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***Randomized Clinical Trial***

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

Wei L *et al*. Daclatasvir/asunaprevir for HCV genotype 1b

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**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 post-treatment 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%); 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 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 gender (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 (≥ 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; Chronic hepatitis C; Direct-acting antiviral; Genotype 1b; Liver disease; NS3; NS5A

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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 SVR12 rate 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 IFN-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.

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# 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, non-ribavirin-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 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 ≥ 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 non-cirrhotic if they met one of the following criteria: liver biopsy within 36 months of screening showing absence of cirrhosis; Fibroscan® result ≤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 > 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 ≥ 34 µmol/L (or ≥ 2 mg/dL) unless the patient had a documented history of Gilbert’s disease; alanine aminotransferase (ALT) ≥ 5 × the upper limit of normal; albumin < 3.5 g/dL; alpha-fetoprotein > 100 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 g/dL; absolute neutrophil count < 0.5 × 109 cells/L; and platelet count < 50 × 109 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, 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 (Applied Biosystems TaqMan assay, CA, United States).

Treatment failure comprised: virologic breakthrough, defined as any confirmed > 1 log10 increase in HCV RNA from nadir, or increase in HCV RNA ≥ 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 ≥ LLOQ in any post-treatment window following HCV RNA < LLOQ TND at EOT.

Resistance testing was performed using population-based sequencing (threshold ≥ 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 ≥ 1000 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 post-treatment 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 AEs (SAEs), 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 weeks 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%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 post-treatment week 12 were imputed using the next value carried backwards approach, where the next and closest available HCV RNA measurement after post-treatment 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 post-treatment 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), seven discontinued treatment with DUAL due to lack of efficacy (*n* = 6) or AEs (*n* = 1), and two discontinued follow-up after post-treatment 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%); 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 pre-existed in 17 (11.0%) patients, nine 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 pre-existed 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 arm who failed to achieve SVR12, eight (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 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 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 a fatal SAE that was 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 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 gender, 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 weeks 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, non-ribavirin-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 peginterferon 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 post-treatment week 12 (SVR12) and to determine if this rate was significantly higher than the historical rate of 70% associated with peg-IFN 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%CI: 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 gender (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 (≥ 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 fatal AE 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 IFN-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.

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**Table 1** **Baseline demographics and disease characteristics**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic, *n* (%)1** | **Immediate treatment*****n* = 1552** | **Placebo-deferred treatment*****n* = 52** | **Overall*****n* = 2072** |
| Age,median (range) years< 65 yr≥ 65 yr | 49 (18-73)142 (92)13 (8) | 49 (23-69)45 (87)7 (14) | 49 (18-73)187 (90)20 (10) |
| Male | 61 (39) | 23 (44) | 84 (41) |
| RaceAsianWhite | 132 (85)23 (15) | 45 (87)7 (14) | 177 (86)30 (15) |
| CountryMainland ChinaRussiaSouth Korea | 119 (77)23 (15)13 (8) | 42 (81)7 (14)3 (6) | 161 (78)30 (15)16 (8) |
| HCV RNA, median (range) log10 IU/mL≥ 6 million IU/mL | 6.78 (3.1–7.6)79 (51) | 6.86 (5.6–7.6)31 (60) | 6.79 (3.1–7.6)110 (53) |
| *IL28B* genotypeCCCTTT | 107 (69)43 (28)5 (3) | 34 (65)17 (33)1 (2) | 141 (68)60 (29)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.

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

|  |
| --- |
| **All patients – immediate treatment arm** |
| ***n* (%)** | **With RAPs at baseline** | **Without RAPs at baseline** |
| **Mainland China** | **Russia** | **South Korea** | **Overall** | **Mainland China** | **Russia** | **South Korea** | **Overall** |
| NS5A-L31M/VY93HL31M/V or Y93H | 1/1 (100)7/13(53.8)8/14 (57.1) | 1/1(100)01/1 (100) | 00/2 (0)0/2 (0) | 2/2 (100)7/15 (46.7)9/17 (52.9) | 108/117 (92.3)102/105 (97.1)101/104 (97.1) | 21/22 (95.5)22/23 (95.7)21/22 (95.5) | 10/13 (76.9)10/11(90.9)10/11(90.9) | 139/152 (91.4)134/139 (96.4)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 post-treatment 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)**

|  |
| --- |
| **Patients with cirrhosis – immediate treatment arm** |
| ***n* (%)** | **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/VY93HL31M/V or Y93H | 000 | 000 | 000 | 000 | 15/16 (93.8)15/16 (93.8)15/16 (93.8) | 000 | 2/3 (66.7)2/3 (66.7)2/3 (66.7) | 17/19 (89.5)17/19 (89.5)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/VY93HL31M/V or Y93H | 1/1 (100)7/13 (53.8)8/14 (57.1) | 1/1 (100)01/1 (100) | 00/2 (0)0/2 (0) | 2/2 (100)7/15 (46.7)9/17 (52.9) | 93/101 (92.1)87/89 (97.8)86/88 (97.7) | 21/22 (95.5)22/23 (95.7)21/22 (95.5) | 8/10 (80.0)8/8 (100)8/8 (100) | 122/133 (91.7)117/120 (97.5)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 post-treatment week 12.

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

|  |
| --- |
| **All patients – placebo-deferred treatment arm** |
| ***n* (%)** | **With RAPs at baseline** | **Without RAPs at baseline** |
| **Mainland China** | **Russia** | **South Korea** | **Overall** | **Mainland China** | **Russia** | **South Korea** | **Overall** |
| NS5A-L31M/VY93HL31M/V or Y93H | 02/8 (25.0)2/8 (25.0) | 000 | 000 | 02/8 (25.0)2/8 (25.0) | 33/41 (80.5)31/33 (93.9)31/33 (93.9) | 6/6 (100)6/6 (100)6/6 (100) | 3/3 (100)3/3 (100)3/3 (100) | 42/50 (84.0) 40/42 (95.2)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 post-treatment week 12.

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

|  |
| --- |
| **Patients with cirrhosis – placebo-deferred treatment arm** |
| ***n* (%)** | **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/VY93HL31M/V or Y93H | 01/3 (33.3)1/3 (33.3) | 000 | 000 | 01/3 (33.3)1/3 (33.3) | 3/5 (60.0)2/2 (100)2/2 (100) | 1/1 (100)1/1 (100)1/1 (100) | 1/1 (100)1/1 (100)1/1 (100) | 5/7 (71.4)4/4 (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/VY93HL31M/V or Y93H | 01/5 (20.0)1/5 (20.0) | 000 | 000 | 01/5 (20.0)1/5 (20.0) | 30/36 (83.3)29/31 (93.5)29/31 (93.5) | 5/5 (100)5/5 (100)5/5 (100) | 2/2 (100)2/2 (100)2/2 (100) | 37/43 (86.0)36/38 (94.7)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 post-treatment week 12.

**Table 6** **Safety during the 12-wk double-blind period**

|  |  |  |
| --- | --- | --- |
| **Parameter, *n* (%)** | **Immediate treatment*n* = 155** | **Placebo-deferred treatment*****n* = 52** |
| **AEs leading to discontinuation** | 0 (0) | 1 (2)1 |
| **Serious AEs** | 5 (3)2 | 3 (6)1,3 |
| **AEs (any grade), ≥ 5%**ALT elevationAST elevationHypertensionUpper respiratory tract infectionPlatelet count decreasePyrexia | 5 (3)2 (1)11 (7)10 (6)3 (2)1 (1) | 12 (23)8 (15)4 (8)3 (6)4 (8)3 (6) |
| **On-treatment grade 3-4 laboratory abnormalities**ALTASTTotal bilirubinHemoglobin | 1 (1)1 (1)1 (1)3 (2) | 5 (10)3 (6)0 (0)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**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter, *n* (%)** | **Immediate treatment*n* = 155** | **Placebo-deferred treatment*****n* = 511** | **Overall*****n* = 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 elevationUpper respiratory tract infectionHypertensionAST elevationINR elevation6Blood bilirubin elevationFatigue | 17 (11)13(8)11 (7)13 (8)11 (7)12 (8)5 (3) | 5 (10)8(16)6 (12)3 (6)2 (4)0 (0)6 (12) | 22 (11)21(10)17 (8)16 (8)13 (6)12 (6)11 (5) |
| **On-treatment grade 3–4 laboratory abnormalities**ALTASTTotal bilirubinHemoglobinPlateletsAbsolute lymphocyte countAbsolute neutrophil countLipase | 7 (5)25 (3)21 (1)3 (2)1 (1)0 (0)1 (1)3 (2) | 2 (4)71 (2)70 (0)0 (0)0 (0)1 (2)0 (0)0 (0) | 9 (4)6 (3)1 (< 1)3 (1)1 (< 1)1 (< 1)1 (< 1)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); 3fatal AE (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 days (patient achieved SVR12). AE: Adverse event; ALT: Alanine transaminase; AST: Aspartate transaminase; INR: International normalized ratio.



**Figure 1** **SVR12 in the immediate treatment arm.** 1Includes the patient with GT 1a infection; 2On-treatment HCV RNA ≥LLOQ after <LLOQ, or increased >1 log10 over nadir; 3Post-treatment HCV RNA ≥LLOQ after <LLOQ without detectable target at end of treatment. EOT: end of treatment; SVR12: sustained virologic response at post-treatment week 12.



**Figure 2** **SVR12 according to selected baseline characteristics in the immediate treatment arm.** SVR12: sustained virologic response at post-treatment week 12.



**Figure 3** **SVR12 in the placebo-deferred treatment arm.** EOT: end of treatment; SVR12, sustained virologic response at post-treatment week 12. 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 non-responders included patients who had HCV RNA < LLOQ (TND) at EOT, but with missing post-treatment week 12 data; 4Death, not considered related to study therapy (stab wound).



**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. EOT: end of treatment; SVR12: sustained virologic response at post-treatment week 12.