

World Journal of *Gastroenterology*

World J Gastroenterol 2018 March 28; 24(12): 1285-1372



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World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents[®]/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch[®]), Journal Citation Reports[®], Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2017 edition of Journal Citation Reports[®] cites the 2016 impact factor for *WJG* as 3.365 (5-year impact factor: 3.176), ranking *WJG* as 29th among 79 journals in gastroenterology and hepatology (quartile in category Q2).

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

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7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
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PUBLICATION DATE
March 28, 2018

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Randomized Clinical Trial

Daclatasvir plus asunaprevir in treatment-naïve patients with hepatitis C virus genotype 1b infection

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Supported by Bristol-Myers Squibb.

Institutional review board statement: The protocol was approved by the institutional review board/human research committee at each participating institution, and conformed to the ethical guidelines of the 2008 Declaration of Helsinki.

Clinical trial registration statement: This study is registered at ClinicalTrials.gov, registration number NCT02496078 (<https://clinicaltrials.gov/ct2/show/NCT02496078>).

Informed consent statement: All patients provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors have no conflicts of interest for this manuscript.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author. Patients gave informed consent regarding the relevant use and sharing of key-coded data.

CONSORT 2010 statement: The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

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Manuscript source: Unsolicited manuscript

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Received: December 22, 2017

Peer-review started: December 22, 2017

First decision: January 4, 2018

Revised: February 9, 2018

Accepted: February 26, 2018

Article in press: February 26, 2018

Published online: March 28, 2018

Abstract

AIM

To assess daclatasvir plus asunaprevir (DUAL) in treatment-naïve patients from mainland China, Russia and South Korea with hepatitis C virus (HCV) genotype 1b infection.

METHODS

Patients were randomly assigned (3:1) to receive 24 wk of treatment with DUAL (daclatasvir 60 mg once daily and asunaprevir 100 mg twice daily) beginning on day 1 of the treatment period (immediate treatment arm) or following 12 wk of matching placebo (placebo-deferred treatment arm). The primary endpoint was a comparison of sustained virologic response at posttreatment week 12 (SVR12) compared with the historical SVR rate for peg-interferon plus ribavirin (70%) among patients in the immediate treatment arm. The first 12 wk of the study were blinded. Safety was assessed in DUAL-treated patients compared with placebo patients during the first 12 wk (double-blind phase), and during 24 wk of DUAL in both arms combined.

RESULTS

In total, 207 patients were randomly assigned to immediate ($n = 155$) or placebo-deferred ($n = 52$) treatment. Most patients were Asian (86%), female (59%) and aged < 65 years (90%). Among them, 13% had cirrhosis, 32% had *IL28B* non-CC genotypes and 53% had baseline HCV RNA levels of ≥ 6 million IU/mL. Among patients in the immediate treatment arm, SVR12 was achieved by 92% (95% confidence interval: 87.2-96.0), which was significantly higher than the historical comparator rate (70%). SVR12 was largely unaffected by cirrhosis (89%), age ≥ 65 years (92%), male sex (90%), baseline HCV RNA ≥ 6 million (89%) or *IL28B* non-CC genotypes (96%), although SVR12 was higher among patients without (96%) than among those with (53%) baseline NS5A resistance-associated polymorphisms (at L31 or Y93H). During the double-blind phase, aminotransferase elevations were more common among placebo recipients than among patients receiving DUAL. During 24 wk of DUAL therapy (combined arms), the most common adverse events ($\geq 10\%$) were elevated alanine aminotransferase and upper respiratory tract infection; emergent grade 3-4 laboratory abnormalities were infrequently observed, and all grade 3-4 aminotransferase abnormalities (alanine aminotransferase, $n = 9$; aspartate transaminase, $n = 6$) reversed within 8-11 d. Two patients discontinued DUAL treatment; one due to aminotransferase elevations, nausea, and jaundice and the other due to a fatal adverse event unrelated to treatment. There were no treatment-related deaths.

CONCLUSION

DUAL was well-tolerated during this phase 3 study, and SVR12 with DUAL treatment (92%) exceeded the

historical SVR rate for peg-interferon plus ribavirin of 70%.

Key words: Asunaprevir; Daclatasvir; Direct-acting antiviral; Chronic hepatitis C; Liver disease; NS3; NS5A; Genotype 1b

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Core tip: This phase 3, placebo-controlled study assessed the efficacy and safety of daclatasvir (NS5A inhibitor) plus asunaprevir (NS3/4A protease inhibitor) in treatment-naïve patients from mainland China, Russia and South Korea with hepatitis C virus (HCV) genotype 1b infection. The rate of sustained virologic response at posttreatment week 12 among patients in the immediate treatment arm was 92%, which was significantly higher than the historical comparator rate (70%). The combination was well tolerated during 24 wk of treatment. These results demonstrate that for countries such as China, where interferon-based combinations are still widely used for the treatment of HCV genotype 1b, daclatasvir/asunaprevir offers a more efficacious and tolerable alternative with a shorter treatment duration.

Wei L, Wang FS, Zhang MX, Jia JD, Yakovlev AA, Xie W, Burnevich E, Niu JQ, Jung YJ, Jiang XJ, Xu M, Chen XY, Xie Q, Li J, Hou JL, Tang H, Dou XG, Gandhi Y, Hu WH, McPhee F, Noviello S, Treitel M, Mo L, Deng J. Daclatasvir plus asunaprevir in treatment-naïve patients with hepatitis C virus genotype 1b infection. *World J Gastroenterol* 2018; 24(12): 1361-1372 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i12/1361.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i12.1361>

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a significant health burden across Asia^[1], and affects 5-7 million people in China alone^[2]. Without effective treatment, patients can develop severe complications, such as hepatocellular carcinoma (HCC)^[3,4], for which HCV infection has become one of the most common causes in Asian and Western countries^[5,6].

DUAL is an all-oral combination of daclatasvir (pan-genotypic NS5A inhibitor with *in vitro* activity against genotypes 1-6)^[7,8] and asunaprevir (NS3 protease inhibitor with *in vitro* activity against genotypes 1 and 4-6)^[9]. This regimen has demonstrated efficacy in several phase 3 studies of patients infected with HCV genotype 1b^[10-13], the predominant genotype in East Asia^[14-16], including those with characteristics known to attenuate response to interferon (IFN)-based treatment^[17-19]. DUAL also has a superior safety profile compared with IFN-based combinations^[20] and in April

2017 became the first all-oral, nonribavirin-containing combination for chronic HCV infection to gain approval in China^[21].

In this study, we evaluated the efficacy and safety of DUAL in treatment-naïve patients from mainland China, South Korea and Russia with HCV genotype 1b infection.

MATERIALS AND METHODS

Study design and treatment

This was a phase 3, double-blind, placebo-controlled study (ClinicalTrials.gov number, NCT02496078) of DUAL, conducted between August 2015 and February 2017 in treatment-naïve patients from mainland China, South Korea and Russia with chronic HCV genotype 1b infection. Patients were randomly assigned (3:1) to receive DUAL (daclatasvir 60 mg tablet once daily and asunaprevir 100 mg soft capsule twice daily) for 24 wk either immediately (immediate treatment arm) or after 12 wk of matching placebo (placebo-deferred treatment arm) via an interactive voice-response system, and stratified according to the presence or absence of cirrhosis. Treatment was blinded to patients, investigators and the sponsor until week 12, and was open label thereafter.

The study was conducted according to local laws and regulatory requirements, and in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization and the principles of the Declaration of Helsinki. Written informed consent was gained prior to study initiation.

Patients

The study population comprised male and female patients aged ≥ 18 years (body mass index: 18-35 kg/m²) with chronic HCV genotype 1b infection (HCV RNA of ≥ 10000 IU/mL at screening) and no prior exposure to any IFN formulation, ribavirin or direct-acting antiviral agent for HCV. Patients with compensated cirrhosis were included (enrollment capped at approximately 25%). Cirrhosis status was defined by a hierarchical algorithm based on available biopsy, Fibroscan[®] or Fibrotest[®] (BioPredictive, Paris, France) and aspartate transaminase (AST):platelet ratio index (APRI) data. Patients were considered noncirrhotic if they met one of the following criteria: liver biopsy within 36 mo of screening showing absence of cirrhosis; Fibroscan[®] result of ≤ 9.6 kPa within 1 year of baseline/day 1; or FibroTest[®] score of ≤ 0.48 with APRI of ≤ 1 (performed during screening). Patients were considered cirrhotic if they met one of the following criteria: liver biopsy showing cirrhosis any time prior to screening; Fibroscan[®] showing cirrhosis or results of > 14.6 kPa within 1 year of baseline; or FibroTest[®] score of > 0.75 and an APRI of > 2 (at screening). Both sets of criteria are listed in decreasing hierarchical order.

Key exclusion criteria included: HCV infection other

than genotype 1b; evidence of a medical condition contributing to chronic liver disease other than HCV, or of decompensated liver disease (*e.g.*, history or presence of ascites, bleeding varices, or hepatic encephalopathy); diagnosed or suspected HCC or other malignancies; uncontrolled diabetes or hypertension; moderate to severe depression (well-controlled mild depression was permitted); total bilirubin $\geq 34 \mu\text{mol/L}$ (or $\geq 2 \text{ mg/dL}$) unless the patient had a documented history of Gilbert's disease; alanine aminotransferase (ALT) $\geq 5 \times$ the upper limit of normal; albumin $< 3.5 \text{ g/dL}$; alpha-fetoprotein $> 100 \text{ ng/mL}$ (patients with alpha-fetoprotein 50–100 ng/mL required a liver ultrasound, and those with findings suspicious of HCC were excluded); hemoglobin $< 8.5 \text{ g/dL}$; absolute neutrophil count $< 0.5 \times 10^9 \text{ cells/L}$; and, platelet count $< 50 \times 10^9 \text{ cells/L}$.

Study assessments

HCV RNA was quantified using the COBAS® *TaqMan*® assay v2.0 (Roche Molecular Diagnostics, Pleasanton, CA, United States) with a lower limit of quantitation (LLOQ) of 25 IU/mL. HCV genotype and subtype were determined using the RealTime HCV Genotype II assay (Abbott Molecular, Des Plaines, IL, United States); if the results were inconclusive, the Versant HCV Genotype 2.0 assay (Siemens, Erlangen, Germany) or population-based sequencing of the NS5A region was employed. *IL28B* rs12979860 single-nucleotide polymorphisms were identified using PCR amplification and sequencing (*TaqMan* assay; Applied Biosystems, Waltham, MA, United States).

Treatment failure comprised: virologic breakthrough, defined as any confirmed $> 1 \log_{10}$ increase in HCV RNA from nadir, or increase in HCV RNA \geq LLOQ after confirmed HCV RNA $<$ LLOQ target detected or not detected (TD or TND) during treatment; HCV RNA $<$ LLOQ but still detectable at end of treatment (EOT); or, relapse, defined as HCV RNA \geq LLOQ in any posttreatment window following HCV RNA $<$ LLOQ TND at EOT.

Resistance testing was performed using population-based sequencing (threshold $\geq 20\%$ of a viral population) of the NS5A and NS3 regions on all available plasma samples at baseline, and on the samples of patients experiencing treatment failure with HCV RNA $\geq 1000 \text{ IU/mL}$.

Safety was monitored based on incidence of adverse events (AEs) and abnormalities in clinical laboratory assessments, vital signs and physical examinations.

Study endpoints

The primary efficacy outcome was the proportion of patients, randomly assigned to the immediate treatment arm, achieving a sustained virologic response (HCV RNA $<$ LLOQ, TD or TND) at posttreatment week 12 (SVR12), and the primary endpoint was comparison of this outcome against a historical SVR rate of 70%

associated with peg-IFN plus ribavirin treatment.

SVR12 in the placebo-deferred treatment arm was a secondary endpoint. Safety-related secondary endpoints included the incidence of AEs, serious (S)AEs, discontinuations due to AEs, deaths, and grade 3–4 laboratory abnormalities observed during the 12-wk double-blind phase (DUAL vs placebo), and in both arms during 24 wk of treatment with DUAL. Efficacy-related secondary endpoints included SVR12 according to rs12979860 single-nucleotide polymorphisms in the *IL28B* gene; the proportion of patients achieving HCV RNA $<$ LLOQ, TD or TND and TND only, in each treatment arm at on-treatment weeks 1, 2, 4, 6, 8, and 12, both on-treatment weeks 4 and 12, EOT, and post-treatment weeks 4 and 24.

Statistical analysis

The statistical methods used in this study were reviewed by the biometrics group at Bristol-Myers Squibb. The primary objective was to determine whether SVR12 among patients in the immediate treatment arm would be significantly higher than the historical 70% SVR rate associated with peg-IFN plus ribavirin. The lower bound of a two-sided 95% confidence interval (CI) for SVR12 was used to compare to the historical SVR rate; if it exceeded 70%, it was concluded that the primary objective was met and SVR12 for patients in the immediate treatment arm was significantly higher than the SVR rate associated with peg-IFN plus ribavirin. A sample size of approximately 150 patients would have provided a 95%CI with a lower bound exceeding 70% for a corresponding SVR12 rate of approximately 77.3% or higher, while an SVR12 rate of 90% would have provided a lower bound not less than 85%. Missing HCV RNA data at posttreatment week 12 were imputed using the next value carried backwards approach, where the next and closest available HCV RNA measurement after posttreatment week 12 was utilized instead.

RESULTS

Patient disposition

In total, 229 patients were enrolled, of whom 207 were randomly assigned to the immediate ($n = 155$) or placebo-deferred ($n = 52$) treatment arms.

Of 155 patients assigned to the immediate treatment arm, all completed the 12-wk double-blind phase, 148 completed 24 wk of treatment with DUAL, and 151 completed 24 wk of follow-up; seven discontinued treatment with DUAL due to lack of efficacy ($n = 6$) or AEs ($n = 1$), and four discontinued follow-up after posttreatment week 12 due to withdrawal of consent ($n = 3$) or inability to attend the visit due to an accident ($n = 1$).

Of 52 patients randomly assigned to placebo-deferred treatment, 51 completed the 12-wk double-blind phase, 44 completed 24 wk of treatment with DUAL, and 48 completed 24 wk of follow-up; one discontinued placebo due to an SAE (hepatitis E),

Table 1 Baseline demographics and disease characteristics *n* (%)¹

Characteristic	Immediate treatment, <i>n</i> = 155 ²	Placebo-deferred treatment, <i>n</i> = 52	Overall, <i>n</i> = 207 ²
Age, median (range) years	49 (18-73)	49 (23-69)	49 (18-73)
< 65 yr	142 (92)	45 (87)	187 (90)
≥ 65 yr	13 (8)	7 (14)	20 (10)
Male	61 (39)	23 (44)	84 (41)
Race			
Asian	132 (85)	45 (87)	177 (86)
White	23 (15)	7 (14)	30 (15)
Country			
Mainland China	119 (77)	42 (81)	161 (78)
Russia	23 (15)	7 (14)	30 (15)
South Korea	13 (8)	3 (6)	16 (8)
HCV RNA, median (range) log ₁₀ IU/mL	6.78 (3.1-7.6)	6.86 (5.6-7.6)	6.79 (3.1-7.6)
≥ 6 million IU/mL	79 (51)	31 (60)	110 (53)
<i>IL28B</i> genotype			
CC	107 (69)	34 (65)	141 (68)
CT	43 (28)	17 (33)	60 (29)
TT	5 (3)	1 (2)	6 (3)
Cirrhosis	19 (12)	7 (14)	26 (13)

¹Unless otherwise stated; ²Includes one patient from mainland China who was subsequently reclassified as having HCV genotype 1a infection by phylogenetic analysis of the HCV NS5A sequence. HCV: Hepatitis C virus.

seven discontinued treatment with DUAL due to lack of efficacy (*n* = 6) or AEs (*n* = 1), and two discontinued follow-up after posttreatment week 12 due to withdrawal of consent (*n* = 1) or initiation of alternative HCV therapy (*n* = 1).

Baseline characteristics

The majority of patients were Chinese (77.8%) and female (60.6%); among them, 12.6% had compensated cirrhosis, 31.9% had *IL28B* non-CC genotypes, 53.1% had baseline HCV RNA ≥ 6 million IU/mL and 9.7% were aged 65 years or older (Table 1). These data include six patients who were found not to meet the study enrollment criteria after treatment initiation; one of these patients, from mainland China, was reclassified as having genotype 1a infection, and five had received prior treatment with ribavirin and/or IFN regimens.

Efficacy endpoints

The study met its primary endpoint, with SVR12 achieved by 142 (91.6%, 95%CI: 87.2-96.0) patients in the immediate treatment arm (including the patient with HCV genotype 1a infection), significantly above the 70% historical comparator (Figure 1). SVR12 was comparable between patients from mainland China (110/119, 92.4%) and Russia (22/23, 95.7%), although lower among the smaller cohort of patients from South Korea (10/13, 76.9%). SVR12 in this arm was also comparable between patients with (17/19, 89.5%) and without (125/136, 91.9%) cirrhosis, with *IL28B* CC (96/107, 89.7%) and non-CC genotypes (46/48, 95.8%), aged < 65 (130/142, 91.5%) and ≥ 65 (12/13, 92.3%) years, with baseline HCV RNA < 6 million (72/76, 94.7%) and ≥ 6 million (70/79, 88.6%) IU/mL, and between male (55/61, 90.2%) and female

(87/94, 92.6%) patients (Figure 2). HCV RNA declined rapidly from baseline, and by week 4 was undetectable in 140 (90.3%) patients.

SVR12 rates in the placebo-deferred treatment arm, overall and according to selected baseline characteristics, are provided in Figures 3 and 4.

Treatment failure

Thirteen (8.4%) patients in the immediate treatment arm failed to achieve SVR12. Six patients experienced virologic breakthrough [mainland China (*n* = 4), South Korea (*n* = 1), and Russia (*n* = 1)], one patient from mainland China had detectable HCV RNA at EOT, and six patients relapsed [mainland China (*n* = 4) and South Korea (*n* = 2)] (Figure 1).

Treatment failure in the placebo-deferred treatment arm is described in Figure 3.

Resistance analysis

Resistance analyses were conducted at baseline for 154 patients in the immediate treatment arm (excluding the patient with HCV genotype 1a infection) (Tables 2 and 3). Daclatasvir resistance-associated polymorphisms at NS5A amino acid positions L31 or Y93H preexisted in 17 (11.0%) patients, 9 of whom (52.9%) achieved SVR12. By contrast, SVR12 was achieved by 132 of 137 (96.4%) patients without baseline NS5A-L31 or NS5A-Y93H, and was comparably high among patients with (17/19, 89.5%) and without (115/118, 97.5%) cirrhosis who did not have baseline resistance-associated polymorphisms.

The asunaprevir resistance-associated polymorphism NS3-D168E preexisted in one (0.6%) patient who did not achieve SVR12; this patient also had NS5A-Y93H at baseline. Of the 13 patients in the immediate treatment

Table 2 SVR12 in hepatitis C virus genotype 1b-infected patients with and without resistance-associated polymorphisms at baseline (immediate treatment arm) *n* (%)

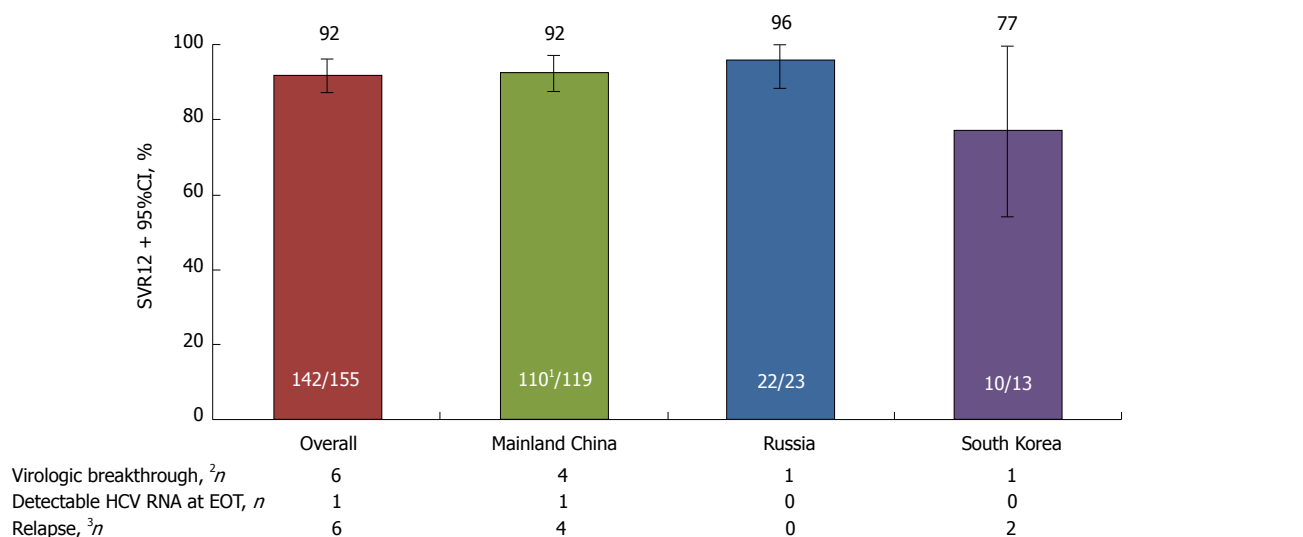
All patients - immediate treatment arm								
	With RAPs at baseline				Without RAPs at baseline			
	Mainland China	Russia	South Korea	Overall	Mainland China	Russia	South Korea	Overall
NS5A-L31M/V	1/1 (100)	1/1(100)	0	2/2 (100)	108/117 (92.3)	21/22 (95.5)	10/13 (76.9)	139/152 (91.4)
Y93H	7/13(53.8)	0	0/2 (0)	7/15 (46.7)	102/105 (97.1)	22/23 (95.7)	10/11(90.9)	134/139 (96.4)
L31M/V or Y93H	8/14 (57.1)	1/1 (100)	0/2 (0)	9/17 (52.9)	101/104 (97.1)	21/22 (95.5)	10/11(90.9)	132/137 (96.4)
NS3-D168E	0/1 (0)	0	0	0/1 (0)	109/117 (93.2)	22/23 (95.7)	10/13 (76.9)	141/153 (92.2)

RAP: Resistance-associated polymorphism; SVR12: Sustained virologic response at posttreatment week 12.

Table 3 SVR12 in cirrhotic and non-cirrhotic hepatitis C virus genotype 1b-infected patients with and without resistance-associated polymorphisms at baseline (immediate treatment arm) *n* (%)

Patients with cirrhosis - immediate treatment arm								
	With RAPs at baseline				Without RAPs at baseline			
	Mainland China	Russia	South Korea	Overall	Mainland China	Russia	South Korea	Overall
Patients with cirrhosis								
NS5A-L31M/V	0	0	0	0	15/16 (93.8)	0	2/3 (66.7)	17/19 (89.5)
Y93H	0	0	0	0	15/16 (93.8)	0	2/3 (66.7)	17/19 (89.5)
L31M/V or Y93H	0	0	0	0	15/16 (93.8)	0	2/3 (66.7)	17/19 (89.5)
NS3-D168E	0	0	0	0	15/16 (93.8)	0	2/3 (66.7)	17/19 (89.5)
Patients without cirrhosis								
NS5A-L31M/V	1/1 (100)	1/1 (100)	0	2/2 (100)	93/101 (92.1)	21/22 (95.5)	8/10 (80.0)	122/133 (91.7)
Y93H	7/13 (53.8)	0	0/2 (0)	7/15 (46.7)	87/89 (97.8)	22/23 (95.7)	8/8 (100)	117/120 (97.5)
L31M/V or Y93H	8/14 (57.1)	1/1 (100)	0/2 (0)	9/17 (52.9)	86/88 (97.7)	21/22 (95.5)	8/8 (100)	115/118 (97.5)
NS3-D168E	0/1 (0)	0	0	0/1 (0)	94/101 (93.1)	22/23 (95.7)	8/10 (80.0)	124/134 (92.5)

RAP: Resistance-associated polymorphism; SVR12: Sustained virologic response at posttreatment week 12.

**Figure 1 SVR12 in the immediate treatment arm.** ¹Includes the patient with genotype 1a infection; ²On-treatment HCV RNA \geq LLOQ after < LLOQ, or increased > 1 log₁₀ over nadir; ³Posttreatment HCV RNA \geq LLOQ after < LLOQ without detectable target at EOT. EOT: End of treatment; HCV: Hepatitis C virus; LLOQ: Lower limit of quantitation; SVR12: Sustained virologic response at post-treatment week 12.

arm who failed to achieve SVR12, 8 (61.5%) had the NS5A-Y93H polymorphism at baseline, including the patient who also had baseline NS3-D168E. At treatment failure, all 13 patients had emergent NS5A-L31 and/or

NS5A-Y93H substitutions, while 10 of these patients also had emergent NS3-D168 substitutions (A/E/H/V/Y).

The impact of baseline resistance-associated polymorphisms on SVR12 in the placebo-deferred arm

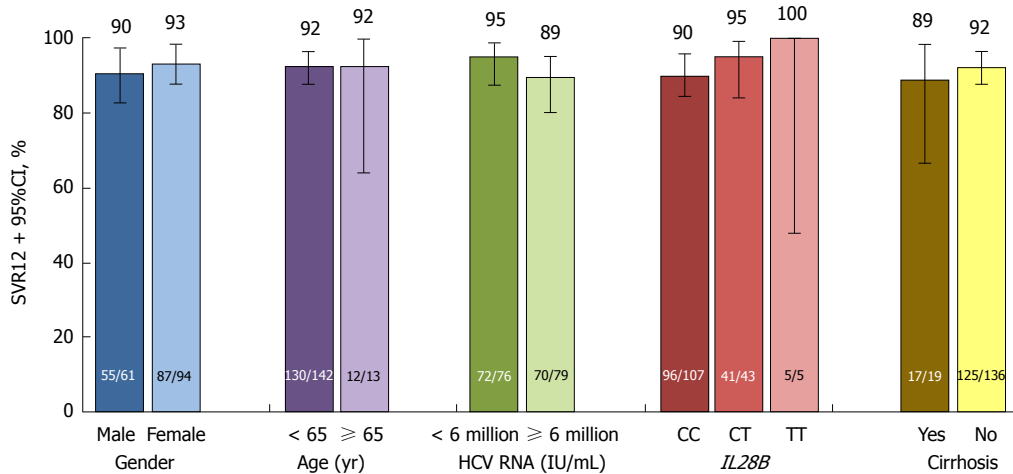
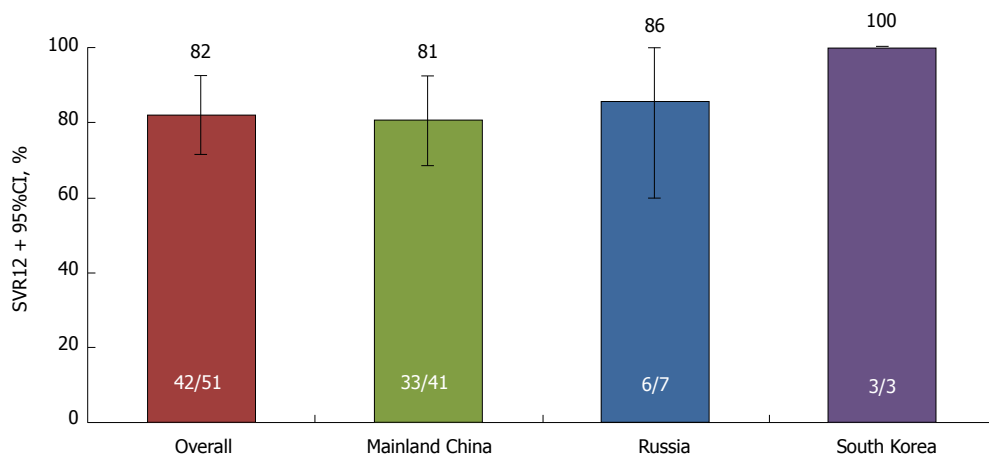


Figure 2 SVR12 according to selected baseline characteristics in the immediate treatment arm. HCV: Hepatitis C virus; SVR12: Sustained virologic response at posttreatment week 12.



Virologic breakthrough, ¹*n*
 Detectable HCV RNA at EOT, *n*
 Relapse, ²*n*
 Other, ³*n*

	Overall	Mainland China	Russia	South Korea
Virologic breakthrough, ¹ <i>n</i>	7	7	0	0
Detectable HCV RNA at EOT, <i>n</i>	0	0	0	0
Relapse, ² <i>n</i>	1	1	0	0
Other, ³ <i>n</i>	1	0	1 ⁴	0

Figure 3 SVR12 in the placebo-deferred treatment arm. ¹On-treatment HCV RNA ≥ LLOQ after < LLOQ, or increased >1 log₁₀ over nadir; ²HCV RNA < LLOQ (TND) at EOT followed by HCV RNA ≥ LLOQ at any follow-up visit; ³Other nonresponders included patients who had HCV RNA < LLOQ (TND) at EOT, but with missing posttreatment week 12 data; ⁴Death, not considered related to study therapy (stab wound). EOT: End of treatment; HCV: Hepatitis C virus; LLOQ: Lower limit of quantitation; SVR12, Sustained virologic response at post-treatment week 12.

is shown in Tables 4 and 5.

Safety and tolerability

The safety outcomes observed during the 12-wk double-blind phase are summarized in Table 6. Five (3.2%) patients in the immediate-treatment arm had SAEs considered related [study drug overdose (*n* = 2)] or unrelated to treatment [ventricular extra-systoles (*n* = 1), acute cholecystitis (*n* = 1) and intervertebral disc protrusion (*n* = 1)], and three (5.8%) patients in the placebo-deferred treatment arm had SAEs [ALT elevation (*n* = 1), coronary artery disease (*n* = 1), and hepatitis E virus infection plus liver injury (*n* = 1; leading to study discontinuation)] while receiving placebo. No treatment-related deaths were observed

during the study.

The most common AEs (any grade) occurring in > 5% of patients in either arm during the initial 12-weeks of treatment with DUAL (immediate treatment arm) compared with placebo (placebo-deferred arm) were elevated ALT (3.2% vs 23.1%), elevated AST (1.3% vs 15.4%), hypertension (7.1% vs 7.7%), upper respiratory tract infection (6.5% vs 5.8%), platelet count decrease (1.9% vs 7.7%) and pyrexia (0.6% vs 5.8%). The most common grade 3-4 laboratory abnormalities during this period (DUAL vs placebo) were related to ALT (0.6% vs 9.6%), AST (0.6% vs 5.8%), total bilirubin (0.6% vs 0%) and hemoglobin (1.9% vs 0%).

The safety outcomes observed during 24 wk of

Table 4 SVR12 in hepatitis C virus genotype 1b-infected patients with and without resistance-associated polymorphisms at baseline (placebo-deferred treatment arm) *n* (%)

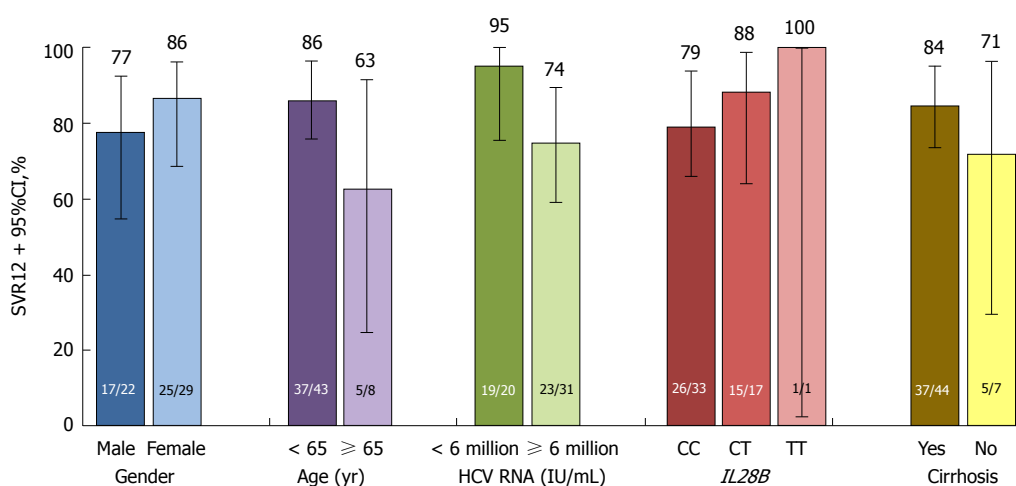
All patients - placebo-deferred treatment arm								
	With RAPs at baseline				Without RAPs at baseline			
	Mainland China	Russia	South Korea	Overall	Mainland China	Russia	South Korea	Overall
NS5A-L31M/V	0	0	0	0	33/41 (80.5)	6/6 (100)	3/3 (100)	42/50 (84.0)
Y93H	2/8 (25.0)	0	0	2/8 (25.0)	31/33 (93.9)	6/6 (100)	3/3 (100)	40/42 (95.2)
L31M/V or Y93H	2/8 (25.0)	0	0	2/8 (25.0)	31/33 (93.9)	6/6 (100)	3/3 (100)	40/42 (95.2)
NS3-D168E	0	0	0	0	33/41 (80.5)	6/6 (100)	3/3 (100)	42/50 (84.0)

RAP: Resistance-associated polymorphism; SVR12: Sustained virologic response at posttreatment week 12.

Table 5 SVR12 in cirrhotic and noncirrhotic hepatitis C virus genotype-1b-infected patients with and without resistance-associated polymorphisms at baseline (placebo-deferred treatment arm) *n* (%)

Patients with cirrhosis - placebo-deferred treatment arm								
	With RAPs at baseline				Without RAPs at baseline			
	Mainland China	Russia	South Korea	Overall	Mainland China	Russia	South Korea	Overall
Patients with cirrhosis								
NS5A-L31M/V	0	0	0	0	3/5 (60.0)	1/1 (100)	1/1 (100)	5/7 (71.4)
Y93H	1/3 (33.3)	0	0	1/3 (33.3)	2/2 (100)	1/1 (100)	1/1 (100)	4/4 (100)
L31M/V or Y93H	1/3 (33.3)	0	0	1/3 (33.3)	2/2 (100)	1/1 (100)	1/1 (100)	4/4 (100)
NS3-D168E	0	0	0	0	3/5 (60.0)	1/1 (100)	1/1 (100)	5/7 (71.4)
Patients without cirrhosis								
NS5A-L31M/V	0	0	0	0	30/36 (83.3)	5/5 (100)	2/2 (100)	37/43 (86.0)
Y93H	1/5 (20.0)	0	0	1/5 (20.0)	29/31 (93.5)	5/5 (100)	2/2 (100)	36/38 (94.7)
L31M/V or Y93H	1/5 (20.0)	0	0	1/5 (20.0)	29/31 (93.5)	5/5 (100)	2/2 (100)	36/38 (94.7)
NS3-D168E	0	0	0	0	30/36 (83.3)	5/5 (100)	2/2 (100)	37/43 (86.0)

RAP: Resistance-associated polymorphism; SVR12: Sustained virologic response at posttreatment week 12.

**Figure 4 SVR12 according to selected baseline characteristics in the placebo-deferred treatment arm¹.** ¹Reasons for patients not achieving SVR12 included virologic breakthrough (*n* = 7), relapse (*n* = 1) or other (*n* = 1; death, not considered related to study therapy). HCV: Hepatitis C virus; SVR12: Sustained virologic response at post-treatment week 12.

DUAL treatment in either arm are summarized in Table 7. Two (1.3%) patients in the immediate treatment arm had SAEs deemed unrelated to treatment [appendicitis (*n* = 1) and retinal detachment (*n* = 1)] in addition to the five patients with SAEs during the 12-wk double-blind phase. One (2.0%) patient in the placebo-deferred

treatment arm (excluding the patient who discontinued during the 12-wk double-blind phase) discontinued due to fatality unrelated to treatment (stab wound). One patient in the immediate treatment arm discontinued after twice meeting the biochemical criteria for Hy's law. On day 118, treatment was interrupted for this

Table 6 Safety during the 12-wk double-blind period *n* (%)

Parameter	Immediate treatment, <i>n</i> = 155	Placebo-deferred treatment, <i>n</i> = 52
AEs leading to discontinuation	0 (0)	1 (2) ¹
Serious AEs	5 (3) ²	3 (6) ^{1,3}
AEs (any grade), ≥ 5%		
ALT elevation	5 (3)	12 (23)
AST elevation	2 (1)	8 (15)
Hypertension	11 (7)	4 (8)
Upper respiratory tract infection	10 (6)	3 (6)
Platelet count decrease	3 (2)	4 (8)
Pyrexia	1 (1)	3 (6)
On-treatment grade 3-4 laboratory abnormalities		
ALT	1 (1)	5 (10)
AST	1 (1)	3 (6)
Total bilirubin	1 (1)	0 (0)
Hemoglobin	3 (2)	0 (0)

¹Hepatitis E virus infection and liver injury (*n* = 1); ²Treatment related: Study drug overdose (*n* = 2); Unrelated to treatment: Ventricular extrasystoles (*n* = 1), acute cholecystitis (*n* = 1) and intervertebral disc protrusion (*n* = 1); ³ALT elevation (*n* = 1) and coronary artery disease (*n* = 1). AE: Adverse event; ALT: Alanine transaminase; AST: Aspartate transaminase.

Table 7 Safety during 24 wk of daclatasvir plus asunaprevir treatment in either arm *n* (%)

Parameter	Immediate treatment, <i>n</i> = 155	Placebo-deferred treatment, <i>n</i> = 51 ¹	Overall, <i>n</i> = 206
AEs leading to discontinuation	1 (1) ²	1 (2) ³	2 (1)
Serious AEs	7 (5) ^{4,5}	1 (2) ³	8 (4)
Deaths	0 (0)	1 (2) ³	1 (< 1)
AEs (any grade), ≥ 5%			
ALT elevation	17 (11)	5 (10)	22 (11)
Upper respiratory tract infection	13 (8)	8 (16)	21 (10)
Hypertension	11 (7)	6 (12)	17 (8)
AST elevation	13 (8)	3 (6)	16 (8)
INR elevation ⁶	11 (7)	2 (4)	13 (6)
Blood bilirubin elevation	12 (8)	0 (0)	12 (6)
Fatigue	5 (3)	6 (12)	11 (5)
On-treatment grade 3-4 laboratory abnormalities			
ALT	7 (5) ²	2 (4) ⁷	9 (4)
AST	5 (3) ²	1 (2) ⁷	6 (3)
Total bilirubin	1 (1)	0 (0)	1 (< 1)
Hemoglobin	3 (2)	0 (0)	3 (1)
Platelets	1 (1)	0 (0)	1 (< 1)
Absolute lymphocyte count	0 (0)	1 (2)	1 (< 1)
Absolute neutrophil count	1 (1)	0 (0)	1 (< 1)
Lipase	3 (2)	0 (0)	3 (1)

¹Excludes the patient who discontinued during the double-blind phase; ²jaundice and nausea, which followed concomitant but reversible treatment-related ALT, AST and total bilirubin elevations (patient met the biochemical criteria for Hy's law; aminotransferases, jaundice and nausea resolved off-treatment and patient achieved SVR12); ³Fatality (stab wound) unrelated to treatment; ⁴Treatment related: Study drug overdose (*n* = 2); ⁵Unrelated to treatment: Ventricular extrasystoles (*n* = 1), acute cholecystitis (*n* = 1), intervertebral disc protrusion (*n* = 1), retinal detachment (*n* = 1) and appendicitis (*n* = 1); ⁶No grade 3-4 INR laboratory abnormalities were observed; ⁷One patient experienced vomiting, decreased appetite and myalgia (all resolved), plus grade 3 ALT and AST abnormalities (both reversible), and interrupted DUAL treatment for 2 d (patient achieved SVR12). AE: Adverse event; ALT: Alanine transaminase; AST: Aspartate transaminase; INR: International normalized ratio.

patient until day 124 due to grade 3 ALT (320 U/L) and AST (237 U/L), grade 2 bilirubin (36.3 μmol/L), and grade 1 alkaline phosphatase (201 U/L). By day 133, the patient's AST level had improved to 195 U/L (grade 3), but levels of ALT (223 U/L) and blood bilirubin (37.6 μmol/L) remained elevated. On day 141, the patient's blood bilirubin and ALT levels had improved to 32.5 μmol/L (grade 2) and 155 U/L (grade 2), respectively; however, he was diagnosed with grade 2 AST (152 U/L) and grade 2 AEs of jaundice and nausea. Given this

patient's already elevated levels of ALT, AST and alkaline phosphatase, he met the biochemical criteria for Hy's law for a second time and discontinued treatment the next day. All events resolved by day 152 and the patient achieved SVR12.

The most common AEs (any grade) occurring in > 5% of patients during 24 wk of treatment with DUAL in either treatment arm were elevated ALT (11%), upper respiratory tract infection (10%), hypertension (8%), elevated AST (8%), elevated international normalized

ratio (6%), elevated blood bilirubin (6%) and fatigue (5%). The most common grade 3-4 laboratory abnormalities were related to ALT (4%), AST (3%), hemoglobin (1%) or lipase (1%) (Table 7).

DISCUSSION

In this study, SVR12 was achieved by 91.6% of patients with HCV genotype 1b infection who were randomly assigned to receive immediate treatment with DUAL. With the lower bound of the corresponding 95%CI (87.2%) greater than the prespecified 70% threshold, the primary endpoint was met, confirming that DUAL is more efficacious than peg-IFN plus ribavirin in patients with HCV genotype 1b infection.

SVR12 was comparable between patients from mainland China (92.4%) and Russia (95.7%). By contrast, SVR12 was lower among patients from South Korea (76.9%); however, this was a small cohort and two of the three patients experiencing virologic failure had the NS5A-Y93H polymorphism at baseline, which has been shown to reduce SVR in patients with HCV genotype 1b infection receiving DUAL^[18,22,23]. SVR12 was also lower among patients in the placebo-deferred arm following treatment with DUAL (42/51, 82.4%); however, again this was a small cohort and six of the eight patients with virologic failure had the NS5A-Y93H polymorphism at baseline. Nonetheless, consistent with the results of other phase 3 studies, SVR12 was high overall and largely unaffected by characteristics known to attenuate response to IFN, namely cirrhosis, *IL28B* non-CC genotypes, male sex, advanced age, and high baseline HCV RNA^[10-13]. Virologic failure in the immediate treatment arm tended to coincide with the presence of baseline NS5A polymorphisms at L31M or Y93H, consistent with previous observations^[18]. Although the prevalence of NS5A-L31 or NS5A-Y93H was relatively low in this study (11.0%), the observed SVR12 rates were, consistent with previous reports, higher among patients without these baseline polymorphisms (132/137, 96.4%), including those with cirrhosis (17/19, 89.5%), compared with cirrhotic patients with these baseline polymorphisms (9/17, 52.9%).

During the 12-wk double-blind phase, SAEs and AEs leading to discontinuation were infrequently observed in the immediate (5/155, 3.2% and none) and placebo-deferred (3/52, 5.8% and 1/52, 1.9%) treatment arms. However, although the AE profiles were broadly comparable between the two arms, elevations of ALT and AST were more common among patients receiving placebo (12/52, 23.1% and 8/52, 15.4%) compared with those receiving DUAL (5/155, 3.2% and 2/155, 1.3%). Consistent with this, grade 3-4 ALT and AST laboratory abnormalities during the blinded phase were more common among patients receiving placebo compared with those receiving DUAL. These elevations most likely reflected ongoing inflammation from untreated HCV infection; indeed, ALT and AST levels in

most of these patients had begun to decrease by week 2 of open-label treatment with DUAL. One patient in the immediate treatment arm met the criteria for Hy's law during treatment with DUAL; however, following treatment discontinuation, the events resolved and the patient achieved SVR12.

DUAL was well tolerated during 24 wk of treatment in both arms, consistent with findings from other phase 3 studies^[10-12,19]. SAEs (8/206, 3.9%) and AEs leading to discontinuation (2/206, 1.0%) were infrequently observed and, except for two cases of study drug overdose, no SAEs were deemed treatment related. Emergent grade 3-4 laboratory abnormalities were similarly uncommon. The most common grade 3-4 laboratory abnormalities were related to ALT (9/206, 4.4%) and AST (6/206, 2.9%), however these reversed rapidly (median reversal times: 11.0 and 8.5 d for ALT and AST abnormalities, respectively) during or after treatment, and their incidences were comparable with those observed in other studies^[10,24-26].

A limitation of this study was the absence of a direct IFN-based comparator for the primary efficacy endpoint. However, despite the continuing importance of IFN-based treatment across much of Asia, it was felt that including an IFN-based treatment arm in the study design would have been unethical. Peg-IFN is associated with a high burden of systemic AEs that include "flu-like" symptoms, neutropenia and thrombocytopenia^[27], while ribavirin is associated with hemolytic anemia, birth defects, nausea, rash, itching, coughing and hyperuricemia^[28,29]. The result is a combination with poor treatment adherence and a high rate of study discontinuations due to AEs^[30]. Comparing DUAL, an all-oral combination with superior efficacy and safety profiles, to peg-IFN plus ribavirin, a combination containing an injectable drug with inferior efficacy and safety profiles, would therefore have lacked clinical equipoise. We also acknowledge that some patients were denied access to DUAL for 12 wk during the double-blind phase; however, as liver disease progresses slowly in patients with HCV infection, we do not believe that giving placebo instead of active treatment for 12 wk in compensated, treatment-naïve patients posed any ethical concerns.

In conclusion, the findings of this study showed that the all-oral DUAL combination of daclatasvir plus asunaprevir was highly effective and well tolerated in treatment-naïve patients from mainland China, Russia and South Korea with HCV genotype 1b infection. For patients in China, where IFN-based combinations have been considered the standard of care for HCV infection, DUAL was the first all-oral, nonribavirin-containing combination to gain approval, providing patients with access to a more efficacious and tolerable alternative for the treatment of HCV genotype 1b infection, with an easier route of administration and shorter treatment duration. DUAL is also predicted to be a cost-effective treatment alternative for HCV genotype 1b in China^[31]. In addition, in countries such as Japan, where all-

oral regimens are considered the standard of care for the treatment of HCV genotype 1b infection, DUAL is expected to be cost-saving compared with sofosbuvir/ledipasvir, with similar health outcomes^[32].

ARTICLE HIGHLIGHTS

Research background

Chronic hepatitis C virus (HCV) infection is a significant health burden across Asia, and affects 5-7 million people in China alone. Without effective treatment, patients can develop severe complications, such as cirrhosis or hepatocellular carcinoma. Previous therapies for the treatment of chronic HCV infection have been based on a combination of peg-interferon and ribavirin, both of which are associated with a high burden of adverse events (AEs) that contribute to poor treatment adherence and high rates of treatment discontinuations.

Research motivation

Daclatasvir plus asunaprevir (DUAL) is an all-oral combination of daclatasvir, an HCV NS5A inhibitor, and asunaprevir, an NS3 protease inhibitor. This regimen has previously demonstrated efficacy in several phase 3 studies of patients infected with HCV genotype 1b, including those characteristics known to attenuate response to interferon-based therapies. In this study, we sought to evaluate the efficacy and safety of DUAL in treatment-naïve patients from mainland China, South Korea and Russia.

Research objectives

The primary efficacy objective of the study was to measure the rate of sustained virologic response at posttreatment week 12 (SVR12) and to determine if this rate was significantly higher than the historical rate of 70% associated with peg-interferon plus ribavirin. Safety was monitored based on incidence of AEs and abnormalities in clinical laboratory assessments, vital signs and physical examinations.

Research methods

This was a phase 3, double-blind, placebo-controlled study of DUAL in treatment-naïve patients from mainland China, South Korea and Russia with chronic HCV genotype 1b infection. Patients were randomly assigned (3:1) to receive DUAL (daclatasvir 60 mg tablet once daily and asunaprevir 100 mg soft capsule twice daily) for 24 wk either immediately (immediate treatment arm) or after 12 wk of matching placebo (placebo-deferred treatment arm).

Research results

An SVR12 rate of 91.6% (95% confidence interval: 87.2-96.0) was observed among patients in the immediate treatment arm, which was significantly higher than the historical comparator rate (70%). SVR12 was largely unaffected by cirrhosis (89%), age ≥ 65 years (92%), male sex (90%), baseline HCV RNA ≥ 6 million (89%), or *IL28B* non-CC genotypes (96%), although SVR12 was higher among patients without (96%) than among those with (53%) baseline NS5A resistance-associated polymorphisms (at L31 or Y93H). DUAL was well tolerated during 24 wk of therapy in this study; the most common AEs ($\geq 10\%$ in the combined arms) were elevated alanine aminotransferase and upper respiratory tract infection. Two patients discontinued DUAL treatment; one due to aminotransferase elevations, nausea and jaundice and the other due to a fatality unrelated to treatment. There were no treatment-related deaths.

Research conclusions

This study demonstrates that the all-oral DUAL combination of daclatasvir plus asunaprevir was highly effective and well tolerated in treatment-naïve patients with HCV genotype 1b infection from mainland China, Russia and South Korea.

Research perspectives

These findings suggest that for patients in many Asian countries, such as China, where interferon-based combinations have been considered the standard of care for HCV infection, DUAL offers a more efficacious and tolerable alternative for the treatment of HCV genotype 1b infection, with an

easier route of administration and shorter treatment duration.

ACKNOWLEDGMENTS

The authors would like to thank Phil Yin for support with the study. Editorial support was provided by Matthew Young of Articulate Science and was funded by Bristol-Myers Squibb.

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P- Reviewer: Köksal AS, Takahashi T **S- Editor:** Ma YJ
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ISSN 1007-9327

