Coblopasvir and sofosbuvir for treatment of chronic hepatitis C virus infection in China: A single-arm, open-label, phase 3 trial

Yanhang Gao | Fei Kong | Guangming Li | Cheng Li | Sujun Zheng | Jianmei Lin | Xiaofeng Wen | Jinghua Hu | Xiaozhong Wang | Xiao Feng Wu | Huichun Xing | Jidong Jia | Zhansheng Jia | Yujuan Guan | Cheng Hao Li | Guicheng Wu | Zhiliang Gao | Zhuangbo Mou | Qin Ning | Qing Mao | Yongfeng Yang | Jing Ning | Li Li | Hai Pan | Desheng Zhou | Yanhua Ding | Hong Qin | Junqi Niu

1Department of Hepatology, the First Hospital of Jilin University, Changchun, China
2Cirrhosis Department, Zhengzhou Sixth Municipal People’s Hospital, Zhengzhou, Henan, China
3Difficult & Complicated Liver Diseases and Artificial Liver Center, Beijing You An Hospital, Capital Medical University, Beijing, China
4Department of Infectious Diseases, Sichuan Provincial People’s Hospital, Chengdu, Sichuan, China
5Department of Hepatology, Liuzhou People’s Hospital, Liuzhou, China
6Liver Failure Treatment and Research Center, the Fifth Medical Center of PLA General Hospital, Beijing, China
7Department of Hepatology, Xinjiang Uygur Autonomous Region Traditional Chinese Medicine Hospital, Urumqi, Xinjiang, China
8Department of Hepatology, Shenyang Sixth People’s Hospital, Shenyang, Liaoning, China
9Department of Hepatology, Xinjiang Uygur Autonomous Region Traditional Chinese Medicine Hospital, Urumqi, Xinjiang, China
10Department of Infectious Diseases, the Second Affiliated Hospital of People’s Liberation Army Air Force Medical University, Xi’an, Shaanxi, China
11Department of Hepatology, Guangzhou Eighth People’s Hospital, Guangzhou, China
12Department of Gastroenterology, Yanbian University Affiliated Hospital, Yanji, Jilin, China
13Department of Gastroenterology, Chongqing University Three Gorges Hospital, Chongqing, China
14Department of Infectious Diseases, the Third Affiliated Hospital of Dr Sun Yat-Sen University, Guangzhou, Guangdong, China
15Department of Hepatology, Ji’nan Municipal Hospital of Infectious Diseases, Ji’nan, Shandong, China
16Department of Infectious Diseases, Tongji Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China
17Institute of Infectious Diseases, the First Affiliated Hospital of People’s Liberation Army Medical University, Chongqing, China
18Department of Hepatology, Nanjing Second Municipal Hospital, Nanjing, China
19Research and Development Center, Beijing Kawin Technology Share-Holding Co., Ltd, Beijing, China
20The Department of Phase I Clinical Trial, the First Hospital of Jilin University, Changchun, Jilin, China

Abstract

Background & Aim: An affordable, pangenotypic regimen remains as an unmet medical need for chronic hepatitis C patients in China. This single-arm, open-label, multicenter, phase 3 trial evaluated the efficacy and safety of coblopasvir, a pangenotypic...
Present address
Hong Qin, Clinical Development, Hangzhou
Sciwind Biosciences Co., Ltd, Hangzhou,
Zhejiang, China

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non-structural protein 5A (NS5A) inhibitor, combined with sofosbuvir for treating
Chinese patients with chronic hepatitis C virus (HCV) infection.

Methods: Treatment-naïve and interferon-experienced adult patients, including
those with advanced fibrosis (F3) or compensated cirrhosis (F4), were treated with a
universal, combinational regimen of coblopasvir 60 mg and sofosbuvir 400 mg, once
daily, for 12 weeks. The primary efficacy endpoint was sustained virological response
at post-treatment week 12 (SVR12).

Results: Overall, 371 patients (men, 51%; age, 47 ± 11 years; genotype 1a < 1%, 1b
48%, 2a 26%, 3a 6%, 3b 7% and 6 12%) were enrolled from 19 sites. Fifty-one pa-
tients (14%) had F3, 39 patients (11%) had F4 and 39 patients (11%) were interferon
experienced. The overall SVR12 was 97% (95% CI, [94%, 98%]) for the full analysis
set and was equal to or above 90% for all predefined subsets. Ten patients (3%) expe-
rienced virological relapse and two patients did not complete follow-up. No adverse
events (AEs) occurred at a frequency ≥5%, and the most often reported AEs (≥1%)
were neutropenia and fatigue. The majority of AEs were mild to moderate and tran-
sient without specific medical intervention.

Conclusions: The universal, pangenotypic combo of coblopasvir plus sofosbuvir is
an efficacious and safe treatment for Chinese patients monoinfected with HCV of
genotype 1, 2, 3 and 6, including those with compensated cirrhosis.

Lay summary: The regimen of coblopasvir and sofosbuvir is a safe and effective
treatment for Chinese patients with genotype 1, 2, 3 and 6 HCV infection, including
those with compensated cirrhosis. Therefore, this regimen would be a novel choice
of treatment for this patient population.

KEYWORDS
coblopasvir, pangenotypic regimen, safety, sofosbuvir, sustained virological response

1 | INTRODUCTION

China has a high prevalence of hepatitis C virus (HCV) infection,
with an estimated infected population of at least 10 million.1 HCV
genotype distribution is also highly diverse across the nationwide
geographical regions, with genotype 1b being the most dominant.
Genotype 2 is more frequent in Northern China and genotypes 3
and 6 are more common in Southern China.2 Furthermore, geno-
type 3b, a subtype specific to China, differs from subtype 3a in
virological response to direct-acting antivirals (DAAs).3 Therefore,
an accessible, potent, standard-course, pangenotypic treatment
regimen remains an unmet medical need in China from the per-
spectives of both clinical practice and public health, although two
imported pangenotypic fixed-dose combinations (velpatasvir-so-
fosbuvir and glecaprevir-pibrentasvir) have been conditionally ap-
proved by the Chinese National Medical Products Administration
(NMPA).

Coblopasvir (formerly coded as KW-136) is a pangenotypic in-
hibitor against HCV non-structural protein (NS) 5A with picomolar
antiviral activities against HCV replicons or cell culture systems
of genotypes 1a, 1b, 2a, 3a, 4a, 5a and 6a in vitro (data on file).
Coblopasvir demonstrates an additive or synergic effect when com-
bined with interferon, NS3/4A protease inhibitor or NS5B nucleotide
analogue, with no detected cross-resistance with protease inhibitors
or nucleotide analogues in vitro (data on file). In early-phase clinical
pharmacology studies, oral coblopasvir shows a favourable pharma-
cokinetics and tolerability profile in healthy participants, enabling
a further efficacy proof-of-concept study, in which a maximal HCV
ribonucleic acid (RNA) reduction of up to 5log10 IU/mL was observed
in non-cirrhotic patients of genotype 1b receiving an ultrashort-du-
ration (72-hour) monotherapy (unpublished data). In a previous
phase 2 study, a standard 12-week treatment regimen of coblopasvir
30 or 60 mg with sofosbuvir 400 mg resulted in a sustained virolog-
ical response (SVR) of 98% among treatment-naïve Chinese patients
infected with HCV of genotypes 1, 2, 3 and 6, including those with
compensated cirrhosis.4

The primary objective of this phase 3 study was to evaluate the
efficacy and safety of a 12-week combo regimen of coblopas-
svir 60 mg plus sofosbuvir 400 mg for Chinese adult patients
chronically monoinfected with HCV of diverse genotypes, in-
cluding those with compensated cirrhosis and those having pre-
viously experienced interferons. We also analysed the possible
confounding effects of HCV genotype, liver fibrosis and interferon experience on SVR.

2 | METHODS

2.1 | Study protocol and participants

This single-arm, open-label, phase 3 study was conducted at 19 clinical sites across China. The study protocol was approved by the Institutional Review Board or Independent Ethics Committee at each participating site, and the study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice and other applicable national regulations. All participants volunteered to provide informed consent in writing before any study procedures.

The eligibility criteria were as follows: men and non-pregnant and non-lactating women aged 18-70 years (inclusive); with documented chronic HCV monoinfection of genotypes 1-6 or any other (sub)types, including mixed and indeterminate types; with a central laboratory confirmed plasma HCV RNA titre ≥10 000 IU/mL on screening; without cirrhosis or with evidenced compensated cirrhosis on precedent liver biopsy (F4 on Ishak, Metavir or GS scoring system) and/or liver transient elastography (FibroScan liver stiffness modulus [LSM] ≥14.6 kPa). Patients who had been previously exposed to interferons at least 6 months before screening could be enrolled, but those previously exposed to DAAs of any sources were excluded. Patients with unstable or uncontrolled medical conditions or co-infected with hepatitis B virus (HBV) or human immunodeficient virus (HIV) were also excluded. Detailed inclusion and exclusion criteria are shown in Table S1 and the definitions of liver fibrosis are shown in Table S2.

2.2 | Procedures

Patients were instructed to self-administer coblapasvir capsules 60 mg and sofosbuvir tablets 400 mg (Kawin Technology Share-Holding Co., Ltd., Beijing, China) with or without meal, once daily for 12 successive weeks. No dose modification was allowed throughout the treatment period.

Efficacy and safety were continuously monitored at treatment weeks 1, 2, 4, 8 and 12, and at post-treatment weeks 4 and 12. Consenting patients entered into an optional extended follow-up study at post-treatment week 24 for the assessment of SVR durability (SVR24). The HCV RNA titre was quantitated using the COBAS AmpliPrep/COBAS Taqman HCV Test version 2.0 Virus Quantitative Detection Kit (Roche Molecular Diagnostics, Indianapolis, IN, USA) with a lower limit of quantitation (LLOQ) of 15 IU/mL and an upper limit of quantitation of 10^8 IU/mL. The HCV genotype and subtype were sequenced using the reverse transcription polymerase chain reaction test (the Sanger method; HCV RNA ≥10^4 IU/mL with a sensitivity of 20%). HCV RNA quantitation, HCV genotyping and HBV surface antigen (HBsAg) testing were conducted at a College of American Pathologists-accredited central laboratory (Kingmed Center for Clinical Laboratory, Guangzhou, China), and other screening and safety laboratory tests were done at the local hospital clinical laboratory.

Pre-existing and treatment-emergent resistance-associated substitutions (RASs) for genotypes 1b and 2a were tested using the population-based sequencing technique at Kingmed (threshold ≥20% of a viral population) for NS5A and NS5B regions in plasma samples with an HCV RNA titre ≥1000 IU/mL from patients who experienced virological failure (including on-treatment virological breakthrough, post-treatment relapse, premature withdrawal and loss to follow-up) compared to those collected at screening.

Safety was monitored at every study visit until post-treatment week 12. Safety measures included adverse events (AEs), vital signs, physical examination, clinical laboratory tests, electrocardiography and upper abdominal ultrasonography. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 20.0 (MedDRA MSSO, McLean, VA, USA) and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The attribution of causality for any AE to the study drug was at the discretion of the investigator according to a national adverse drug reaction (ADR) vigilance procedure. ADR is defined as any AE definitely, probably, or possibly caused by use of the study drug, as assessed by the investigator.

2.3 | Outcome measures

Efficacy and safety were assessed in all patients receiving at least one dose of the study drug. The primary efficacy endpoint was SVR12, defined as the proportion of patients with virological response (HCV RNA titre below LLOQ or target not detected) at 12 weeks after the completion or discontinuation of treatment. The secondary efficacy endpoints included the proportions of patients who achieved virological response at treatment weeks 1, 2, 4, 8 and 12 and at post-treatment week 4, the proportion of patients who experienced on-treatment virological breakthrough at treatment weeks 2, 4, 8 and 12 and the proportions of patients who experienced post-treatment virological relapse at post-treatment weeks 4 and 12. The exploratory efficacy endpoint was SVR24, defined as the proportion of patients who achieved SVR at 24 weeks after the completion of treatment among those who achieved SVR12 and completed the post-treatment week 24 visit. Safety endpoints included AE, serious AE, vital signs, physical examination, clinical laboratory tests, 12-lead electrocardiography and other safety tests. Detailed definitions of the virological responses are shown in Table S3.

2.4 | Sample size estimation and statistical analysis

The sample size was estimated based on a superiority hypothesis test. For the FAS, the overall SVR12 for patients receiving coblapasvir
plus sofosbuvir was conservatively estimated at 90% and that for a historical control was set at 85% in communication with the regulatory agency. A sample size of 324 patients would provide a statistical power of 85% at a one-sided significance level of 0.025. In consideration of enrolling an adequate number of patients with genotypes 3 and 6, the sample size was set at 360 patients; genotype distribution was also set as follows to represent the real-world HCV genotype profile in China: genotype 1 and others at 50%, genotype 2 at 25%, genotype 3 at 12.5% and genotype 6 at 12.5%. The proportion of patients with advanced fibrosis (F3) or compensated cirrhosis (F4) was capped at 20%, and that of interferon-experienced patients was also capped at 10%.

Point estimates and two-sided 95% confidence intervals (95% CIs) were calculated using the Clopper-Pearson method for primary and secondary efficacy endpoints. Missing HCV RNA data for any reason were counted as treatment failure for the full analysis set (FAS) using the intention-to-treat principle. Exploratory efficacy endpoints and safety endpoints were descriptively summarized. The SVR of patient subsets and the potential effects of genotype, liver fibrosis and interferon experience on SVR (expressed as odds ratio [OR] and 95% CI) were analysed in a post hoc manner using the logistic regression model with bootstrapping. All statistical summaries and analyses were performed using the SAS software package version 9.4 (SAS Institute Inc, Cary, NC, USA).

3 | RESULTS

3.1 | Patient characteristics

Between June and August, 2017, 435 patients were screened, 64 of whom were excluded mainly as a result of not meeting the eligibility criteria for laboratory tests. Overall, 371 patients were enrolled in this study and treated withcoblovasvir plus sofosbuvir. All patients completed the 12-week treatment and additional 12-week follow-up visits, except for one patient prematurely withdrawn from treatment at week 2 for unknown reasons and another patient lost to post-treatment week 12 follow-up after completion of treatment as a result of institutionalized drug abstinence (Figure 1).

Overall, the study population consisted of a similar proportion of men and women (51% vs 49%), with a median age of 49 years (range, 19-69 years) and a body mass index of 18 - 32 kg/m², the majority of whom were Han Chinese (80%) in ethnicity (Table 1). All patients were seronegative to HBV and HIV. The genotype distribution was as follows (n = 371): genotype 1a, <1% (n = 2); 1b, 48% (n = 178); 2a, 26% (n = 95); 3a, 6% (n = 23); 3b, 7% (n = 27); 6, 12% (n = 46); no genotype

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**FIGURE 1** Study flow chart
4 or 5 was detected or enrolled. Fifty-one patients (n = 51, 14%) had F3 fibrosis and 39 patients (11%) had F4 fibrosis (compensated cirrhosis). Thirty-nine patients (n = 39, 11%) had been previously exposed to interferons, most of whom had virological relapse or intolerance. None of the patients had a serum creatinine clearance below 50 ml/min (using the Cockcroft-Gault formula) per the eligibility criteria. The most often reported concomitant medical conditions were non-alcoholic fatty liver disease and essential hypertension.

### 3.2 Virological responses

All compliant patients achieved a virological response by treatment week 8. Detailed on-treatment virological responses are shown in Table S4. Among the 371 patients enrolled, 359 patients (97%; 95% CI [95%, 99%]) achieved the primary efficacy endpoint of SVR12 (Table 2). This high SVR12 was significantly greater than the pre-specified 85% performance goal (P < .001), meeting the primary efficacy endpoint for this study. Per protocol set analysis also showed a similar result (358/368, 97%; 95% CI [96%, 99%), P < .001). Three hundred and fifty-one patients (n = 351) who achieved SVR12 completed the post-treatment week 24 visit, all of whom achieved SVR24 with the exception of one patient, representing a consistence of >99% between SVR24 and SVR12.

Subset analysis by genotype (Table 2) showed that patients with genotype 1 had the highest SVR12 (99%, 95% CI [96%, >99%]), compared to 96% (95% CI [90%, 99%]) for those with genotype 2, 90% (95% CI [78%, 97%]) for those with genotype 3 and 98% (95% CI [88%, >99%]) for those with genotype 6 respectively. Post hoc subset analysis of genotype 3 showed a similar SVR12 between subtypes 3a and 3b (91% [21/23] vs 89% [24/27]). Further sensitivity analysis for patients with genotype 3 showed an SVR12 of 96% (45/47; 95% CI [85%, >99%]) with three non-compliant patients excluded. A high

### Table 1: Patient demographics and baseline characteristics

|                        | Patients (n = 371)        |
|------------------------|---------------------------|
| Age, years, median (range) | 49 (19-69)                |
| Gender                 |                           |
| Male                   | 190 (51%)                 |
| Female                 | 181 (49%)                 |
| Ethnicity              |                           |
| Han Chinese            | 295 (80%)                 |
| Others                 | 76 (20%)                  |
| Body mass index, kg/m², median (range) | 24 (18-32)            |
| HCV genotype           |                           |
| 1                      | 180 (49%)                 |
| 1a                     | 2 (<1%)                   |
| 1b                     | 178 (48%)                 |
| 2                      | 95 (26%)                  |
| 2a                     | 95 (26%)                  |
| 3                      | 50 (13%)                  |
| 3a                     | 23 (6%)                   |
| 3b                     | 27 (7%)                   |
| 6                      | 46 (12%)                  |
| 6a                     | 41 (11%)                  |
| 6e                     | 3 (<1%)                   |
| 6n                     | 2 (<1%)                   |
| Others                 | 0 (0%)                    |
| HCV RNA titre, IU/mL, median (range) | 1,760,000 (10,000-18,800,000) |
| Liver fibrosis         |                           |
| F0-2                   | 281 (76%)                 |
| F3                     | 51 (14%)                  |
| F4                     | 39 (11%)                  |
| Previous interferon experience |                     |
| No                     | 332 (89%)                 |
| Yes                    | 39 (11%)                  |
| Non-responder          | 4 (1%)                    |
| Breakthrough           | 2 (<1%)                   |
| Relapse                | 17 (5%)                   |
| Intolerance            | 15 (4%)                   |
| Serum creatinine clearance, ml/min, median (range) | 102 (50-226)            |
| Concomitant medical conditions (≥10%) |                     |
| Fatty liver disease    | 52 (14%)                  |
| Essential hypertension | 54 (15%)                  |

*All with compensated cirrhosis (Child-Pugh class A). Data are in n (%) unless otherwise specified. HCV, hepatitis C virus; RNA, ribonucleic acid.

### Table 2: SVR12 by genotype, fibrosis and interferon experience for full analysis set (n = 371)

| SVR12          | Overall (n = 371) |
|----------------|-------------------|
| Overall        | 97% (359/371) [94%, 98%] |
| By genotype    |                   |
| Genotype 1     | 99% [178/180] [96%, >99%] |
| Genotype 2     | 96% [91/95] [90%, 99%]  |
| Genotype 3     | 90% [45/50] [78%, 97%]  |
| Genotype 3a    | 91% [21/23] [72%, 99%]  |
| Genotype 3b    | 89% [24/27] [71%, 98%]  |
| Genotype 6     | 98% [45/46] [88%, >99%] |
| By fibrosis    |                   |
| F0-2           | 97% [272/281] [94%, 99%] |
| F3             | 98% [50/51] [90%, >99%]  |
| F4             | 95% [37/39] [83%, >99%]  |
| By interferon experience |                |
| Naive          | 96% [320/332] [94%, 98%] |
| Experienced    | 100% [39/39] [91%, 100%] |

Note: Data are in % (n/N) [95% confidence interval] using the Clopper-Pearson method. ND, not done.
TABLE 3 Virological failures for full analysis set (n = 371)

| Patients |
|----------|
| Virological failures <sup>a</sup> | 12 (3%) |
| Virological relapse | 10 (3%) |
| At post-treatment week 4 | 8 (2%) |
| at post-treatment week 12 | 2 (<1%) |
| Virological breakthrough <sup>b</sup> | 0 (0%) |
| Lost to follow-up and others <sup>c</sup> | 2 (<1%) |

<sup>a</sup>Defined as not achieving SVR12 (sustained virological response at post-treatment week 12).

<sup>b</sup>One compliant patient of genotype 3b with F3 experienced virological breakthrough at treatment week 2 but achieved SVR12.

<sup>c</sup>Including one patient of genotype 3b with F0-2 who prematurely withdrew from treatment at week 2 for unknown reasons and one patient of genotype 3a with F0-2 lost to follow-up at post-treatment week 12 as a result of institutionalization. Data are in n (%).

SVR12 was also observed among patients with fibrosis of variable severity (Table 2), 97% (95% CI [94%, 99%]) for F0-2, 98% (95% CI [90%, >99%]) for F3 and 95% (95% CI [83%, >99%]) for F4 respectively. Interferon-experienced patients achieved a SVR12 of 100% (95% CI [91%, 100%]) (Table 2).

Univariate analysis showed that genotypes 3a (odds ratio [OR]=8.48 [1.13, 63.4], \( P < .002 \)) and 3b (OR = 11.1 [1.77, 70.0], \( P < .001 \)) were associated with a lower SVR12 compared to genotype 1, while fibrosis stages F3 (OR = 0.60 [0.08, 4.88], \( P = .296 \)) and F4 (OR = 1.63 [0.34, 7.85], \( P = .424 \)) did not significantly affect SVR12 compared to F0-2 (Tables S5 and S6). Further multivariate analysis showed no interactive effect between genotype and fibrosis stage (\( P = .646 \)). Adjustment of fibrosis slightly increased the SVR12 OR for genotype 3a (unadjusted OR = 8.48 [1.13, 63.4], \( P = .002 \); adjusted OR = 9.01 [1.20, 67.9], \( P < .001 \)) or 3b (unadjusted OR = 11.1 [1.77, 70.0], \( P < .001 \); adjusted OR = 12.0 [1.88, 76.6], \( P < .001 \)) compared to genotype 1, while adjustment of genotype did not significantly affect the SVR12 OR for fibrosis staging (Table S6).

No univariate or multivariate analysis was performed for interferon treatment experience as interferon-experienced patients achieved a SVR12 of 100%.

3.3 | Virological failure

Of 371 patients, 12 patients (3%) did not achieve SVR12 (Table 3), all of whom were naïve to interferon treatment. Ten patients (n = 10, 3%) experienced virological relapse, including two patients (n = 2) with genotype 1 and with F0-2 or F4, four patients (n = 4) with genotype 2a and with F0-2, three patients (n = 3) with genotype 3 and with F0-2 (genotype 3a, voluntary interruption of self-dosing between treatment weeks 2 and 4 followed by virological breakthrough at treatment week 4), F3 or F4 (both of genotype 3b), and one patient (n = 1) with genotype 6n with F0-2.

One treatment-naïve patient with genotype 1b and with F0-2 experienced virological relapse at post-treatment week 4 but achieved SVR12. One treatment-naïve patient with genotype 6e with F0-2 achieved SVR12 but relapsed at post-treatment week 24.

One compliant patient of genotype 3b with F3 experienced virological breakthrough at treatment week 2 (87 IU/mL) from <15 IU/mL at treatment week 1 but achieved SVR12. One patient (genotype 3b with F0-2) prematurely withdrew from the study after completing 2-week treatment for unknown reasons, and one patient (genotype 3a with F0-2) was lost to follow-up as a result of institutionalization at post-treatment week 12.

All of these patients achieved virological response at the time of treatment completion, withdrawal or the last visit before they were lost to follow-up. A detailed description of virological failure is shown in Table S7.

3.4 | Resistance monitoring

Fifteen patients (n = 15) were eligible for predefined polymorphism sequencing for NS5A and NS5B. Polymorphism sequencing was performed for six patients (n = 6) with genotype 1b (n = 2) or 2a (n = 4), but not for nine patients (n = 9) with genotype 1a (n = 1), 3a (n = 2), 3b (n = 4), 6e (n = 1) and 6n (n = 1) as a result of unavailability of subtype-specific polymorphism sequencing methodology at the time of conducting this study. Among six patients (n = 6) with NS5A polymorphism data available, the common pre-existing RAS included Y93H for NS5A of genotype 1b (n = 2) and L31M for NS5A of genotype 2a (n = 4), and no treatment-emergent NS5A polymorphism was detected. No pre-existing or treatment-emergent S282T, the major NS5B RAS, was detected in these six patients (n = 6) with NS5B polymorphism data available. A detailed description of the NS5A and NS5B polymorphisms is shown in Table S7.

3.5 | Safety data

Treatment-emergent AEs (TEAEs) were reported for 292 patients (79%), comprising 193 patients with grade 1 (52%), 86 patients with grade 2 (23%), 11 patients with grade 3 (3%) and 2 patients with grade 4 (<1%) (Table 4). Grade 4 AEs were acute pancreatitis and hypertensive crisis, which resolved after in-hospital symptomatic treatment. None of the grade 3 and 4 AEs were judged by the investigators to be associated with use of the study drug. No patients discontinued or interrupted treatment because of AEs.

One hundred and two patients (n = 102, 27%) experienced TEAEs related to study drug, including 83 patients with grade 1 (22%) and 19 patients with grade 2 (5%); none of the patients experienced grade 3 or 4 TEAEs related to study drug. No AEs or TEAEs related to study drug were reported at a frequency ≥5%, and the most often reported TEAEs related to study drug (≥1%, excluding laboratory abnormalities) were fatigue (3%), headache (2%), dizziness (2%), diarrhoea (2%), nausea (1%), abdominal pain (1%), lethargy (1%) and fatty liver (1%). The majority of AEs and TEAEs related to study drug were transient and required no specific medical intervention.
Twelve patients \((n = 12, 3\%)\) experienced serious AEs, which were mainly hospitalizations as a result of elective or emergency operations. None of the serious AEs were judged to be related to the study drug. No deaths occurred.

No grade 3 or 4 laboratory abnormalities of clinical significance were reported. The most often reported laboratory abnormalities \((\geq 1\%)\) were neutropenia \((4\%)\), hypoalbuminemia \((3\%)\), hyperuricemia \((2\%)\) and thrombocytopenia \((1\%)\). No clinically significant, non-isolated worsening was reported for haematology, urinalysis, clinical biochemistry or coagulation. General liver function tests, including alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase, showed a significant trend of normalization throughout the study period (Figure S1A-C). FibroScan also showed a trend in improved LSM, especially for patients with F3 or F4 (Figure S1D). Isolated, elevated creatinine was reported for three patients \((n = 3)\) and assessed to be not clinically significant.

Of two patients \((n = 2)\) with increased alfa-fetal protein, one patient with genotype 1b and with F4 relapsed at post-treatment week 12 (HCV RNA titre approximating 100 IU/mL) and was further diagnosed with hepatocellular carcinoma on increased serum alfa-fetal protein combined with contrast liver imaging. One patient had a prolonged QT interval on treatment, which resolved without medical intervention 1 month later.

### DISCUSSION

Our study population was highly representative of Chinese real-world patients infected with HCV and comparable to that reported for the China phase 3 study of velpatasvir-sofosbuvir in terms of age, gender, genotype (also no genotype 4 or 5 detected), HCV titre, fibrosis and previous treatment history. \(^3\) After a universal, standard 12-week, fixed-dose combo treatment with cobolpasvir plus sofosbuvir, the SVR12 was 97% \((359/371)\) for the patients overall and above 95% for patients with genotypes 1, 2 and 6. The SVR for patients with genotype 3 was slightly lower but still at 90% \((45/50)\). The slightly lower virological response was primarily driven by three patients with poor on-treatment or post-treatment follow-up compliance; with the poorly compliant patients excluded, SVR12 was achieved in 96% \((45/47)\) of patients with genotype 3. SVR12 was also high for patients with compensated cirrhosis \((95\%)\) and was achieved by 100% of interferon-experienced patients. The high SVR after treatment with cobolpasvir plus sofosbuvir showed no significant effect confounded by the HCV genotype, baseline fibrosis, previous interferon exposure or the interactive effects of these factors.

Together with the rest of the world, China aims to achieve ‘No HepC’ by the year 2030, requiring at least 80% of patients cured by that year. \(^5\) Therefore, a simple-to-use, highly effective and publicly affordable pangenotypic treatment regimen is mandatory to achieve this public health goal. The combo regimen of cobolpasvir plus sofosbuvir requires no sophisticated pre-treatment genotyping or baseline liver fibrosis assessment and, therefore, enables the delivery of care to patients in the setting of real-world general practice. Use of this domestic-made combo regimen as a first-line, general purpose candidate is expected to be cost saving and meet the ‘unmet medical needs’ of HCV-infected patients in China.\(^6\)

SVR12 after 12-week treatment with cobolpasvir plus sofosbuvir \((97\%)\) was generally similar to that with velpatasvir-sofosbuvir for Chinese patients \((96\%)\) (Table S8). \(^3\) As Wei \textit{et al}\(^2\) reported a lower efficacy \((76\%)\) of velpatasvir-sofosbuvir in Chinese patients with genotype 3b, a post \textit{hoc} genotype 3 subtype SVR analysis was conducted, showing a comparable response rate between patients with genotypes 3a and 3b \((91\% \text{[21/23]} \text{ vs} 89\% \text{[24/27]})\) in our study. However, a further analysis with non-compliant patients excluded showed a higher SVR for patients with genotype 3a \((100\% \text{[21/21]}\) compared to that for genotype 3b patients \((92\% \text{[24/26]}\)). The SVR12 for genotype 3 with cobolpasvir plus sofosbuvir \((90\% \text{[45/50]})\) was also noted to be greater than that with velpatasvir-sofosbuvir \((83\% \text{[49/59]}\)). With non-compliant patients excluded, the difference in the response rate was even greater \((96\% \text{[45/47]} \text{ vs} 84\% \text{[49/58]}\)). Further subtype analysis

### TABLE 4 Adverse events and laboratory abnormalities

| Patients \((n = 371)\) |
|------------------|
| **Any TEAEs** | 292 (79%) |
| Grade 3 | 11 (3%) |
| Grade 4 | 2 (<1%) |
| **Any serious AEs** | 12 (3%) |
| **Any AEs leading to discontinuation of study drug** | 0 (0%) |
| **Death** | 0 (0%) |
| **Any TEAE-related study drug** | 102 (27%) |
| Grade 1 | 83 (22%) |
| Grade 2 | 19 (5%) |
| Grade 3 or 4 | 0 (0%) |
| **Any TEAEs or TEAE-related study drug ≥ 5%** | 0 (0%) |
| **Any TEAE related to study drug ≥ 1%** | 10 (3%) |
| Fatigue | 7 (2%) |
| Dizziness | 6 (2%) |
| Nausea | 4 (1%) |
| Abdominal pain | 4 (1%) |
| Lethargy | 4 (1%) |
| Fatty liver | 4 (1%) |
| Grade 3 or 4 laboratory abnormalities of clinical significance | 0 (0%) |
| **Laboratory abnormalities ≥ 1%** | 14 (4%) |
| Neutropenia | 10 (3%) |
| Hyperuricemia | 6 (2%) |
| Thrombocytopenia | 5 (1%) |

Note: Data are n (%). AE, adverse events; TEAEs, treatment-emergent adverse events.

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As Wei \textit{et al}\(^3\) reported a lower efficacy \((76\%)\) of velpatasvir-sofosbuvir in Chinese patients with genotype 3b, a post \textit{hoc} genotype 3 subtype SVR analysis was conducted, showing a comparable response rate between patients with genotypes 3a and 3b \((91\% \text{[21/23]} \text{ vs} 89\% \text{[24/27]})\) in our study. However, a further analysis with non-compliant patients excluded showed a higher SVR for patients with genotype 3a \((100\% \text{[21/21]}\) compared to that for genotype 3b patients \((92\% \text{[24/26]}\)). The SVR12 for genotype 3 with cobolpasvir plus sofosbuvir \((90\% \text{[45/50]})\) was also noted to be greater than that with velpatasvir-sofosbuvir \((83\% \text{[49/59]}\)). With non-compliant patients excluded, the difference in the response rate was even greater \((96\% \text{[45/47]} \text{ vs} 84\% \text{[49/58]}\)). Further subtype analysis
revealed this difference was primarily driven by that for genotype 3b (FAS, 89% [24/27] vs 78% [29/37]; compliant, 92% [24/26] vs 78% [29/37]) rather than genotype 3a (FAS, 91% [21/23] vs 91% [20/22]; compliant, 100% [21/21] vs 95% [20/21]). This finding should be cautiously interpreted as only three patients (n = 3) with genotype 3b with cirrhosis were enrolled in this study compared to 14 patients in the China phase 3 study of velpatasvir-sofosbuvir. The actual response of cirrhotic patients with genotype 3b to coblapasvir plus sofosbuvir requires more clinical data from post-marketing real-world studies. However, the public health effect of a lower response for patients with genotype 3b, especially in cirrhotic patients, is expected to be minimal from the perspective of ‘No HepC’ as the prevalence of this subpopulation accounts for only 0.7% in China.  

Two patients (n = 2) with genotypes 6e and 6n experienced post-treatment relapse. These two less common subtypes were not evaluated in the China phase 3 study of velpatasvir-sofosbuvir, but is relatively more common in Thai patients (predominance accounting for 1% and 22% of genotype 6, respectively) and was also detected in Chinese injection drug users (predominance accounting for 9% and 3% of injection drug users respectively). The treatment efficacy of coblapasvir, along with other pangenotypic NSSA inhibitors, plus sofosbuvir warrants further evaluation in this special population infected with HCV of profound genetic diversity.

Owing to the small number (n = 5) of patients with genotype 1b (n = 1, with F4) or 2a (n = 4, with F0-2) who failed treatment with coblapasvir plus sofosbuvir, the effect of pre-existing and/or treatment-emergent RASs for NSSA or NS5B on the virological response could not be analysed for patients with genotype 1b or 2a; however, no treatment-emergent RAS was detected in these five patients. In the previous efficacy proof-of-concept study of an ultrashort-duration (72-hour) coblapasvir monotherapy, pre-existing RASs for NSSA or NS5B on the virological response had not been analysed for patients with genotype 1b or 2a; however, no treatment-emergent RAS was detected in these five patients, in the previous efficacy proof-of-concept study of an ultrashort-duration (72-hour) coblapasvir monotherapy, pre-existing RASs for NSSA or NS5B on the virological response could not be analysed for patients with genotype 1b or 2a; however, no treatment-emergent RAS was detected in these five patients. 

The proportions of HCV genotype, liver fibrosis and previous interferon exposure were capped from the regulatory perspective, although the study population maximally represented the real-world population of HCV-infected patients in China. Therefore, the generalization of the results of this study should be further validated in post-marketing studies and observations in Chinese patients with highly diversified baseline characteristics, especially for these special populations.

In conclusion, the ribavirin-free, all-oral, pangenotypic combo regimen of coblapasvir plus sofosbuvir demonstrates a high SVR and a favourable safety profile for Chinese adult patients chronically monoinfected with HCV, including those with compensated cirrhosis. This regimen requires no pretreatment assessment of HCV genotype or liver fibrosis, and the treatment duration is fixed at 12 weeks for all patients regardless of the baseline characteristics. These clinical benefits and the affordability of this combo regimen address the
'unmet medical needs' for chronic hepatitis C in China and facilitate the goal of a 'No HepC' China by the year 2030.

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CONFLICT OF INTEREST
Jing Ning, Hai Pan and Hong Qin were employees of Kawin Technology when executing this trial, and Li Li and Desheng Zhou are employees and stakeholders of Kawin Technology. The other authors have no conflict of interest to declare.

ORCID
Jinghua Hu  https://orcid.org/0000-0002-0647-9898
Qin Ning  https://orcid.org/0000-0002-2027-9593
Junqi Niu  https://orcid.org/0000-0002-9857-6520

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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