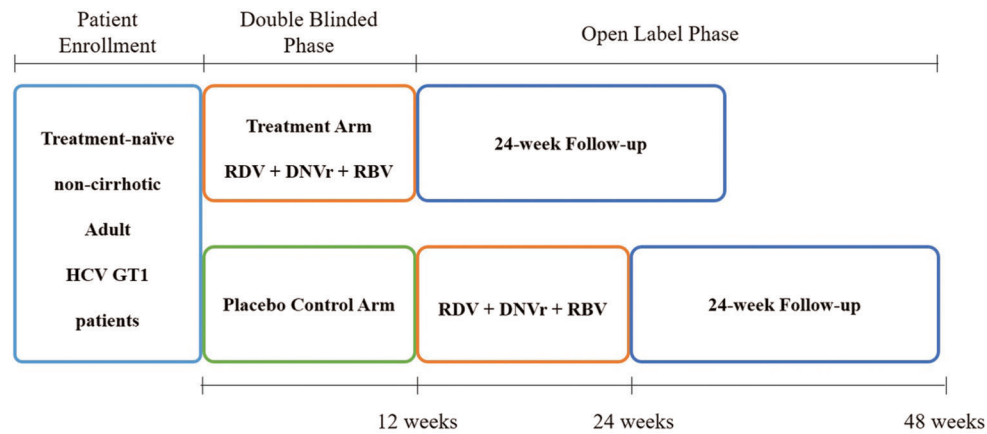
### Study oversight

All the subjects provided written informed consent. The protocol of this study conformed to the International Conference on Harmonisation guidelines, applicable regulations, and ethical guidelines of the Declaration of Helsinki. The research was approved by the ethical committee of each participating site and was registered at clinicaltrials.gov (trial registration: NCT03362814). All authors had full access to the database and vouch for the completeness and accuracy of the data and analyses as presented.

### Efficacy assessments

Vital signs were measured and samples were collected and stored at screening and on study visits at weeks 1, 2, 4, 8, and 12 and at post-treatment weeks 4, 12 and 24 for analyses spanning biochemistry, hematology, viral load, and urinalysis.

The lower limit of quantitation of HCV RNA was defined as 15 IU/mL, which was determined by using CAP/CTM HCV 2.0 assay. The primary end-point was SVR12 after the end of the treatment. Viral breakthrough was defined as a one log increase in HCV RNA from postbaseline nadir, or a confirmed positivity in HCV RNA from undetectable level. Post-treatment relapse was defined as HCV RNA returning positivity from previously achieved HCV RNA negativity before or at end of treatment.



**Fig. 1. Study design.**

Abbreviations: RDV, ravidasvir; DNVr, ritonavir-boosted danoprevir; RBV, ribavirin.

We performed resistance analysis by using population sequencing on samples obtained at baseline, when patients had experienced virologic breakthrough during treatment, or relapse during follow up after the treatment, in order to evaluate the role and impact from substitutions potentially rendering resistance to NS5A or NS3/4A inhibitors.

#### Safety assessment

Adverse events (AEs) were assessed at each study visit and documented for all patients who received at least one dose of medications. Data for all treatment-emergent AEs, laboratory abnormalities, clinically significant changes of vital signs and electrocardiogram testing were obtained from the start of drug administration until 4 weeks after the end of study. AEs were categorized using the Medical Dictionary for Regulatory Activities.

#### Statistical comparison groups and subgroups

Analysis population included the FAS subgroup of all randomized subjects who received at least one dose of the study drug and provided at least one point of data; the per protocol population of patients from FAS subjects who met the inclusion criteria without reasons for exclusion and completed the study treatment and follow-up; the safety population of all randomized subjects who received at least one dose of the study drug and provided safety data for appraisal.

#### Statistical methods

Demographics and baseline characteristics were collected for the FAS population. Efficacy analyses were performed on the FAS and per protocol set populations, and safety analyses were performed on the per protocol set population. For the primary efficacy end-point (SVR12), a two-sided 95% confidence interval (CI) was calculated using the normal approximation to the binomial distribution. Subgroup efficacy analyses of SVR12 (including stratification by genotype, baseline HCV RNA level, IL28B genotypes, and baseline polymorphisms in NS5A) were performed for the per protocol set population.

To evaluate the superiority of the RDV plus DNVr and RBV regimen to the historical control in HCV GT1 patients, the lower boundary of the 95% CI for SVR12 in the treatment and placebo group entering deferred active treatment had to exceed the calculated historical control rate of 75%. The control rate, which was based on response rates among previously untreated noncirrhotic patients who received pegylated-interferon/RBV, was determined from a meta-analysis and experts' clinical experience.

All statistical tests and 95% CIs were two-sided, and *p* values <0.05 were considered statistically significant. Descriptive statistics for quantitative data used are reported as mean ± standard deviation and median (interquartile range), while qualitative data is summarized as counts and percentages. Data analysis was performed using SAS Proprietary Software 9.4 (Licensed to PEKING UNIVERSITY HEALTH SCIENCE CENTER, Site 11202165).

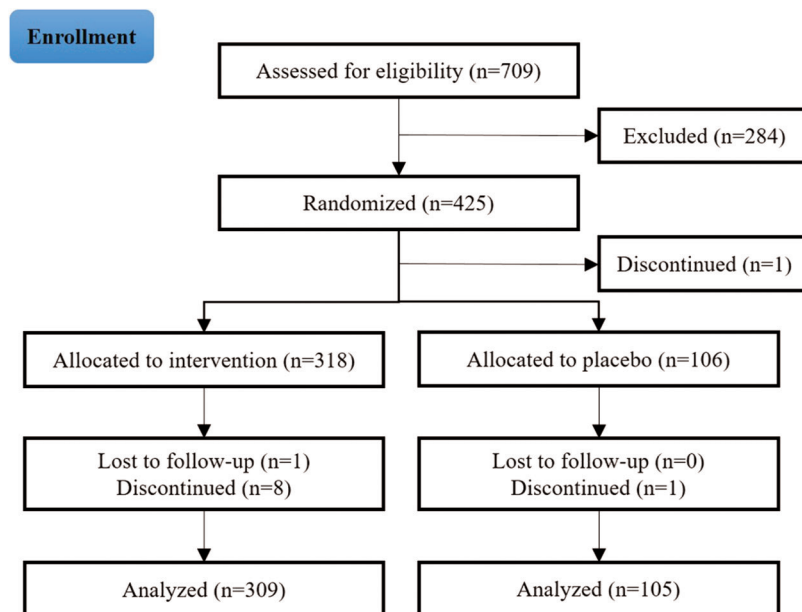
## Results

#### Baseline characteristics and demographics

A total of 709 subjects were screened, and 425 qualified patients were assigned to randomization. Among whom, 424 (318 patients in the treatment arm and 106 in the placebo arm) received at least one dose of investigational medication and were included in the FAS population for the primary efficacy and safety analyses. A total of 309 patients in the treatment arm and 101 patients in the placebo arm completed the 12-week follow-up and fulfilled the inclusion criteria for the per protocol population (Fig. 2). The demographic and baseline characteristics of the study population are shown in Table 1.

#### Efficacy

Overall, the SVR12 rate in the FAS analysis was 96% (306/318, 95% CI, 94~98%) in the treatment arm and 95% (101/106, 95% CI, 93~100%) in the placebo arm. In the per protocol population, the SVR12 reached 99% (306/309, 95% CI, 97~100%) in the treatment arm and 99% (100/101, 95% CI, 95~100%) in the placebo arm (Table 2).



**Fig. 2. Consolidated Standards of Reporting Trials (known as CONSORT) flow diagram showing participants flow through each stage of the randomized controlled trial (enrollment, intervention allocation, follow-up, and data analysis).** Two hundred and eighty-four patients who failed to meet the standards were excluded from this clinical study and among 425 randomized patients, one voluntarily discontinued without being administered medication. One patient from the placebo arm discontinued due to relocation overseas. Eight patients from the intervention arm discontinued and only one was considered due to an adverse event related to the active treatment.

All subjects receiving RDV + DNVr + RBV had a rapid decline of serum HCV RNA levels (Fig. 3). By week 4 during the double-blinded treatment phase, the HCV RNA level was below the lower limit of quantitation (15 IU/mL) in 98% of the patients who were treated by the active regimen (303 of the 309 patients in the treatment group), and at the end of the treatment the proportion reached 99% (306/309).

The SVR12 subanalysis in various subgroups showed that the SVR12 rates were similarly high in all subgroups, including those defined by gender (99% with male and 99% with female, per protocol set), IL28B genotypes (99% with CC and 100% with non-CC, per protocol set), age (99% among people <65 years-old and 100% among people ≥65 years-old), and initial baseline HCV RNA levels (100% with a level

<400,000 IU/mL, 97% with a level of 400,000~800,000 IU/mL, 99% with a level ≥800,000 IU/mL).

**Resistance analyses**

NS5A resistance-associated species were detected in 76 patients (25%, 76/309) in the treatment arm and 29 subjects in the placebo-controlled arm (29%, 29/101, per protocol set) at baseline (for details of the resistance-associated species see Table 3). The most common NS5A resistance-associated species detected were R30Q (38/309, 12.3%), Y93H (21/309, 6.8%) and R30Q + Y93H (8/309, 2.6%) in the treatment arm and R30Q (21/101, 20.7%), Y93H (6/101, 5.9%) and R30Q + Y93H (1/101, 0.99%) in the

**Table 1. Baseline characteristics and demographic data of subjects**

Parameter	Treatment arm, n = 318	Placebo arm, n = 106	p value
Female, n (%)	165 (52%)	58 (55%)	0.613
Age, median (range), years	48 (21-73)	45 (23-72)	0.01
BMI, mean ± SD, kg/m <sup>2</sup>	23.2 ± 2.8	22.8 ± 2.8	0.192
HCV RNA (log10 IU/mL), median	6.31	6.22	0.475
<400,000 IU/mL, n (%)	53 (16.67%)	21 (19.81%)	
400,000 IU/mL-800,000 IU/mL, n (%)	32 (10.06%)	13 (12.26%)	0.569
≥ 800,000 IU/mL, n (%)	233 (73.27%)	72 (67.92%)	
IL28B CC genotype, n (%)	259 (81%)	89 (84%)	0.559
HCV genotype 1a, n (%)	6 (2%)	2 (2%)	1
HCV genotype 1b, n (%)	312 (98%)	104 (98%)	1

Abbreviations: BMI, body mass index; HCV, hepatitis C virus.

**Table 2. Sustained virologic response at post-treatment week 12 among all patients after receiving the active regimen**

Group	Subgroup	Response/total	SVR 12*	95% CI	Historical control with PR	p value
Treatment arm	FAS	306/318	96%	(94%, 98%)	75%	<0.001
	per protocol set	306/309	99%	(97%, 100%)	75%	<0.001
Placebo arm	FAS	101/106	95%	(93%, 100%)	75%	<0.001
		100/101	99%	(95%, 100%)	75%	<0.001

\*SVR12, sustained response rate at post-treatment week 12 was defined as HCV RNA <15 IU/mL (lower limit of quantitation).

placebo-controlled arm. All patients with baseline NS5A resistance-associated species from both arms achieved SVR12 (Fig. 4).

**Treatment failure**

Among 309 patients in the treatment arm, the 76 patients reported with baseline NS5A resistance-associated species all (76/76, per protocol set) achieved SVR12 showing potency of this regimen. Three patients (0.97%) experienced a virologic breakthrough during the treatment phase, and no patient relapsed by post-treatment week 12. Serum samples from two of the three subjects who experienced virologic breakthrough showed positivity for resistance-associated species that confer resistance to both NS3/4A and NS5A. The resistance-associated species were Q80k, V36M, R155K in the protein NS3/4A, and Q30K, Q30H, H58D in the region NS5A. The third patient with virologic breakthrough had no detectable RAS at both baseline and on rise, but the genotype turned out as genotype-2a instead of GT1b as initially diagnosed. This case could not be ruled out from potential mechanisms such as a misdiagnosed genotype on enrollment, viral superinfection with GT1b dominance, or re-infection with genotype-2a during treatment. In the placebo arm, one subject relapsed and showed resistance-associated species R155K in the NS3/4A region and L31V in the NS5A region.

**Safety and tolerability**

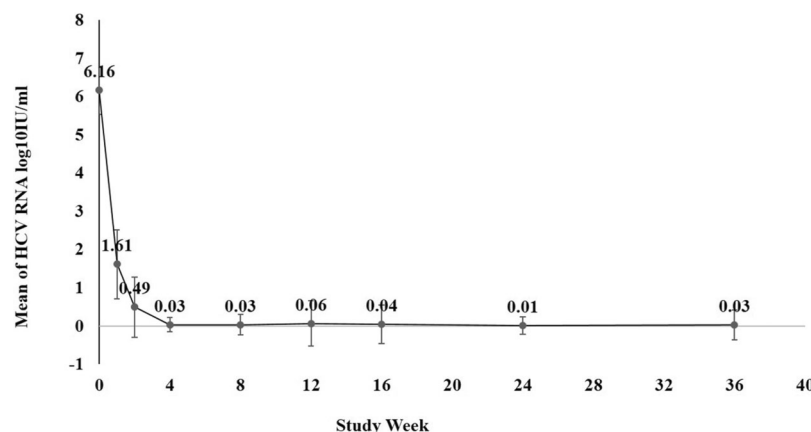
During the double-blinded phase, 94% of the subjects in the treatment arm (298/318), experienced adverse events (AEs) compared to 79% of those in the placebo arm (84/106). The

majority of AEs were mild. Only 15 of the 318 subjects in the treatment arm (15/318, 5%) and 9 subjects (9/103, 9%) in the placebo arm had grade 3 treatment-related AEs. The laboratory abnormality tests revealed evaluated liver functions (ALT, AST, total bilirubin, direct bilirubin) in the treatment arm were mostly of grade 1 or 2 and no grade 4 AEs occurred. No treatment-related severe AEs or death occurred during the full treatment course. The most common AEs reported were anemia (in 40% of the subjects in the treatment arm and 5% in the placebo arm) and upper respiratory tract infection (in 21% of the subjects in the treatment arm and 21% in the placebo arm). Hemobilirubin elevation (16% vs. 6%) was also seen among the patients with the most frequent treatment-related AEs that occurred but was in <10% of subjects (Table 4).

Discontinuation due to any AE occurred in one patient in the treatment arm, owing to drug allergy. One death was reported due to traffic accident but was not considered treatment-related. Most of the liver function abnormalities were mild or moderate (grade 1 or 2), and no grade 4 abnormalities were observed. In the treatment arm, four of the three hundred-eighteen patients had grade 3 treatment-related elevated total bilirubin level and one had grade 3 elevated ALT. In the placebo arm, three patients experienced grade 3 ALT elevation and two with AST elevation, respectively.

**Discussion**

A cross-sectional observational study conducted in 2014 in China revealed HCV GT1b to be the most prevalent subtype at 56.8% and to be associated with low response to traditional treatment with pegylated-interferon plus RBV for 48 weeks. Recently, some DAA regimens were approved in China but



**Fig. 3. Mean of HCV RNA log<sub>10</sub> IU/mL to the end of follow-up (per protocol set).** When HCV RNA <15 IU/mL or reported as target not detected, HCV RNA was counted as 1 IU/mL, or log<sub>10</sub>1 IU/mL in the Figure.

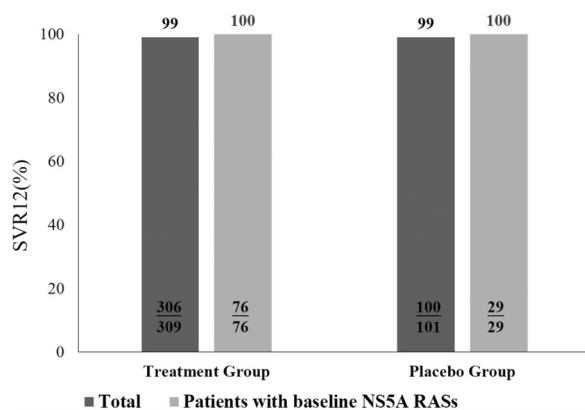


**Table 3. Baseline resistance-associated substitution analysis of HCV NS5A (per protocol set)**

Baseline with NS5A resistance-Associated species	Treatment arm, n = 309	Placebo arm, n = 101
R30Q, n (%)	38 (12.3%)	21 (20.8%)
Y93H, n (%)	21 (6.8%)	6 (5.9%)
R30Q + Y93H, n (%)	8 (2.6%)	1 (1.0%)
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%)	1 (1.0%)
Total, n (%)	76 (24.6%)	29 (28.7%)

with pre-requisition according to results from a baseline resistance-associated species test. Baseline resistance-associated species in HCV are somehow prevalent and may pose a necessity of intervention in either diagnosis or treatment. Hence, there is a strong desire for a new treatment option with higher cure rate and good resistance barrier profile. In this randomized, double-blinded, placebo-controlled phase 2/3 trial, we demonstrated the excellent efficacy of an interferon-free, all-oral antiviral therapy in treatment naïve, noncirrhotic, GT1 subjects, without resistance-associated species test before treatment initiation. The SVR12 rate in the treatment arm was 96% (306/318) in the FAS and 99% (306/309) the per protocol set models, respectively. The SVR12 for the placebo-controlled arm was 95% (101/106) in the FAS and 99% (100/101) the per protocol set sets.

In the interferon and RBV era, SVR was associated with several host-, viral- and drug-related characteristics, such as age, sex, baseline viral load, treatment duration, etc.<sup>8,9</sup> Our results using subanalysis covering these factors showed there was little impact from age, gender, IL28B genotypes,



**Fig. 4. Virological response of patients with baseline resistance-associated species.**

Abbreviation: SVR12, Sustained virologic response at post-treatment week 12.

and baseline viral load, and the efficacy was similarly high among all subgroups. The traditional negative predictors herein no longer delineate different response in SVR12 rates, whereas the potency of the investigational drug combination was demonstrated concordantly. The lower boundary of the 95% CI for the SVR12 rates in both arms were marginally higher than the historical control value (75%) from the pegylated-interferon + RBV regimen, hence confirming the superiority hypothesis. Sensitivity analysis also reached a consistent conclusion.

Baseline resistance-associated substitutions (of resistance-associated species) in HCV NS5A are not uncommon in Chinese GT1b patients and may account for up to 19% prevalence with detrimental response in certain patients.<sup>10</sup> Heretofore, the first generation NS5A inhibitors (such as daclatasvir, ledipasvir, and ombitasvir) have relatively lower NS5A resistance barriers and share cross-drug resistance, which undermines the efficacy of DAA therapies.<sup>11</sup> According to drug labels and guidelines, the NS5A resistance-associated species test is recommended for elbasvir/grazoprevir in GT1a, for daclatasvir plus asunaprevir in GT1b, and even for sofosbuvir/velpatasvir treatment in genotype 3 treatment-naïve patients with cirrhosis and treatment-experienced patients (with or without cirrhosis).<sup>12</sup> Nonetheless, consensus from clinicians is still the simplified testing as the preferable choice. Different from the NS5A inhibitors aforementioned, RDV is a pangenotypic HCV NS5A inhibitor with high resistance barrier and more potent antiviral activity in accordance with a higher administration dose at 200 mg per day boosting to garner greater exposure.<sup>4</sup> Besides, the wild-type HCV virus, conversely, in a previous study of RDV also demonstrated its potency to fully inhibit single NS5A substitution variants.<sup>13</sup> In this study, GT1 NS5A resistance-associated species were detected in 76 of the participating subjects (24.6%, 76/309) in the treatment arm and 29 in the control arm (29%, 29/101, per protocol set) at baseline (Fig. 2). All subjects with baseline NS5A resistance-associated species from both arms achieved SVR12. These results support a clinical use of this regimen without posing a baseline NS5A resistance-associated species test in the studied population, which was treatment naïve, noncirrhotic, and GT1 HCV subjects.

As to safety, the RDV + DNVr + RBV combination was well tolerated in the studied cohort in this trial. Most AEs were mild or moderate in intensity and were considered less relevant to results reported from the previous phase 2 studies using the same regimen. Severe AEs occurred in 2.8% (12/424) of the study population (7 in the treatment arm and 5 in the placebo arm), whereas none was assessed as related to study medication per discretion of the investigators. One patient died during the study due to a traffic accident and this event was considered not related to study drugs. One patient discontinued due to drug allergy. Most of the laboratory abnormalities in liver function were of mild to moderate severity (grade 1 and grade 2). Presence of the placebo arm in the study design hereby allowed for comparison of the safety profile with the active treatment arm. The resultant safety profile in the overall population was quite similar and comparable between the two arms, with exception of more anemia from the treatment arm which was not surprising due to the use of RBV.

In pharmacology, both RDV and danoprevir are pangenotypic anti-HCV inhibitors,<sup>4,5</sup> possessing potent antiviral activities against HCV GT1 through genotype 6 species from *in vitro* and *in vivo* results. In phase 1 trials, RDV monotherapy showed potent antiviral activity and excellent safety profile in

**Table 4. Adverse Events and Laboratory Abnormalities During the Double-Blinded Treatment Phase (FAS)**

Patients, <i>n</i> (%)	Treatment arm, <i>n</i> = 318	Placebo arm, <i>n</i> = 106
Any AEs	298 (94%)	84 (79%)
Treatment-related AEs leading to treatment discontinuation	1 (0.3%)*	0
Any SAEs	7 (2%) <sup>†</sup>	5 (5%) <sup>‡</sup>
Treatment-related SAEs	0	0
Deaths	1 (0.3%)*	0
Common adverse events (≥10%), <i>n</i> (%)		
Anemia	128 (40%)	5 (5%)
Upper respiratory tract infection	67 (21%)	22 (21%)
Hemobilirubin rise	52 (16%)	6 (6%)
Laboratory abnormalities (grade 3), <i>n</i> (%)		
Alanine aminotransferase rise	1 (0.31%)	3 (2.83%)
Aspartate aminotransferase rise	0	2 (1.89%)
Total bilirubin increase	4 (1.26%)	0

\* Discontinuation due to any adverse event occurred in one patient in the treatment group owing to drug allergy.

<sup>†</sup>Serious adverse events in the treatment arm were vasovagal syncope, multiple bilateral rib fractures, died from a car accident. Hemorrhoids, cerebral infarction, infectious diarrhea, and community-acquired pneumonia, occurred in one patient each.

<sup>‡</sup>Serious adverse events in the placebo arm were acute exacerbation of chronic bronchitis, acute appendicitis and traumatic ciliary body detachment of the right eye, occurring in one patient each; left clavicle fracture and left third rib fracture in one; and, acute pelvic inflammatory disease and urinary tract infection in one.

<sup>‡</sup>One patient died due to traffic accident, and the event was not considered treatment-related.

Abbreviations: AEs, adverse events; SAEs, serious adverse events.

treatment-naïve subjects infected with GT1, genotype 2, and genotype 3.<sup>12</sup>

The strength of this study is its being the first large scale, double-blinded, randomized, multicenter trial that confirms the efficacy and safety profiles of the new RDV + DNVr + RBV combination. The SVR12 of 99% regardless of pre-existing baseline NS5A resistance-associated species may provide a simple to use choice to clinicians in the defined study population. Good tolerability and safety profile further endorse application of this regimen in a large population. Nonetheless, this study may have some limitations. First, the use of RBV resulted in more anemia. However, most of the AEs were of mild or moderate severity and returned to normal after proper handling or intervention, as indicated from the trial results. The paradoxical role of RBV from the beneficial side may be eliminating quiescent viruses under other mechanisms apart from DAAs and reducing hepatocellular carcinoma incidence as reported before. The prolonged duration of using pegylated-interferon + RBV for 24 to 48 weeks preferably once plagued clinicians with safety concerns. Under this new combination, the duration was shortened to 12 weeks without interferon; therefore, the safety profile was very appreciable. Second, this study did not recruit cirrhosis subjects, due to insufficient proof of concept study results. We may look into the cirrhosis cohort further, including it in our future study design. Third, the use of ritonavir may trigger some potential concern in drug-drug interaction in clinical practice. Per the outcome of the safety results, there was limited discontinuation due to drug-drug interaction and little drug dose adjustment. This may be partially due to the observation that noncirrhosis patients are less sick and not taking complex concomitant comedications, while a shortened treatment duration of only 12 weeks may also help. Nevertheless, this may warrant a real-world observation to further understand the outcome.

In conclusion, treatment with all-oral RDV and DNVr in combination with RBV for 12 weeks resulted in SVR12 of 96% (FAS subgroup) and 99% (per protocol set subgroup) and was well tolerated in treatment-naïve noncirrhotic HCV GT1 Chinese patients.

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#### Conflict of interest

Lai Wei was consultant for AbbVie, Abbott, BMS, Gilead Sciences, Johnson & Johnson, MSD, Novartis, and Roche, speaker for Abbott, BMS, Gilead Sciences, MSD, Novartis, Roche, and Asclepis, and received grant support from BMS and Roche. The other authors have no conflict of interests related to this publication.

#### Author contributions

Article conception and design (LW), acquisition of data (XX, BF, YG, SZ, JS, XY, YM, YH, YK, XW, JL, YT, QH, QX, MW, PA, GG, HL, QN, RH, BN, WX, JZ, WH, YY, ML, YZ, YY, JJ, DY, LC, YY, YN, ZG, QZ, PH, FW, YL, DL, ZJ, JH, CC, and JJW), drafting and critical revision of the manuscript (LW).

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