A Multi-centered, Open Label, Phase III Study on Efficacy, Safety of Ritonavir-boosted ASC08 (Danoprevir) in Combination With Peg-IFN and RBV in Treatment-Naive Non-Cirrhotic Patients Who Have Chronic Hepatitis Genotype 1

Clinical Trial Protocol

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Sponsor: Ascletis Pharmaceuticals Co., Ltd.

Study protocol version No.: 3.0
Established: January 16, 2017

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List of Abbreviations

Abbreviation	Chinese name	Abbreviation	Chinese name
AE	Adverse events	EO	Acidophil
AFP	Alpha-fetoprotein	EPO	Erythropoietin
ALB	Albumin	ERY	Urine red blood cell
ALT	Alanine aminotransferase	FAS	Full Analysis Dataset
ALP	Alkaline phosphatase	FBG	Fasting plasma glucose
AMA	Antimitochondrial antibody	FDA	Food and Drug Administration
ANA	Antinuclear antibody	Fg	Fibrinogen
ANC	Absolute neutrophil count	GCP	Good Clinical Practice
APTT	Activated partial thromboplastin time	G-CSF	Granulocyte colony stimulating factor
ASC08/r	Ritonavir-fortified ASC08	GI	Gastrointestinal
AST	Aspartate aminotransferase	GLU	Glucose
BASO	Basophils	Γ-GT	Gamma-glutamyltransferase
BMI	Body mass index	HB	Hemoglobin
BUN	Urea nitrogen	HbA1c	Glycosylated hemoglobin
CFDA	China Food and Drug Administration	HCV	Hepatitis C Virus
CHC	Chronic hepatitis C	HDL-c	High density lipoprotein cholesterol
CK	Creatine kinase	INR	International normalized ratio
Cr	Creatinine	LDH	Lactate dehydrogenase

ECRF	Electronic Case Report Form	LDL-c	Low-density lipoprotein cholesterol
CTCAE	Common Terminology Criteria for Adverse Events	LEU	Urine leukocyte
DAA	Direct antiviral drugs	LLN	Lower limit of normal
DBIL	Direct bilirubin	LLOQ	Lower limit of quantitation
DC	Differential leukocyte count	LYMPH	Lymphocyte
DMC	Data Safety Monitoring Board	MONO	Monocyte
ECG	Electrocardiogram	NCI	National Cancer Institute
EMA	European Medicines Agency	NEUT	Neutrophils
Abbreviation	Chinese name	Abbreviation	Chinese name
NS	Non-structural	RVR	Rapid virological response
OATP	Organic anion-transporting polypeptide	SAE	Serious adverse event
PEG-IFN α	Pegylated interferon alfa	SMA	Anti-smooth muscle antibody
PK	Pharmacokinetics	SS	Safety data set
PLT	Platelets	SVR	Sustained virologic response
PPS	Per-Protocol Set	TBIL	Total bilirubin
P/R	PEG-IFNα/RBV	TC	Total cholesterol
PRO	Urine protein	TG	Triglyceride
PT	Prothrombin time	TP	Total protein
RBC	Red blood cell	TPO	Thrombopoietin

RBV	Ribavirin	TSH	Thyroid-stimulating hormone
Ret	Reticulocyte	UA	Uric acid
RGT	Response-guided therapy	ULN	Upper limit of normal
RTV	Ritonavir	WBC	Leucocyte

Protocol Synopsis

Test name	A Multi-centered, Open Label, Phase III Study on Efficacy, Safety of Ritonavir-boosted ASC08 (Danoprevir) in Combination With Peg-IFN and RBV in Treatment-Naive Non-Cirrhotic Patients Who Have Chronic Hepatitis Genotype 1
Sponsor	Ascletis Pharmaceuticals Co., Ltd.
Leading site of clinical trial	Peking University People's Hospital
Statistical unit	Peking University Clinical Research Institute
Contract Research Organization	Shanghai Tigermed Consulting Co., Ltd
Test objective	**Primary objective** (1) To evaluate the rate of subjects achieving SVR12 after 12 weeks of ASC08/r in combination with PEG-IFN α and RBV in treatment-naive non-cirrhotic subjects with chronic hepatitis C genotype 1 virus infection. (2) To evaluate the safety of ASC08/r combined with PEG-IFN α and RBV in treatment-naive non-cirrhotic subjects with chronic hepatitis C genotype 1 virus infection. **Secondary objectives** (1) To evaluate the proportion of subjects achieving RVR4, SVR4, and SVR24; (2) To evaluate changes in virological response rates over time; (3) To evaluate the kinetics of viral load changes; (4) To evaluate the recurrence rate after combination therapy; (5) To evaluate the resistance characteristics of the virus to

	ASC08.	
Test design	Multi-center, open single-arm clinical study.	
Investigational drug	Investigational drug: ASC08 tablets, 100 mg/tablet.	
	Intensive drug: ritonavir tablets, 100 mg/tablet.	
	Concomitant drugs	Peginterferon alfa-2a Injection, 180 μg/0.5 mL;
		Ribavirin Tablets, 100 mg/tablet.
Number of cases	A total of 127 subjects were included. All included subjects entered the ASC08/r treatment group.	
Test Flow	**The subjects should receive the screening examination within 28 days before the start of drug treatment, and eligible subjects should be enrolled in this clinical study for treatment.** During the treatment phase, subjects received a 12-week combination of ASC08/r + PEG-IFN α + RBV. **All subjects were followed post-treatment for 24 weeks after the end of combination therapy. After treatment, the follow-up will be completed, and the subjects will be withdrawn from the study.**	
Subject Selection Criteria	**Inclusion criteria** (1) Aged 18 years and above, male or female; (2) Establish the diagnosis of CHC must meet one of the following conditions: (1) hepatitis C virus infection ≥ 6 months (6 months ago anti-HCV antibody positive, or HCV RNA positive); (2). Liver tissue biopsy within 1 year before inclusion consistent with CHC pathological features. (3) Anti-HCV positive. (4) Serum HCV RNA ≥ 1.0 × 104 IU/mL; (5) HCV genotyping is genotype 1.	

	(6) Patients who have not received any interferon and/or other DAA treatment (regardless of the length of time); (7) Patients with non-cirrhosis; Non-cirrhosis is defined as: (1) Fibroscan value ≤ 9.6kPa during screening, or liver biopsy within 1 year before inclusion confirmed as non-cirrhosis (Metavir score ≤ 3 points); (2). 9.6 < Fibroscan value ≤ 12.9 during screening, must be confirmed as non-cirrhotic by liver biopsy. (8) Patients who voluntarily sign the informed consent form; **Exclusion Criteria** (1) Patients with Fibroscan > 12.9kPa, or patients with liver cirrhosis by histopathological examination; (2) Patients with previous or existing evidence of chronic liver disease caused by non-HCV (such as hemochromatosis, autoimmune liver disease, Wilson's disease, α 1 antitrypsin deficiency, alcoholic liver disease, chronic drug-induced liver disease, etc.); (3) Patients with a history of hepatocellular carcinoma, or patients with suspected hepatocellular carcinoma before screening or screening, or patients with suspected hepatocellular carcinoma on color Doppler ultrasonography at screening, or AFP > 50 ng/mL; (4) Anti-HAV (IgM), HBsAg, anti-HEV (IgM), anti-HIV one of the positive; (5) BMI < 18 or ≥ 30 kg/m2; (6) ANC < 1.5 × 109/L, PLT < 100 × 109/L, HB < 110 g/L (female) or < 120 g/L (male); INR > 1.5; ALP ≥ 1.5 times ULN; ALT or AST ≥ 5 times ULN; TBIL ≥ 2 times ULN (DBIL ≥ 35% TBIL); Cr ≥ 1.5 times ULN; TSH > ULN or TSH < LLN; (7) Patients who have or have had neurological and/or psychiatric psychiatric disorders, have poor self-control, and cannot express

	their wishes with certainty; (8) Patients with obvious cardiovascular dysfunction, such as heart function grade III or above or score < 50%; or patients with severe cardiovascular disease (such as ventricular tachyarrhythmia, myocardial infarction, angina pectoris, coronary artery disease or other serious cardiovascular disease); or patients with existing uncontrolled hypertension (systolic blood pressure ⩾ 160 mmHg and/or diastolic blood pressure ⩾ 100 mmHg); or patients with obvious clinical abnormal ECG results; (9) Patients with severe acute or chronic respiratory or severe urinary system diseases; (10) Have received solid organ transplantation or corneal transplantation or bone marrow transplantation, or plan to receive organ transplantation during this clinical study; (11) Patients with autoimmune diseases (such as dermatomyositis, immune (congenital) thrombocytopenic purpura, inflammatory bowel disease, interstitial lung disease, interstitial nephritis, polymyositis, psoriasis, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, etc.) (ANA > 1:80 and/or AMA positive and/or SMA positive); (12) Patients with uncontrolled diabetes (HbA1c > 7.0%) or thyroid disease (such as hypothyroidism, hyperthyroidism) and other endocrine system diseases, or fundus examination suggests the presence of clinically significant retinal diseases (such as retinal hemorrhage, cotton wool exudation spots, papilledema, optic neuropathy, retinal artery or vein occlusion, etc.); (13) Patients with severe hematologic diseases or at increased risk of anemia (e.g., thalassemia, sickle cell anemia, spherocytosis, history of gastrointestinal bleeding); (14) Patients with or suspected malignant tumors; (15) Patients with gastrointestinal disorders or postoperative diseases that may interfere with the absorption of investigational drugs or severe digestive system diseases that may interfere with

	the absorption of investigational drugs; (16) Patients who are receiving or plan to receive hormone replacement therapy during clinical studies; (17) Patients who need to take the following drugs during clinical study: (1) liver enzyme CYP3A4 inducers (such as rifampicin, rifampicin, phenobarbital, phenytoin, carbamazepine) and CYP3A inhibitors (such as ketoconazole, voriconazole); (2). OATP inhibitors (e.g., cyclosporine, rifampicin) or substrates (e.g., rosuvastatin); III. Drugs with a narrow therapeutic window and extensively metabolized by CYP3A and/or substrates for p-glycoprotein transporters (e.g., alfuzosin, astemizole, terfenadine, dihydroergotamine, ergometrine, ergotamine, methylergometrine, cisapride, pimozide, midazolam, triazolam, atorvastatin, lovastatin, simvastatin, fluticasone propionate); IV. Hormonal contraceptives; V. Probenecid and bile acid-binding resins; VI. Immunosuppressive drugs; VII. Have cytotoxic effects or chemotherapeutic agents; VIII. Antiarrhythmic drugs (e.g., amiodarone, bepristone, flecainide, propafenone, quinidine); IX. Corticosteroids (other than topical hydrocortisone and dexamethasone); X. PDE5 inhibitors (sildenafil, tadalafil, vardenafil). The above list of drugs does not contain all drugs that are contraindicated for concomitant use with ritonavir. For a complete list of contraindicated drugs, refer to the Ritonavir Tablets package insert. (18) Blood donation or blood loss more than 400 mL within 2 months before inclusion; or received G-CSF, EPO, TPO within 6 months before inclusion, or received blood transfusion within 6 months before inclusion, or received other treatments with improved hematological parameters within 6 months before inclusion; (19) Allergic to test drugs (including RTV, PEG-IFN α, RBV), or have a history of multiple drug allergies, or have a history of specific reactions; (20) Women of childbearing age (18 years to 1 year after

	menopause) who are pregnant, lactating and take effective contraceptive measures and maintain until at least 6 months after stopping the experimental drug treatment; (21) Male patients with female partners of childbearing potential who take effective contraceptive measures and maintain them for at least 6 months after stopping the treatment with the investigational drug; (22) Patients with a history of alcoholism, drug abuse or drug abuse within 6 months before enrollment that affects the evaluation of the test results; (23) Patients who participated in other clinical studies and received study drug treatment within 3 months before inclusion; (24) In addition to the above, patients who are not suitable for this clinical trial as judged by the investigator.
Dosing Regimen	(1) ASC08 Tablets Oral; 100 mg (1 tablet) twice daily for 12 weeks. (2) RTV Oral; 100 mg (1 tablet) twice daily for 12 weeks. (3) PEG-IFNα Subcutaneous injection in the abdomen or thigh; 180 μg (1 vial) once weekly for 12 weeks. (4) RBV Oral; weight < 75 kg, 500 mg (5 tablets) twice daily, weight ≥ 75 kg, 600 mg (6 tablets) twice daily; for 12 weeks.
Clinical observation items	Screening Period (1) Vital signs and physical examination. (2) BMI determination. (3) Laboratory tests: I. Blood routine examination; Urinalysis;

	III. blood biochemical tests; IV. blood electrolyte examination; V. Coagulation test; VI. thyroid function tests. (4) HbA1c. (5) Immunological examination. (6) AFP. (7) Color Doppler ultrasound. (8) HAV, HBV, HEV and HIV detection. (9) Fundus examination. (10) Pregnancy test. (11) Electrocardiography. (12) IL28B and HCV genotyping assays. (13) HCV detection. (14) HCV RNA detection. (15) Examination for cirrhosis. (16) Drug resistance monitoring. Baseline (1) Vital signs and physical examination. (2) Laboratory tests. (3) HCV RNA detection. (4) Pregnancy test. (5) Electrocardiography.

	(6) Drug resistance monitoring. Treatment period (1) Vital signs and physical examination. (2) Laboratory tests. (3) HCV RNA detection. (4) Pregnancy test. (5) Electrocardiography. (6) Drug resistance monitoring. Post-Treatment Follow-up Period Vital signs and physical examination, laboratory tests, HCV RNA testing, pregnancy test, electrocardiogram, and drug resistance monitoring were completed at each follow-up visit.
Efficacy evaluation indicators	**Main evaluation indicators** Rate of subjects achieving SVR12. **Secondary evaluation indicators** (1) Rate of subjects achieving RVR4. (2) Rate of subjects achieving SVR4. (3) Rate of subjects achieving SVR24. (4) Virological response rate at different visit times. (5) HCV RNA over time. (6) Recurrence rate. (7) Changes in viral resistance.
Safety evaluation indicators	(1) Adverse events observed by the investigator and reported by the subject during the study; (2) Clinically significant changes in vital signs before and after

	treatment; (3) Clinically significant changes in laboratory values before and after treatment; (4) Changes in electrocardiogram before and after treatment.
Statistical Analysis	Measurement data will be described and mean, standard deviation, median, minimum and maximum will be calculated. Enumeration data were described using the number and percentage of cases in each category. All statistical tests were performed using the test, and a P value of less than 0.05 was considered to indicate a statistically significant difference.
Estimated duration of trial	The entire trial is expected to be completed within 15 months.

1. research background

1.1 Clinical Need for Hepatitis C Treatment

The World Health Organization estimates that more than 170 million people (about 3% of the global population) are infected with hepatitis C virus (HCV) worldwide. HCV infection can not only lead to chronic hepatitis C (CHC), but also progress to cirrhosis, hepatocellular carcinoma and liver failure, ultimately leading to death. According to the annual incidence data published by the National Health and Family Planning Commission, the annual number of reported hepatitis C cases in China has exceeded 200,000 since 2012. Studies have shown that the viral gene infected by most CHC patients in China is type 1 (GT1). Hepatitis C has a low public awareness and is the notifiable disease with the highest missed diagnosis rate in China, with a missed diagnosis rate of 52%. The incidence of hepatitis C in China is very high, and the number of deaths has exceeded that of AIDS, avian influenza and a

variety of other infectious diseases, but hepatitis C has not received public attention, and only 2% of hepatitis C patients receive standardized treatment.

At present, the main regimen for the treatment of CHC in China is pegylated interferon α (PEG-IFN α) combined with ribavirin (RBV), that is, P/R regimen. The course of treatment (48 weeks) with this P/R regimen for HCV GT1 infection was very significant, and the patient's tolerance was poor. In 2011, the Food and Drug Administration (FDA) approved two first-generation direct-acting antiviral drugs (DAAs) — boceprevir and telaprevir, both small molecule drugs that are new protease inhibitor drugs. Boceprevir and telaprevir are clinically used in combination with PEG-IFN α and RBV for the treatment of HCV GT1 infection. This therapy improves the proportion of treatment-naive and treatment-experienced patients achieving sustained virological response (SVR), but there are still conditions with long course of treatment, adverse drug reactions and no significant improvement in patient tolerance. In November and December 2013, the US FDA successively approved two second-generation DAA new drugs that can be used to treat HCV GT1 infection — Simeprevir (protease inhibitor) and Sofosbuvir (polymerase inhibitor). Simeprevir and Sofosbuvir in combination with PEG-IFN α and RBV were applied to clinically treat treatment-naïve and treatment-experienced patients with CHC genotype 1, with further improvements in efficacy, course of treatment, and safety. However, to date, no new DAA drugs have been marketed in China.

ASC08 tablet (Danoprevir tablet, DNV) belongs to the protease inhibitors in the second-generation DAA. ASC08 is a macrocyclic peptidomimetic compound that competitively inhibits the activity of HCV nonstructural (NS) protein gene 3/4 A protease, which plays a key role in HCV polypeptide post-translational modification and viral replication. The results showed that low-dose ASC08 (ASC08/r) fortified with low-dose ritonavir (RTV) had the characteristics of high antiviral activity, strong specificity, good pharmacokinetics (PK) and sustained virological response (SVR) and high safety.

1.2 Nonclinical Studies

1.2.1 Nonclinical Pharmacodynamics

ASC08 is a potent and specific inhibitor that selectively inhibits HCV NS3/4A protease activity in HCV replicons and has a synergistic effect with PEG-IFN α and other direct antiviral drugs. ASC08 has unique in vitro kinetic properties and binds to

NS3/4A in two steps to form a stable complex. The low dissociation rate of this complex significantly improved the inhibitory activity of ASC08.

ASC08 had a potent effect on HCV NS3/4A proteases isolated from HCV genotypes 1 to 6 in the sub- to nanomolar order. In transient replicon analysis, ASC08 was less active than the Con1 reference against one genotype 2b isolate (> 2000-fold) and four genotype 3a isolates (372- to 3666-fold) containing NS3 protease from clinical isolates, but remained potent against two genotype 4a isolates (less than 2-fold EC50 transfer).

In vitro, increased concentrations of ASC08 led to variants in HCV genotype 1b replicon with reduced susceptibility to ASC08: substitution of amino acid D168 in NS3 confers in vitro resistance to ASC08. At high concentrations, other substitutions were also observed, mostly at F43S, A156S, and A156V. The sensitivity of HCV replicons with other substitutions to ASC08 was significantly lower than that of replicons with only D168 substitution. Varying degrees of cross-resistance are also observed between different amino acid substitutions, resulting in reduced sensitivity to ASC08, or to other HCV protease inhibitors under investigation.

1.2.2 Non-clinical kinetics

PK assessment of oral or intravenous administration of ASC08 in rats and cynomolgus monkeys showed low (rat) to medium/high (monkey) total clearance, moderate volume of distribution, high protein binding (protein), and high liver-to-plasma ratio, and no gender differences in PK parameters.

After oral administration of 14C-ASC08 to rats, the highest level of radioactivity was observed in the liver. Elimination of radioactivity was rapid (primarily in bile) with only a few tissues containing quantifiable levels at 24 hours.

ASC08 has low permeability and can bleed through P-glycoprotein, non-breast cancer resistance protein. It is also a substrate of organic anion transporting polypeptide (OATP) 1B1 and OATP1B3.

In vitro, the ASC08 metabolite was similar across species. ASC08 is primarily metabolized by CYP3A4, and RTV improves pharmacokinetics primarily by inhibiting the formation of ASC08 metabolites. A number of hydroxyl metabolites are present in low amounts in human plasma. Co-administration of RTV can reduce its content below the detection limit. The human mass balance test confirmed that ASC08 was the predominant form present in plasma. When co-administered with

RTV, individual metabolite production in plasma did not exceed 10% of the total dose.

In vitro, ASC08 was a weak inhibitor of CYP2C8, 2C9, and 3A4, and human multidrug resistance protein 1; it was a strong inhibitor of OATP1B1, OATP1B3, and UDP glucuronosyltransferase-1A1. ASC08 did not induce CYP1A2, 2B6, 2C9, or 3A4 activity. ASC08 did not induce mRNA expression in the inducers of human multidrug resistance protein 1, rat multidrug resistance protein, or human hepatocyte UDP glucuronosyltransferase-1A1.

1.2.3 Toxicology

ASC08 was tolerated up to 2000 mg/kg (oral administration) in rats and 600 mg/kg (oral administration) and 60 mg/kg (intravenous administration) in monkeys in a topical study.

In the repeated-dose study, rats administered ASC08600 mg/kg/day died, and monkeys administered ASC08600 mg/kg/day showed persistent vomiting or/and diarrhea. Pregnant Animals: Rats given 800 mg/kg/day and rabbits (including non-pregnant) given greater than 200 mg/kg/day developed toxic effects.

After repeated dosing, the only clinically relevant local irritant toxicities observed in monkeys and rats were gastrointestinal (GI) side effects. Four monkeys were euthanized after gastrointestinal adverse reactions such as persistent vomiting or/and diarrhea occurred at doses greater than 300 mg/kg/day for 8 consecutive days. In monkeys, dose-limiting but reversible GI-related adverse effects were observed at doses greater than 200 mg/kg/day and included: periodic loose or soft stools and/or vomiting, decreased food consumption, decreased body weight with dehydration, and changes in serum electrolyte parameters. The GI adverse effects observed in monkeys at doses less than 150 mg/kg/day generally did not affect the overall clinical condition of this animal; chronic lesions occurred only in the study at 600 mg/kg/day for 6 months with incomplete recovery after a 5-week recovery period. GI-related findings were likely due to local irritation of the dose and were not related to systemic exposure. The No observed adverse effect level (NOAEL) of GI adverse reactions after 6-month administration was 200 mg/kg/day in rats and 60 mg/kg/day in monkeys. The NOAEL for systemic effects from chronic gavage administration was 150 mg/kg/day in the monkey toxicity study regardless of local GI irritation due to gavage administration.

In safety pharmacology studies, ASC08 was administered at doses up to 600 mg/kg and had no significant effect on cardiovascular function in vitro, nor on cardiovascular or pulmonary function in monkeys in vivo. Doses of up to 600 mg/kg in rats had no significant effect on neurobehavioral function, doses of up to 60 mg/kg had no significant effect on GI motility (decreased GI motility at 200 and 600 mg/kg), and doses of up to 200 mg/kg had no significant effect on renal function (slight changes in urine parameters at 600 mg/kg).

ASC08 was not mutagenic or teratogenic in in vitro and in vivo assays. In reproductive toxicity studies, there were no ASC08-related effects on embryo-fetal development in rats (300 mg/kg/day) or rabbits (120 mg/kg/day), and no ASC08-related effects on fertility parameters in rats (300 and 800 mg/kg/day in females and males, respectively).

1.3 Clinical Studies

1.3.1 Clinical kinetics

The PK of ASC08 co-administered with low-dose RTV (ASC08/r) has been evaluated in healthy adult volunteers and patients with CHC.

RTV showed significant "intensified" PK of ASC08 in healthy volunteers. In healthy Caucasian volunteers, administration of RTV 100 mg and ASC08 100 mg significantly increased AUC0- ∞, Cmax, and C12h of ASC08 by approximately 5.5-fold, 3.25-fold, and 42-fold, respectively, compared with administration of ASC08 100 mg. In healthy Chinese volunteers, AUC0- ∞, Cmax, and C12h of ASC08 were also significantly increased by approximately 6.6-fold, 3.6-fold, and 56-fold, respectively, when administered with RTV 100 mg and ASC08 100 mg compared with ASC08 100 mg at steady state; AUC0- ∞ and Cmax of ASC08 were also significantly increased by approximately 7.3-fold and 5.6-fold, respectively, when administered with multiple doses of RTV 100 mg and ASC08 100 mg at steady state.

Multiple oral doses of ASC08/r (100 mg capsule formulation) 100/100 mg q12h, 200/100 mg q24h, and 200/100 mg q12h in patients with CHC genotype 1, combined with PEG-IFNα/RBV for 15 days (NP22660, groups 1-3). After oral administration of ASC08/r with food, the Tmax of ASC08 was in the range of 1.0 h and 3.0 h. During the initial 2 days, ASC08 concentrations increased and then decreased gradually until steady state was reached by day 6 – 10 of dosing. The AUC value of ASC08 on Day 14 was less than 30% to 40% of that on Day 1. Similar to the results in healthy

volunteers, the exposure-dose relationship of ASC08 in ASC08/r was greater than linear increase at 100/100 mg and 200/100 mg. Doubling the dose of ASC08 administered (100/100 mg q12h and 200/100 mg q12h) resulted in an approximately 4-5-fold increase in exposure.

When ASC08 was administered as a 100 mg film-coated tablet with RTV, a high- or low-fat meal had no effect on ASC08 AUC0- ∞ or C12, but Cmax was decreased by nearly 40% and Tmax was delayed by nearly 1 to 2 hours. RTV showed dose- and time-dependent inhibition/induction of CYP3A and P-gp, but inhibition was more common. Dose-dependent inhibition of CYP2D6 was also observed. RTV is known to induce CYP1A2, 2B6, 2C9, 2C19, and UGT.

The results of the human mass balance test showed that the majority of the radioactive dose was present in the feces when 100 mg of 14C-ASC08 was administered in combination with 100 mg of RTV. The oxidative metabolites in feces were approximately 25% and 2% of the total radioactivity in subjects administered 100 mg 14C-ASC08 and in combination with 100 mg RTV, respectively.

Two clinical trials were conducted with CHC patients as subjects: NV22776 (DAUPHINE) in Caucasian subjects and YV28218 (DAPSANG) in Taiwanese subjects to observe the PK difference of ASC08/r between Taiwanese and Caucasian subjects. The results of the trial showed that plasma exposure was 66% higher in Taiwanese subjects than in Caucasian subjects at similar doses. In the clinical PK trial NP25297 in healthy Japanese subjects, the in vivo exposure at the 100 mg/100 mg ASC08/r dose group was 58% higher than in healthy Caucasian subjects at the same dose.

In a clinical study of NP27946 (RUSHMORE) in Caucasian subjects, the in vivo exposure in subjects with cirrhosis was approximately 3-fold higher at the 100 mg/100 mg ASC08/r dose compared to non-cirrhotic subjects. In the clinical study of YV28218 (DAPSANG) in Taiwanese subjects, the in vivo exposure in subjects with cirrhosis was approximately 2-fold higher than that in subjects without cirrhosis at the equivalent dose.

1.3.2 Clinical Efficacy

Two major clinical studies of ASC08/r in the treatment of HCV-infected patients are: DAUPHINE and DAPSANG.

DAUPHINE is a completed Phase 2b study in Caucasian subjects with CHC. This study compared three different ASC08/r doses when combined with PEG-IFN α /RBV for 24 weeks and PEG-IFN α /RBV alone; an ASC08/r100/100 mg dose response-guided therapy (RGT) group tested a shorter overall treatment duration (12 weeks) for subjects who achieved HCV RNA < 15 IU/mL from Week 2 to Week 10 and compared with those who did not (24 weeks). High SVR24 was achieved in 89%, 79%, 66%, and 69% of all ASC08/r dose groups 200/100 mg, 100/100 mg, 50/100 mg, and RGT, respectively, and 36% of PEG-IFN α /RBV alone. One hundred and eighty-seven Caucasian subjects were assigned to the 100/100 mg ASC08/r dose group, and 49 of these HCV genotype 1 subjects were treated for 12 weeks. The results showed that SVR was 100% in Caucasian subjects with 1b/IL28B CC genotype at 100/100 mg ASC08/r dose, regardless of 12-week treatment or 24-week treatment.

The DAPSANG study was an open-label, parallel-group phase II study of ASC08/r fixed-dose combinations (FDCs) combined with PEG-IFN α and RBV in treatment-naive East or Southeast Asian patients with genotype 1 CHC with or without cirrhosis. Thirty-four subjects entered the non-cirrhotic group, including 17 Taiwanese subjects; subjects in this group received ASC08/r FDC (125 mg/100 mg) in combination with PEG-IFN α and RBV for 12 weeks. The study results showed that the SVR12 of all subjects in the non-cirrhotic group was 88.2%; the SVR12 of subjects with genotype 1a and genotype 1b was 25% and 96.7%, respectively. The SVR12 of Taiwanese subjects in the non-cirrhotic group was 94.1%; the SVR12 of genotype 1b subjects was 100%.

In an ongoing phase II study of ASC08/r in combination with PEG-IFN α and RBV in treatment-naïve non-cirrhotic patients with genotype 1 CHC (ASC-DNVr-II/III-CTP-01) in mainland China, all 15 subjects who had received 4 weeks of treatment had achieved rapid virological response (RVR4) at 4 weeks.

1.3.3 Clinical Safety

In both multiple-dose and repeat-dose clinical pharmacology trials, ASC08/r was generally well tolerated when administered to healthy subjects or patients with CHC.

More than 500 patients were treated with ASC08/r for 12 to 24 weeks in phase I and II clinical trials. ASC08/r was generally well tolerated, and ACTG grade 4 ALT elevations have occurred so far with ASC08/r treatment.

No Grade 4 ALT was observed with ASC08/r treatment in either ASC08/r dose-finding (50/100 mg, 100/100 mg, and 200/100 mg BID). Grade 3/4 laboratory abnormalities were consistent between the groups with ASC08/r and the control group, mainly anemia, lymphopenia, neutropenia and thrombocytopenia. Although the incidence of grade 3/4 combined neutrophil abnormalities was similar in all groups, there was a higher incidence of grade 4 neutrophil abnormalities including ASC08/r. Considering the baseline neutrophil values of the affected patients, the mean and median values in the ASC08/r treatment group compared to the control group, and the incidence of serious infections and terminations, the increase in grade 4 neutrophils does not appear to be clinically significant. The slight increases in triglycerides observed in the 4 ASC08/r treated subjects were not clinically significant and may be due to the addition of RTV to the treatment regimen.

ASC08/r was generally well tolerated during the 12-week combination therapy period in Asian (including Taiwanese) CHC populations. There were no deaths during the study. There were no discontinuations due to adverse events (AEs) during the treatment period. No serious adverse events (SAEs) were reported during the study for subjects in the non-cirrhosis group.

The types and severity of AEs during treatment of genotype 1 CHC with ASC08/r combined with PEG-IFNα and RBV were basically the same as those during P/R treatment; no new AEs were found during ASC08/r treatment, and the severity of AEs related to P/R treatment was not aggravated. The only AE related to ASC08/r that was observed at a higher incidence during the treatment period in the available clinical trials was diarrhea. Overall, RTV-intensified ASC08 for CHC had a high safety profile and was generally well tolerated by subjects.

A clinical phase I study in healthy subjects in China showed that ASC08 was generally well tolerated, with no SAEs, no discontinuations due to AEs, and no withdrawals due to AEs. Clinical phase II study in domestic patients with genotype 1 CHC showed that after 4 weeks of treatment with ASC08/r combined with PEG-IFN α and RBV, the subjects generally tolerated well, without SAE or withdrawal due to AE; the AEs experienced by the subjects were common adverse reactions during PEG-IFN α and RBV treatment.

ASC08 tablets are DAAs with independent intellectual property rights developed by Ascletis Pharmaceuticals Co., Ltd. in China. ASC08 tablets are now proposed for

the treatment of non-cirrhotic patients with chronic hepatitis C genotype 1 virus infection who are initially treated in China.

2. test purpose

The primary objective of this study was to (1) evaluate the rate of subjects achieving SVR12 after 12 weeks of ASC08/r in combination with PEG-IFN α and RBV in treatment-naive non-cirrhotic subjects with chronic hepatitis C genotype 1 virus infection. 2) To evaluate the safety of ASC08/r in combination with PEG-IFN α and RBV in treatment-naive non-cirrhotic subjects with chronic hepatitis C genotype 1 virus infection.

The secondary objectives of this clinical study were: (1) to evaluate the rate of subjects achieving RVR4; (2) to evaluate the rate of subjects achieving SVR4; (3) to evaluate the rate of subjects achieving SVR24; (4) to evaluate the change in virological response rate over time during the clinical study; (5) to evaluate the kinetics of viral load changes during the clinical study; (6) to evaluate the relapse rate of combination therapy; and (7) to evaluate the viral resistance profile to ASC08.

3. trial design

This clinical study is a multicenter, open-label, single-arm clinical study with historical data as the control. All screened eligible subjects received the same treatment: 100 mg ASC08 tablets/100 mg RTV (ASC08/r) combined with PEG-IFN α and RBV therapy (triple therapy) for 12 weeks, followed by 24 weeks of post-treatment follow-up.

3.1 Rationality

3.1.1 RTV Enhancement Strategy Rationale

RTV is a peptidomimetic inhibitor that inhibits human immunodeficiency virus (HIV) -1 and HIV-2 proteases; it is used in combination with other antiretroviral agents for the treatment of HIV infection; the approved therapeutic dose is 600 mg twice daily (BID) (Norvir ®). Due to its poor tolerability and the availability of more effective HIV protease inhibitors, therapeutic doses of RTV are no longer available. Currently, RTV mostly uses low-dose, subtherapeutic doses (e.g., 100 − 200 mg/day) to increase or intensify the exposure of other protease inhibitors that can be extensively metabolized by cytochrome P450 (CYP) 3A isoenzymes. For example,

intensive HIV protease inhibitors with 100 mg RTV have been widely used in clinical practice for more than 10 years with good safety.

The purpose of using RTV to strengthen ASC08 strategy is to improve the PK of ASC08, reduce the clinical dose of ASC08, ensure the clinical efficacy of ASC08, and enhance the safety of ASC08.

The kinetics of ASC08 (ASC08/r) fortified with 100 mg RTV have been studied in healthy volunteers and CHC patients, respectively. In healthy Caucasian volunteers, RTV showed significantly "fortified" PK of ASC08; AUC0- ∞, Cmax of ASC08 100 mg fortified with RTV were significantly increased by approximately 5.5-fold and 3.25-fold, respectively, compared to unfortified ASC08 100 mg; and Cmin was particularly significantly increased by up to 42-fold. In healthy Chinese volunteers, RTV also showed significantly "fortified" PK of ASC08; AUC0- ∞, Cmax of ASC08 100 mg fortified with RTV were significantly increased by approximately 6.6-fold and 3.6-fold, respectively, compared to unfortified ASC08 100 mg. In CHC patients, the PK parameters of ASC08 fortified with RTV from the DAUPHINE study were compared with those fortified with ATLAS (Table 1).

Table 1 Comparison of steady-state (4-week) PK parameters in treatment-naïve patients with CHC genotype 1

		DAUPHINE (REINFORCED ASC08)			**ATLAS (unfortified ASC08)**	
		50/100 mg BID	**100/100 mg BID**	**200/100 mg BID**	**600 mg BID**	**900 mg BID**
	Number of cases	16	33	16	15	7
AUC0-12h (ng · h/mL)	Mean value Median CV%	121 83.4 81.9	320 208 114	750 458 97.6	878 433 92.2	2450 964 131
Cmax (ng/mL)	Mean value Median CV%	48.9 33.4 95.1	126 64.6 130	355 195 117	915 344 129	2150 1100 99.6
Cmin (ng/mL)	Mean value Median CV%	1.21 0.91 98.4	2.24 0.97 134	5.36 1.92 159	0.62 0.50 62.6	1.37 0.76 102

The comparison results showed that low-dose RTV (100 mg) fortified ASC08 significantly improved the PK parameters of ASC08. The trough concentration (Cmin) of RTV fortified 100 mg ASC08 was similar compared to unfortified 900 mg ASC08. One of the most important parameters (Cmin) required for ASC08 to produce clinical efficacy was still ensured with a 9-fold reduction in the dose.

In the Phase 2 clinical study NV21075 (ATLAS), which did not intensify ASC08, a small proportion of subjects treated with ASC08 (4 subjects in total) experienced reversible ACTG Grade 4 ALT elevations. However, no ACTG grade 4 ALT elevation was observed during treatment in any of the clinical trials of ASC08 for CHC with RTV intensification.

The literature confirms that the formation of reactive metabolites is associated with drug-induced liver dysfunction. The completed ASC08 study suggested that the reason why low-dose RTV improved the safety of ASC08 may be through reducing the formation of ASC08 metabolites. The ACTG grade 4 ALT elevations that have occurred in clinical studies of unintensified ASC08 are likely to be caused by reactive metabolites of ASC08. Qualitative analysis of human metabolites revealed that up to 20 different metabolites were found in pooled plasma samples from 3 subjects receiving unfortified ASC08 900 mg q12h, whereas metabolites were detected in pooled plasma samples from 3 subjects receiving ASC08/r 200/100 mg q12h. The results of the mass balance study confirmed that the metabolism of [14C] -ASC08 included a large number of oxidative metabolites as well as hydrolytic metabolites, and the levels of oxidative metabolites were greatly reduced in the excreta after the addition of RTV. The oxidative metabolites were approximately 25% of the total radioactivity in the excreta without ASC08 fortification, and approximately 2% of the total radioactivity in the excreta with ASC08 fortification, i.e., the oxidative metabolite of ASC08 fortified with RTV was decreased by 12.5-fold. In vitro experiments using human liver microsomes incubated with 14C-labeled ASC08 showed that ASC08 caused significant covalent protein binding (512 pmol/mg/30 min), presumably as a result of reactive metabolite formation. RTV was added to the incubation and covalent protein binding was reduced to background levels (11.5 pmol/mg/30 min). These findings suggest that the ALT elevation observed in the unfortified ASC08 study may be related to the reactive metabolite of ASC08, and RTV may decrease the formation of reactive metabolites by inhibiting the metabolism of ASC08, thereby reducing the possibility of ALT elevation events and the degree of

ALT elevation and enhancing the safety of ASC08 application.

3.1.2 Rationale for Dose Selection

The dose of ASC08/r selected for this clinical study was: 100 mg/100 mg twice daily. The primary rationale for this dose selection is:

The results of DAUPHINE study showed that, compared with control group E, SVR12 (32.5%) and SVR24 (35.0%) (Table 2), subjects with CHC genotype 1 infection treated with ASC08/r achieved higher SVR rate, and SVR12 and SVR24 were equal, 92.5% for group A, 81.5% for group B and 67.5% for group C (all results of PP set analysis), showing significant dose-dependent response relationship. The SVR of group C was significantly lower than that of groups A and B. The results showed that the dose of 50 mg/100 mg of ASC08/r for the treatment of CHC was significantly too low, and this dose for the treatment of CHC not only had low clinical efficacy but also easily made HCV virus resistant, which would be not conducive to the clinical treatment of CHC patients. Therefore, from the perspective that meeting the clinical efficacy is conducive to the treatment of patients, the clinical dose selection of 100 mg/100 mg or 200 mg/100 mg is more appropriate than 50 mg/100 mg when ASC08/r is used to treat CHC.

Table 2 SVR of three doses of ASC08/r for 24-week course treatment of genotype 1 CHC in DAUPHINE study

Test	**DAUPHINE**			
Treatment	**Group A: ASC08/r + PEG-IFNα + RBV**	**Group B: ASC08/r + PEG-IFNα + RBV**	**Group C: ASC08/r + PEG-IFNα + RBV**	**Group E: P/R**
ASC08/r dose	200 mg/100 mg	100 mg/100 mg	50 mg/100 mg	-
Number of cases	84	85	86	41
SVR12 n/N (%)	74/80 (92.5%)	66/81 (81.5%)	54/80 (67.5%)	13/40 (32.5%)
SVR24 n/N (%)	74/80 (92.5%)	66/81 (81.5%)	54/80 (67.5%)	14/40 (35.0%)

The results of NP25297 study showed that the plasma exposure of ASC08 in healthy Japanese subjects was approximately 1.6 times higher than that in Caucasian

subjects at the dose of ASC08/r 100 mg/100 mg (Table 3), and 2.9 times higher than that in Caucasian subjects at the dose of ASC08/r 200 mg/100 mg. The study results also showed that in Japanese subjects, the plasma exposure in the ASC08/r 200 mg/100 mg dose group was approximately 7-fold higher than that in the 100 mg/100 mg dose group (Table 4), which greatly exceeded the proportion of dose increase. This may increase the safety risk of clinical medication, but has no significant effect on the efficacy. Therefore, ASC08/r 100 mg/100 mg is a more appropriate dose for Asian population.

Table 3 Differences in ASC08 plasma exposure between Japanese and Caucasian populations in NP25297 study

ASC08/r dose	Number of cases	Study Day	Parameter	Caucasian Subjects	Japanese subjects	Ratio
100 mg/100 mg	18	1	AUC0-∞ (ng · h/mL)	108	170	1.57
		9	AUC0-τ (ng · h/mL)	104	165	1.58
200 mg/100 mg	9	1	AUC0-∞ (ng · h/mL)	444	1290	2.90
		9	AUC0-τ (ng · h/mL)	391	1140	2.90

Table 4 Differences in Plasma Exposure to ASC08 by Dose in Japanese Population in NP25297 Study

ASC08/r dose	Number of cases	Study Day	Parameter	Japanese subjects	Ratio
100 mg/100 mg	18	1	AUC0-∞ (ng · h/mL)	170	--
		9	AUC0-τ (ng · h/mL)	165	--
200 mg/100 mg	9	1	AUC0-∞ (ng · h/mL)	1290	7.59
		9	AUC0-τ (ng · h/mL)	1140	6.9

Combining the study data of efficacy and plasma exposure in DUPHINE and NP25297, we speculated that the possible appropriate dose of ASC08/r was 100 mg/100 mg when ASC08/r combined with PEG-IFN α + RBV was used for the

treatment of Asian CHC genotype 1 virus-infected population.

According to relevant literature reports, the proportion of HCV genotype 1b patients in HCV genotype 1 infected population in Europe and the United States is less than 40%, while the proportion of HCV genotype 1b patients in HCV genotype 1 infected population in China is 98%. Through computational analysis, we speculated that the use of ASC08/r 100 mg/100 mg dose and 12-week course of treatment in Chinese CHC genotype 1 infected population will have a higher rate of SVR than the Caucasian population treated for CHC genotype 1 infection, which may exceed 90%. To test the hypothesis, we conducted the DAPSANG study in an Asian population with CHC genotype 1 infection.

The fixed-dose combination (ASC08/r FDC) was used in the DAPSANG trial. The results of NP28136 study showed that the plasma exposure of ASC08 at 125 mg/100 mg of ASC08/r FDC was only 17% higher than that at 100 mg/100 mg of ASC08/r mono (Table 5), and this increase in exposure was not clinically significant.

Table 5 Plasma exposure of FDC vs. ASC08/r

Parameter	Drug	Dose	Number of cases	Mean value	Ratio
AUC (0-inf) (ng · h/mL)	ASC08/r unilateral	100 mg/100 mg	42	65.5	-
	ASC08/r FDC	100 mg/100 mg	40	51.5	0.78
		125 mg/100 mg	42	76.7	1.17

The results of the DAPSANG study (Table 6) showed that the primary endpoint, SVR12, after 12 weeks of treatment with ASC08/r FDC combined with PEG-IFN α + RBV in non-cirrhotic Asian subjects with CHC genotype 1 infection was 88.2%, and SVR12 in subjects with CHC genotype 1a and 1b infection was 25% and 96.7%, respectively. SVR12 was 94.1%, 0, and 100% in genotype 1, genotype 1a, and genotype 1b infected Chinese subjects with CHC genotype 1 infection who received ASC08/r FDC in combination with PEG-IFN α + RBV for 12 weeks, respectively.

Table 6 SVR12 of ASC08/r FDC in treatment of genotype 1 CHC in DAPSANG study

Test		**DAPSANG**	
Treatment		**ASC08/r FDC + PEG-IFNα + RBV**	
Number of cases		Asia	Taiwan
		34	17
		Response n/N (%)	
SVR12	GT1	30/34 (88.2)	16/17 (94.1)
	GT1a	1/4 (25)	0/1 (0)
	GT1b	29/30 (96.7)	16/16 (100)

The results of the DAPSANG study not only verified the study prediction that ASC08/r FDC 125 mg/100 mg dose combined with PEG-IFNα + RBV could achieve good efficacy in the treatment of CHC genotype 1 infection in Asian population for 12 weeks, but also found that this treatment regimen was more effective for CHC genotype 1 infection in Taiwanese population, especially for CHC genotype 1b infection in Taiwanese population.

In an ongoing phase II study of ASC08/r in combination with PEG-IFN α and RBV in treatment-naïve non-cirrhotic patients with genotype 1 CHC (ASC-DNVr-II/III-CTP-01) in mainland China, RVR4 has been obtained in all 15 subjects who had received 4 weeks of 100 mg/100 mg dose of ASC08/r in combination with PEG-IFN α and RBV.

Therefore, 100 mg/100 mg q12h ASC08/r was selected in this clinical study to well demonstrate the safety and clinical efficacy of ASC08 in Chinese CHC subjects. Combined with PEG-IFN α and RBV, it would bring significant clinical benefits to the newly diagnosed non-cirrhotic Chinese subjects with chronic hepatitis C genotype 1 infection who participated in this clinical study.

3.1.3 Rationale for Course of Treatment

The treatment cycles for the 100 mg/100 mg q12h ASC08/r dose group in the DAUPHINE study were 12 and 24 weeks. One hundred and eighty-seven Caucasian CHC subjects were assigned to the 100 mg/100 mg ASC08/r dose group, and 49 of these HCV genotype 1 subjects were treated for 12 weeks. The results showed that SVR was 100% in Caucasian subjects with 100 mg/100 mg ASC08/r dose 1b/IL28B CC

genotype, regardless of 12-week treatment or 24-week treatment. However, at the 100 mg/100 mg ASC08/r dose, SVR values were not the same in Caucasian subjects with the 1b/IL28B non-CC genotype after 12 and 24 weeks of treatment, with an SVR of 62.5% in the 12-week course and 95.5% in the 24-week course. Therefore, the use of a 100 mg/100 mg ASC08/r dose and a 12-week course of treatment will make Caucasian CHC subjects with 1b/IL28B non-CC genotype less than the optimal treatment effect. However, among HCV genotype 1b patients in China, the proportion of patients with 1b/IL28B non-CC genotype is much lower than that in Europe and the United States, only 16%; and 84% for patients with 1b/IL28B CC genotype. Therefore, SVR12 in domestic patients with HCV genotype 1b infection treated with 100 mg/100 mg ASC08/r dose and 12-week course of treatment can be simply speculated as follows (SVR of 1b/IL28B CC and 1b/IL28B non-CC is 100% and 62.5%, respectively): SVR12 = 100% × 84% + 62.5% × 16% = 94%.

Among HCV genotype 1 infected patients in China, the proportion of HCV1b is about 98%. Therefore, it can be predicted that SVR12 can reach more than 90% in treatment-naive, non-cirrhotic patients with HCV genotype 1 infection treated with 100 mg/100 mg ASC08/r dose and a 12-week course of treatment.

According to the results of NP25297 study and DAPSANG study data, it is speculated that the plasma exposure of Chinese CHC patients receiving 100 mg/100 mg ASC08/r dose should be slightly higher than the exposure of Caucasians receiving 100 mg/100 mg ASC08/r dose. Therefore, SVR at the dose of 100 mg/100 mg ASC08/r and a 12-week course in Chinese CHC patients will result in a corresponding improvement in clinical efficacy due to an increase in ASC08 plasma exposure. The results of data analysis of Taiwanese CHC patients in the DAPSANG study further confirmed that SVR12 reached 94.1% in Taiwanese CHC patients and 100% in genotype 1b subjects after 12 weeks of treatment at an approximate 100 mg/100 mg ASC08/r dose. The results of the DAPSANG study not only verified the study prediction that ASC08/r combined with PEG-IFN α + RBV could achieve good efficacy in the treatment of CHC genotype 1 infection in Asian populations for 12 weeks, but also found that this treatment regimen was more effective for CHC genotype 1 infection in the Taiwanese population, especially for CHC genotype 1b infection in the Taiwanese population. The CHC population in mainland China has the same ethnic characteristics as the CHC population in Taiwan. Genotype 1 is

predominant in the CHC population in mainland China (approximately 60% of the total CHC population), with genotype 1b accounting for approximately 98% of the genotype 1 population. Based on these epidemiological characteristics and the results of the DAPSANG study, we believe that ASC08/r combined with PEG-IFN α + RBV for 12 weeks will be suitable for the treatment of genotype 1 CHC in mainland China.

In an ongoing phase II study (ASC-DNVr-II/III-CTP-01) in mainland China, the treatment duration of ASC08/r in combination with PEG-IFN α and RBV for treatment-naive patients with genotype 1 CHC without cirrhosis was also 12 weeks; RVR4 had been obtained in all 15 subjects who had received 4 weeks of ASC08/r at the dose of 100 mg/100 mg in combination with PEG-IFN α and RBV.

Therefore, 12 weeks was selected as the treatment cycle of ASC08/r in this clinical study.

3.1.4 Reasons for using an open single-arm trial design

(1) After the marketing of DAA, a breakthrough has been made in the treatment of chronic hepatitis C internationally. However, so far, the current main treatment regimen for HCV genotype 1 chronic hepatitis C in China is still pegylated interferon combined with ribavirin for 48 weeks, with a low percentage of achieving SVR (about 73.9%) and a long treatment cycle; in addition, the percentage of achieving SVR in HCV genotype 1 virus infection treated with common interferon combined with ribavirin in China is lower, about 40-50%. At present, there is no new DAA drug marketed in China, so no new DAA-based treatment regimen has been formed. The treatment regimen of ASC08 for HCV genotype 1 chronic hepatitis C is DAA-based triple therapy (ASC08/r + PEG-IFN α + RBV) administered for 12 weeks, so there is no appropriate treatment regimen that can be used as a control.

(2) If the existing P/R regimen in China is used as a control, the 12-week treatment cycle of ASC08/r triple therapy is too different from the 48-week treatment cycle of P/R regimen, and it is difficult to implement a double-blind parallel control. After 12 weeks of treatment, subjects in the ASC08/r triple therapy group ended treatment, and the clinical trial needed to be unblinded so that subjects in the P/R group could continue treatment; the double-blind parallel control design could not be further implemented after unblinding, so the double-blind parallel control could not be conducted in this clinical trial.

(3) The clinical efficacy of ASC08/r triple therapy is quite different from that of existing P/R regimens, and the implementation of parallel control is not conducive to ensuring the interests of subjects. The phase II clinical study (DAUPHINE) with P/R regimen as the control that has been completed in foreign countries has confirmed that ASC08 triple therapy has a significant clinical efficacy advantage over P/R regimen (SVR12 and SVR24 were 81.5% (66/81) in genotype 1 subjects and 35% (14/40) in P/R treatment group; SVR12 and SVR24 were 96.4% (27/28) in genotype 1b subjects in 100/100 mg ASC08 treatment group). The P/R regimen had more adverse effects and was also more severe and poorly tolerated by patients. Therefore, subjects in the control group who receive the P/R regimen for 12 weeks will have to continue to receive treatment and suffer adverse effects for up to 36 weeks, and have lower clinical efficacy than the experimental group even after completing treatment. This will not only harm the subject's own interests; but also cause the subject to continue to participate in the clinical trial and withdraw voluntarily due to the fact that the subject has generally received a long course of interferon treatment, resulting in a higher dropout rate, thus seriously imbalance the number of subjects in the control group and further causing serious bias in the clinical trial results.

(4) In the case that the efficacy advantage has been verified in phase II clinical studies, there is also a precedent for no control group in phase III clinical studies of new anti-hepatitis C drugs approved by the FDA. In the phase III clinical study of Sofosbuvir, a new drug for the treatment of hepatitis C approved by the US FDA for marketing in December 2013 (NEUTRINO trial, Sofosbuvir + P/R), P/R was not used as a control group. The NEUTRINO trial used an open single-arm design to evaluate the treatment of genotype 1 CHC. The results of this trial were accepted by the FDA and became the only phase III clinical trial approved by the US FDA for Sofosbuvir for the treatment of genotype 1 CHC. In recent years, more and more phase III clinical trials of DAA studies have used single-arm design, for example, Gilead carried out phase III international multicenter clinical trials Sofosbuvir + P/R study (CTR20150250) and Harvoni (Ledipasvir/sofosbuvir) study in China without P/R control group.

3.1.5 Reason for Drug Resistance Monitoring

Multiple clinical trials have been completed confirming that the most common mutation regarding treatment failure in ASC08 treatment regimens is R155K in NS3 protease, and most of them are in genotype 1a and less in genotype 1b. Different ASC08 resistance profiles were observed in subjects infected with HCV genotype 1b;

single mutations occurred at positions 168 and 80, and double mutations occurred at positions 155 and 168. The only current response to a treatment-emergent viral mutation is discontinuation of drug therapy. The mutated virus reverts to wild-type after stopping ASC08 treatment, rather than remaining resistant for a long time; the reverted virus reresponds to antiviral therapy. Therefore, this clinical study will monitor the occurrence and development of ASC08 resistance and reveal the characteristics of viral resistance to ASC08 through phenotypic and/or sequence analysis of drug-resistant viruses.

3.2 Multicenter

This clinical study is a multi-center clinical study. The leading site is Peking University People's Hospital and the principal investigator is Professor Wei Lai. All the units participating in clinical trials are drug clinical trial institutions approved by China Food and Drug Administration.

Statistical institution: Peking University Clinical Research Institute.

3.3 Number of cases

According to the requirements of Provisions for Drug Registration and other relevant regulations and in combination with statistical requirements, a total of 127 subjects were planned to be included in this clinical study.

Regarding the P/R treatment response rate in Chinese genotype 1 chronic hepatitis C population, a meta-analysis showed that the percentage of patients achieving SVR24 was approximately 73.9% (see Reference 19 for details); the estimate of domestic clinical experts was also similar, approximately 65% ~ 75%. Therefore, the single-arm target value of the proportion of subjects achieving SVR12 in this trial is set as 75%. The proportion of subjects achieving SVR12 after triple therapy with ASC08 is expected to be 85% based on the results of previous clinical trials. It was estimated by statistical methods that 127 subjects had 80% power, and there was a significant difference in the rate of subjects achieving SVR after treatment with ASC08/r combined with PEG-IFN α and RBV compared with P/R when the α was 0.025 and the lower limit of 95% confidence interval of the primary efficacy evaluation indicator (the rate of subjects achieving SVR12) was greater than 75%.

There is only one group in this clinical study, i.e., the ASC08/r treatment group, and all included subjects will enter this group. The final number of enrolled and completed subjects is based on the number of subjects actually enrolled and

completed at the end of this clinical study.

3.4 Study procedures

3.4.1 Clinical study process

(1) Screening period

The subjects should receive the screening examination within 28 days before the start of drug treatment, and eligible subjects should be enrolled in this clinical study for treatment. Subjects may be re-screened only if there is a change in past medical history and/or treatment status and/or signs.

(2) Baseline

Baseline examination was done before the first dose in the morning of Day 1 of combination therapy.

(3) Treatment period

During the treatment phase, subjects received a 12-week combination of ASC08/r + PEG-IFN α + RBV.

(4) Post-treatment follow-up period

All subjects were followed post-treatment for 24 weeks after the end of combination therapy.

The trial procedures of this clinical study are shown in Appendix 4.

3.4.2 End of Clinical Observations

After treatment, the follow-up will be completed, and the subjects will be withdrawn from the study. The clinical observation of this clinical study will be completed after all the enrolled subjects have completed the trial (including drop-out subjects).

The end of clinical observation is defined as the last subject completed the last visit specified in the trial protocol or the last data collection required for statistical analysis. The latest of these two events is used as the end time of clinical observation in this clinical study.

4. subjects

4.1 Inclusion Criteria

(1) Aged 18 years and above, male or female;

(2) Establish the diagnosis of CHC must meet one of the following conditions:

(1) hepatitis C virus infection ≥ 6 months (6 months ago anti-HCV antibody positive, or HCV RNA positive); (2). Liver tissue biopsy within 1 year before inclusion consistent with CHC pathological features.

(3) Anti-HCV positive.

(4) Serum HCV RNA ≥ 1.0 × 104 IU/mL;

(5) HCV genotyping is genotype 1.

(6) Patients who have not received any interferon and/or other DAA treatment (regardless of the length of time);

(7) Patients without cirrhosis; Non-cirrhosis is defined as: (1) Fibroscan value ≤ 9.6kPa during screening, or liver biopsy within 1 year before inclusion confirmed as non-cirrhosis (Metavir score ≤ 3 points; See Appendix 1 for details of scoring method); II. 9.6 < Fibroscan value ≤ 12.9 during screening, must be confirmed as non-cirrhotic by liver biopsy.

(8) Patients who voluntarily sign the informed consent form;

4.2 Exclusion criteria

(1) Patients with Fibroscan > 12.9kPa, or patients with liver cirrhosis by histopathological examination;

(2) Patients with previous or existing evidence of chronic liver disease caused by non-HCV (such as hemochromatosis, autoimmune liver disease, Wilson's disease, α 1 antitrypsin deficiency, alcoholic liver disease, chronic drug-induced liver disease, etc.);

(3) Patients with a history of hepatocellular carcinoma, or patients with suspected hepatocellular carcinoma before screening or screening, or patients with suspected hepatocellular carcinoma on color Doppler ultrasonography at screening, or AFP > 50 ng/mL;

(4) Anti-HAV (IgM), HBsAg, anti-HEV (IgM), anti-HIV one of the positive;

(5) BMI < 18 or ≥ 30 kg/m2;

(6) ANC (AbsoluteNeutrophil count) < 1.5 × 109/L, PLT < 100 × 109/L, HB < 110 g/L (female) or < 120 g/L (male); INR > 1.5; ALP ≥ 1.5 times ULN (upper limits of normal); ALT or AST ≥ 5 times ULN; TBIL ≥ 2 times ULN (DBIL ≥ 35% TBIL); Cr ≥ 1.5 times ULN; TSH > ULN or TSH < LLN (lower limits of normal);

(7) Patients who have or have had neurological and/or psychiatric psychiatric disorders, have poor self-control, and cannot express their wishes with certainty;

(8) Patients with obvious cardiovascular dysfunction, such as heart function grade III or above or score < 50%; or patients with severe cardiovascular disease (such as ventricular tachyarrhythmia, myocardial infarction, angina pectoris, coronary artery disease or other serious cardiovascular disease); or patients with existing uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg); or patients with obvious clinical abnormal ECG results;

(9) Patients with severe acute or chronic respiratory or severe urinary system diseases;

(10) Have received solid organ transplantation or corneal transplantation or bone marrow transplantation, or plan to receive organ transplantation during this clinical study;

(11) Patients with autoimmune diseases (such as dermatomyositis, immune (congenital) thrombocytopenic purpura, inflammatory bowel disease, interstitial lung disease, interstitial nephritis, polymyositis, psoriasis, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, etc.) (ANA > 1:80 and/or AMA positive and/or SMA positive);

(12) Patients with uncontrolled diabetes (HbA1c > 7.0%) or thyroid disease (such as hypothyroidism, hyperthyroidism) and other endocrine system diseases, or fundus examination suggests the presence of clinically significant retinal diseases (such as retinal hemorrhage, cotton wool exudation spots, papilledema, optic neuropathy, retinal artery or vein occlusion, etc.);

(13) Patients with severe hematologic diseases or at increased risk of anemia (e.g., thalassemia, sickle cell anemia, spherocytosis, history of gastrointestinal bleeding);

(14) Patients with or suspected malignant tumors;

(15) Patients with gastrointestinal disorders or postoperative diseases that may interfere with the absorption of investigational drugs or severe digestive system diseases that may interfere with the absorption of investigational drugs;

(16) Patients who are receiving or plan to receive hormone replacement therapy during clinical studies;

(17) Patients who need to take the following drugs during the clinical study: (1) liver enzyme CYP3A4 inducers (such as rifampicin, rifampicin, phenobarbital, phenytoin, carbamazepine) and CYP3A inhibitors (such as ketoconazole, voriconazole); (2) OATP inhibitors (such as cyclosporine, rifampicin) or substrates (such as rosuvastatin); Drugs with a narrow therapeutic window and extensively metabolized by CYP3A and/or substrates for p-glycoprotein transporters (e.g., alfuzosin, astemizole, terfenadine, dihydroergotamine, ergometrine, ergotamine, methylergometrine, cisapride, pimozide, midazolam, triazolam, atorvastatin, lovastatin, simvastatin, fluticasone propionate); IV. Hormonal contraceptives; V. Probenecid and bile acid-binding resins; VI. Immunosuppressive drugs; VII. Have cytotoxic effects or chemotherapeutic agents; VIII. Antiarrhythmic drugs (e.g., amiodarone, bepristone, flecainide, propafenone, quinidine); IX. Corticosteroids (other than topical hydrocortisone and dexamethasone); X. PDE5 inhibitors (sildenafil, tadalafil, vardenafil). The above list of drugs does not contain all drugs that are contraindicated for concomitant use with ritonavir. For a complete list of contraindicated drugs, refer to the Ritonavir Tablets package insert.

(18) Blood donation or blood loss more than 400 mL within 2 months before inclusion; or received G-CSF, EPO, TPO within 6 months before inclusion, or received blood transfusion within 6 months before inclusion, or received other treatments with improved hematological parameters within 6 months before inclusion;

(19) Allergic to test drugs (including RTV, PEG-IFN α, RBV), or have a history of multiple drug allergies, or have a history of specific reactions;

(20) Women of childbearing age (18 years to 1 year after menopause) who are pregnant, lactating and take effective contraceptive measures and maintain until at least 6 months after stopping the experimental drug treatment;

(21) Male patients with female partners of childbearing potential who take effective contraceptive measures and maintain them for at least 6 months after stopping the treatment with the investigational drug;

(22) Patients with a history of alcoholism, drug abuse or drug abuse within 6 months before enrollment that affects the evaluation of the test results;

(23) Patients who participated in other clinical studies and received study drug treatment within 3 months before inclusion;

(24) In addition to the above, patients who are not suitable for this clinical trial as

judged by the investigator.

4.3 Drop-out cases

4.3.1 Determination of dropout cases

All subjects who have signed the informed consent form and passed screening to enter the trial have the right to withdraw from the clinical trial at any time; no matter when or why they withdraw, they are all dropouts as long as they do not complete the whole observation of the clinical trial.

4.3.2 Reasons for dropout

(1) Subjects actively withdraw from the trial, or do not clearly propose to withdraw from the trial, but no longer accept visits and lose follow-up;

(2) Adverse events or adverse reactions, which are not suitable to continue the trial as judged by the investigator;

(3) It is necessary to take measures to improve or restore the health status of subjects in violation of the trial protocol;

(4) During the trial, it is not suitable to continue the trial due to special reasons as judged by the investigator.

4.3.3 Handling of Drop-out Cases

(1) The investigator should actively take measures (telephone, door-to-door, appointment for follow-up, letter, etc.) to contact the subjects who drop out of the trial, complete the follow-up items that can be completed as far as possible, and fill in the follow-up records.

(2) For subjects who withdraw due to adverse events, the investigator should take corresponding treatment measures according to the actual situation of the subjects.

(3) For all drop-out cases, the reason for drop-out should be filled in the case report form (CRF); if the adverse event is judged to be related to the investigational drug, the investigator should notify the sponsor.

4.4 Excluded cases

4.4.1 Reasons for removal

(1) Subjects misincluded;

(2) No medication after enrollment;

(3) There is no evaluable record after medication;

(4) Concomitant use of prohibited drugs, resulting in inability to perform efficacy and/or safety evaluation.

4.4.2 Handling of excluded cases

(1) Reasons should be stated for excluded cases, and their records should be retained for future reference.

(2) No efficacy analysis of data will be performed for the excluded cases; however, the excluded cases who receive at least one treatment and have safety data records can be included in the safety analysis as appropriate.

4.5 Terminating the trial

4.5.1 Reason for termination

(1) Major errors in the clinical trial protocol, or serious deviations in the implementation of the protocol, making it difficult to evaluate the efficacy and/or safety of the drug;

(2) The sponsor requests termination of the trial;

(3) The national drug regulatory authority cancels the trial;

(4) Other investigators believe that it is not appropriate to continue the trial or that it is difficult to continue the trial;

4.5.2 Handling of terminating the trial

In case of terminating the clinical trial, all parties shall be notified in a timely manner. The investigator shall record in detail the reasons for trial termination and the process leading to trial termination, etc., and all the records shall be retained for future reference.

4.6 Subject Management

4.6.1 Withdrawal

Subjects participating in this clinical study should be withdrawn from the clinical study if they:

(1) The subject is not willing to continue to participate in this clinical study, and actively requests to withdraw from this clinical study or his legal representative requests to withdraw from this clinical study.

(2) The subject's serum HCV RNA content is > 1,000 IU/mL at week 4 of the treatment period and confirmed 2 times later (at least 2 consecutive measurements); or the subject's HCV RNA continues to increase by ≥ 1 log10 IU/mL (at least 2 consecutive measurements) compared with the lowest value during the treatment period (≥ 1 log10 IU/mL reduction from baseline HCV RNA after at least 2 weeks of treatment).

(3) Subjects with grade 4 ALT elevation, or grade 3 ALT elevation with TBIL (DBIL ≥ 35% TBIL) > 2 times ULN, or grade 3 ALT elevation with INR > 1.5; and retest and confirm at 2.

(4) Subjects with neutropenia and/or anemia, after adjusting the dose of PEG-IFN α and/or RBV or using other drugs to improve neutropenia and/or anemia are ineffective;

(5) Subjects with grade 3 and above and intolerable adverse events other than the above (3) and (4) are not suitable to continue to participate in clinical studies.

(6) Received other treatments during the clinical study that affect the efficacy and safety evaluations specified in this protocol.

(7) During the clinical study, the subject has other diseases requiring treatment, and the investigator judges that the disease will significantly affect the evaluation of the subject's clinical condition, and the treatment specified in this clinical study protocol needs to be stopped.

(8) If a female subject becomes pregnant during combined treatment, she should withdraw from this clinical study; if a female subject becomes pregnant during post-treatment follow-up, she may not withdraw from this clinical study.

(9) Other situations that the investigator considers it inappropriate for the subject to continue to participate in this clinical study.

4.6.2 Compliance

Each subject will receive a diary to record the medication during the clinical trial, including investigational drug and concomitant medication and dietary contraindication information, as well as AEs during the clinical trial.

Each use of all investigational drugs must be recorded in a diary, including the name of the drug, strength, dosage each time, storage conditions, etc. The subject must return all used and unused medication and cartons at the time of the visit. The investigator should count the doses taken by the subject and make a record. All used drug and its containers returned by subjects and unused drug and containers must be returned to the investigator for destruction by the sponsor or by the sponsor's delegated site for destruction.

All concomitant medications and dietary contraindications specified in the trial protocol must also be recorded in a diary, including the drug name (generic name), strength, dosage each time, duration of medication, name of diet, amount

of food eaten, number of meals, etc.

All AEs occurring during study participation, whether or not related to the study drug, must be recorded in a diary. Such information includes type, severity, duration, treatment and outcome of AEs.

5. investigational drugs

5.1 Drug Name and Strength

5.1.1 Investigational drug

ASC08 Tablets

Strength: 100 mg/tablet, 30 tablets/bottle.

Storage condition: Sealed and stored at room temperature, protected from light.

5.1.2 Intensive Medications

Ritonavir tablet (abbreviation: RTV)

Strength: 100 mg/tablet, 30 tablets/bottle.

Storage condition: Store at room temperature (below 30℃).

5.1.3 Concomitant Medications

(1) Pegylated interferon alfa-2a injection (trade name: Pegasys ®; abbreviation: PEG-IFN α)

Strength: 180 μg/0.5 mL/vial/box, 135 μg/0.5 mL/vial/box.

Storage condition: 2 ~ 8 sealed, protected from light.

(2) Ribavirin Tablets (trade name: Changle; abbreviation: RBV)

Strength: 100 mg/tablet, 24 tablets/plate/box.

Storage condition: Sealed storage.

The above investigational drugs were uniformly provided by the Ascletis Pharmaceuticals Co., Ltd. to the clinical study site for this clinical study.

5.2 Concomitant Medications and Diet

5.2.1 Prohibited Drugs

During this clinical study, except for the investigational drugs specified in this trial protocol, the following drugs are prohibited:

(1) any traditional Chinese medicine or medicine containing traditional Chinese medicine ingredients; (2) other anti-HCV drugs, including anti-HCV drugs that are still under research and development; (3) liver drug enzyme CYP3A4 inducers (such as rifampicin, rifampicin, phenobarbital, phenytoin, carbamazepine) and CYP3A

inhibitors (such as ketoconazole, voriconazole); (4) OATP inhibitors (such as cyclosporine, rifampicin) or substrates (such as suvastatin, atorvastatin); (5) drugs with a narrow therapeutic window, and extensively metabolized by CYP3A and/or substrates for p-glycoprotein transporters (such as alfuzosin, astemizole, terfenadine, dihydroergotamine, ergometrine, ergotamine, methysergide, piazimod, midazolam, triazolam, lovastatin, simvastatin, fluticasone propionate); (6) oral contraceptives; (7) probenecid and bile acid binding resins; (8) Immunosuppressive drugs; (9) cytotoxic or chemotherapeutic drugs; (10) antiarrhythmic drugs (such as amiodarone, bepristone, flecainide, propafenone, quinidine); (11) corticosteroids (except topical hydrocortisone and dexamethasone); (12) PDE5 inhibitors (sildenafil, tadalafil, vardenafil).

Refer to the ritonavir tablets package insert for more detailed information on contraindicated drugs.

5.2.2 Available Medications

During this clinical study, G-CSF (granulocyte colony-stimulating factor), TPO (thrombopoietin) and EPO (erythropoietin) can be used if needed to treat neutropenia, thrombocytopenia and anemia, but other drugs should not be used.

When other drug therapy or other treatments are necessary during the study (such as other concomitant diseases with non-neutropenia and anemia), the investigator should obtain the consent in advance, and the drug should be used without affecting the efficacy and safety judgment of the study drug or for the purpose of protecting the health rights and interests of the subjects. All the used concomitant medications should be recorded in detail (including drug name, dosage, usage and medication duration).

5.2.3 Dietary Contraindications

Subjects should refrain from alcohol consumption during this clinical study.

5.3 Drug Labeling

Investigational drugs are packaged separately according to different strengths, and each packaging box and bottle is labeled for instructions. The format of drug package label is as follows:

Clinical Trial Approval Letter No.: Subject No.:

Investigational drug for ASC08 Tablets

(For clinical trial use only, to avoid accidental ingestion by children)

Number of deliveries:.

Dispensing date: DD MMM YYYY.

Drug name: Packaging specification:.

Dosage and Administration:.

Production lot number:. Expiry date:

Storage condition:

5.4 Drug Storage

The Site shall establish management system for investigational drugs. The investigational drugs should be kept by the person specially assigned by the director of the site. The investigational drugs should be stored in a special place. The investigational drugs should be stored according to the drug storage conditions provided by the sponsor, and the storage conditions of the investigational drugs should be inspected according to the investigational drug management system to ensure that the investigational drugs are applicable to this clinical trial.

5.5 Drug Dispensing and Recovery

The investigator should dispense the drugs in the order of subject time and subject number, and should not select the drugs. The investigator should timely and accurately record drug distribution, usage and recovery, including subject, date of distribution, quantity dispensed, date of recovery, quantity recovered and other information. The investigator should timely check the investigational drugs, and return the remaining drugs and their packages to the sponsor for destruction after the quantity is verified correct or the sponsor entrusts the study site to destroy them.

6. Treatment regimen

6.1 Dosage and Administration

(1) ASC08 Tablets

Oral; 100 mg (1 tablet) twice daily for 12 weeks.

(2) RTV film

Oral; 100 mg (1 tablet) twice daily for 12 weeks.

(3) PEG-IFN α

Subcutaneous injection in the abdomen or thigh; 180 μg (1 vial) once weekly for 12 weeks.

(4) RBV

Oral; body weight < 75 kg, 500 mg (5 tablets) twice daily for a total of 1000 mg/day; body weight ≥ 75 kg, 600 mg (6 tablets) twice daily for a total of 1200 mg/day; for 12 weeks.

Take ASC08 tablets and RTV together with food or within 1 hour after a meal; RTV must be taken orally with ASC08 tablets; RBV can be taken with ASC08 tablets

and RTV; the interval between doses is 12 ± 2 hours. Subjects may receive PEG-IFN α injections at sites participating in this clinical study, and PEG-IFN α administration will be completed by the investigator or other study personnel participating in this clinical study. Subjects can also take the drug home to complete PEG-IFN α injection by themselves, provided that the subjects have received training on self-injection drugs provided by the investigator, and the investigator determines that the subjects can independently complete PEG-IFN α injection administration without the help of professional staff and be fully aware of the storage and management of the drug and return the used and unused drug and its package in accordance with the requirements of the trial protocol.

6.2 Dose Modifications

The investigator should clearly inform the subjects that it is important to follow the treatment regimen to receive the complete drug treatment to achieve the purpose of this clinical study and treat their CHC. If dose adjustment is necessary due to adverse events during the clinical study, the following principles should be followed for dose adjustment.

(1) ASC08 and RTV

During this clinical study, subjects were not advised to interrupt or discontinue taking ASC08 and RTV unless an intolerable AE occurred; neither the investigator nor the subject was able to increase or decrease the dose of ASC08 and RTV.

If a subject forgets to take a daily dose of ASC08 and RTV, they may still take a daily dose of ASC08 and RTV, but must be at least 4 hours away from their next dose of ASC08 and RTV. Subjects cannot combine two doses of ASC08 and RTV at the same time, nor take two doses of ASC08 and RTV within 4 hours apart.

(2) PEG-IFN α and RBV

During this clinical study, the investigator can adjust the dose of PEG-IFN α and RBV according to the AE experienced by the subjects (see Appendix 2 for details of dose adjustment principles); the investigator can also adjust the dose of PEG-IFN α and RBV according to his/her clinical experience and refer to the dose adjustment principles.

If PEG-IFN α administration is delayed, the following principles should be followed when administering the next scheduled dose:

I. Dose Delay 1-2 Days: Administer the next dose on the regular dosing day of the week (e.g., if Monday is the regular dosing day and the dose is delayed until Wednesday of the same week, the next dose may be given as usual on Monday of the following week).

II.Delay in Dosing for 3 to 5 Days: Subsequent doses should be given at 5- or 6-day intervals until the subject returns to their original dosing schedule (e.g., if a Monday is a normal dosing day and the dose is postponed to a Saturday of the same week, the next dose should be given on the Thursday of the next week, and the next dose should be given on the Tuesday of the next week, after which the subsequent dose may be given on the Monday as usual).

Delay in III. dosing by 6 days: Stop the dose for the week and then continue the dose as normally scheduled for the following week (e.g., if Monday is a normal dosing day, but the subject does not receive the dose until the next day of the week, the dose is considered discontinued and the next dose will be given on the Monday of the following week).

A 7-day delay in IV.dosing: The investigator may resume the test dose at any time and, if necessary, may administer subsequent doses at 5- or 6-day intervals until the subject returns to their original dosing schedule.

7. Clinical observation items

Subjects will be required to undergo each evaluation according to the scheduled visits outlined in the trial procedures (Appendix 4). Baseline values for this clinical study were obtained on Day 1 of the Treatment Period prior to investigational product administration. In this clinical study, HCV genotyping and IL28B genotyping, HCV RNA detection and drug resistance testing were performed at the central laboratory, and the collection, processing, storage and transportation of blood samples from subjects for these four tests were performed according to the operation manual provided to each site; the Metavir scoring of liver biopsy specimens was performed at the central laboratory and performed according to the operation manual provided to each site. Other clinical observation items were completed in each study site. In this clinical study, if an unscheduled visit is required for a subject, the investigator may determine the evaluations required for the unscheduled visit according to the requirements of this trial protocol and the subject's personal condition.

7.1 Screening Period

Demographic data, medical and medication history and other information of subjects should be collected within 28 days before the start of the trial, and relevant clinical examinations should be performed.

(1) Vital signs and physical examination

Complete examination of vital signs should include examination of pulse, blood pressure, respiratory rate, body temperature, etc.; complete physical examination should include at least examination of height, weight, skin, lymph nodes, head and neck, facial features, chest, heart and blood vessels, lungs, abdomen, spine and limbs, lymphatic system, nervous system, etc.

(2) Determination of body mass index (BMI)

Subject weight (kg) and height (m) were measured and BMI was calculated according to the following formula:

BMI = weight/height2 (kg/m2)

(3) Laboratory tests

I. Hematology should include WBC with DC (NEUT, LYMPH, MONO, EO, BASO), RBC, HB, PLT;

II.Urinalysis should include PRO, GLU, ERY, LEU;

III. Blood biochemistry should include ALT, AST, ALP, γ-GT, TP, ALB, TBIL, DBIL, BUN, Cr, FBG, TC, TG, HDL-c, LDL-c, CK, LDH, UA;

IV. Blood electrolyte examination should include K +, Na +, Ca2 +, Cl-;

V. Coagulation tests should include APTT, PT, INR, Fg;

VI.Thyroid function tests should include TSH, T3, and T4.

(4) Glycosylated hemoglobin HbA1c

HbA1 content was measured in the blood of diabetic subjects.

(5) Immunological examination

Antinuclear antibody (ANA), antimitochondrial antibody (AMA) and anti-smooth muscle antibody (SMA) were detected.

(6) AFP

Serum AFP content was measured.

(7) Color Doppler ultrasound

Test the subject's abdomen (at a minimum, liver, gallbladder, pancreas, and spleen).

(8) HAV, HBsAg, HEV and HIV tests

Detect anti-HAV (IgM), HBsAg, anti-HEV (IgM), and anti-HIV.

(9) Fundus examination

The subject's retinal condition was examined.

(10) Pregnancy test

HCG level was measured in female subjects of childbearing age (18 years to 1 year after menopause).

(11) Electrocardiogram

Electrocardiogram (ECG) examination was routine 12 ECG examination.

(12) IL28B and HCV genotyping assays

IL28B and HCV genotypes and their subtypes were determined.

(13) HCV test

Detect anti-HCV antibody.

(14) HCV RNA detection

Blood samples were collected for HCV RNA content in the serum of the subjects.

(15) Examination for liver cirrhosis

The subject's liver status will be checked by FibroScan (transient liver elastography) or liver biopsy.

(16) Drug resistance monitoring

Blood samples were collected for viral phenotyping and/or sequence analysis.

7.2 Baseline

(1) Vital signs and physical examination.

(2) Laboratory tests.

(3) HCV RNA detection.

(4) Pregnancy test.

(5) Electrocardiography.

(6) Drug resistance monitoring.

See Appendix 4 for details.

7.3 Treatment Period

(1) Vital signs and physical examination.

(2) Laboratory tests.

(3) HCV RNA detection.

(4) Pregnancy test.

(5) Drug resistance monitoring.

See Appendix 4 for details.

7.4 Post-Treatment Follow-up Period

(1) Vital signs and physical examination.

(2) Laboratory tests.

(3) HCV RNA detection.

(4) Pregnancy test.

(5) Drug resistance monitoring.

See Appendix 4 for details.

8. Efficacy evaluation

8.1 Primary evaluation indicators

Rate of subjects achieving SVR12.

SVR12 definition: HCV RNA < LLOQ at 12 weeks after the end of treatment.

8.2 Secondary evaluation indicators

(1) Rate of subjects achieving RVR4.

RVR4 definition: HCV RNA < LLOQ at week 4 of treatment.

(2) Rate of subjects achieving SVR4.

SVR4 definition: HCV RNA < LLOQ at 4 weeks after the end of treatment.

(3) Rate of subjects achieving SVR24.

SVR24 definition: HCV RNA < LLOQ at week 24 after the end of treatment.

(4) Virologic response rate over time: percentage of subjects with HCV RNA < LLOQ at each visit.

(5) Change of HCV RNA over time: the logarithmic difference of serum HCV RNA content between subjects at each visit time point and baseline value.

(6) Recurrence rate: the percentage of subjects who relapsed at the end of follow-up compared with subjects who achieved virological response at the end of treatment and had at least one post-treatment HCV RNA evaluation.

(7) Changes in viral resistance

Blood samples will be collected from all subjects during this clinical study for monitoring of ASC08 resistance; however, only those subjects with viral breakthrough, partial response, non-response, and relapse will have phenotypic and/or sequence analysis performed to reveal the profile of changes in viral resistance. HCV

RNA ≥ 1000 IU/mL is necessary for sequence determination.

Subjects who develop viral resistance should demonstrate one of the following:

Viral breakthrough

Subjects with sustained increase in HCV RNA of ≥ 1 log10 IU/mL (at least 2 consecutive measurements) compared with the nadir during the treatment period (≥ 1 log10 IU/mL decrease from baseline HCV RNA after at least 2 weeks of treatment).

II. Partial response

During ASC08/r treatment, HCV RNA in subjects first decreased (≥ 1 log10 IU/mL decrease from baseline after at least 2 weeks of treatment) and then remained stable (< 1 log10 IU/mL increase from nadir for at least 2 consecutive measurements); or at the end of ASC08/r treatment (at least 4 weeks), HCV RNA in subjects ≥ 1000 IU/mL (at least 2 consecutive measurements).

III. No response

The subject has a reduction in HCV RNA of < 1 log10 IU/mL from baseline (at least 2 consecutive measurements) after 2 weeks of treatment; or < 2 log10 IU/mL (at least 2 consecutive measurements) after 4 weeks of treatment.

IV.RECURRENT

The subject had a virological response to treatment at the end of treatment, but had a quantifiable viral load in the body (at least 2 consecutive measurements) at post-treatment follow-up.

9. Safety evaluation

9.1 Safety indicators

(1) Adverse events observed by the investigator and reported by the subject during the study;

(2) Clinically significant changes in vital signs before and after treatment;

(3) Clinically significant changes in laboratory values before and after treatment;

(4) Changes in electrocardiogram before and after treatment.

9.2 Adverse Events

9.2.1 Definitions

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical product, including placebo, and which does not necessarily have a causal relationship with this treatment. An AE can be any

unfavorable and unintended symptom (including an abnormal laboratory finding), sign, or temporary disease.

AEs included the following:

(1) All suspected adverse drug reactions.

(2) All reactions due to overdose, abuse, discontinuation, allergy, or toxicity.

(3) Obviously unrelated diseases, including aggravation of pre-existing diseases;

(4) Injury or accident.

(5) Abnormal results found by physical examination or laboratory tests, requiring further examination or clinical treatment;

Significant adverse event: It refers to any adverse event and hematological or other significant laboratory abnormalities resulting in the use of targeted medical measures (such as drug withdrawal, dose reduction and other important treatment) in addition to serious adverse events.

9.2.2 Recording of adverse events

At each follow-up visit, the investigator asked the subject about AEs. The investigator should describe all AEs directly observed or spontaneously reported by the subjects with concise medical terms, and record truthfully and in detail any AE occurred during the trial in the AE form of CRF, including the onset time, symptoms, severity, duration, treatment measures and outcome of AE, etc.

9.2.3 Severity of Adverse Events

All AEs were assessed by the investigator for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) v.4.03 published by the National Cancer Institute (NCI), and adverse events were graded and described (see Appendix 3 for common adverse events in CTCAE v.4.03).

Grade 1 (mild): asymptomatic or mildly symptomatic, clinical or diagnostic observations not requiring medical intervention.

Grade 2 (moderate): minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3 (severe): serious or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Grade 4 (Life-threatening): Life-threatening, urgent medical intervention indicated.

Grade 5 (Death): Death related to adverse event.

Comments:

(1) Instrumental activities of daily living refer to cooking, purchasing daily necessities or clothes, using the telephone, financial management, and so on.

(2) Self-care activities of daily living refer to bathing, dressing and undressing, eating, washing, and taking medication and are not bedridden.

9.2.4 Judgment on the relationship between adverse events and investigational drug

9.2.4.1 Basis for Judging Interrelationships

All adverse events in the clinical study, including any abnormal symptoms, signs, laboratory tests or other special examinations experienced by the subjects, should be evaluated for relevance while being recorded in detail; the investigator should track and obtain sufficient information to judge whether the cause of adverse events is related to the investigational product. Judgment criteria are as follows:

①Whether there is a reasonable temporal relationship between drug administration and the occurrence of suspected adverse event.

②Whether the suspected adverse event is a known adverse reaction of the drug.

③Whether the suspected adverse event can be explained by the subject's clinical condition, concomitant medication, current therapy and previous therapy.

④Suspected adverse events can be relieved or disappeared after drug withdrawal or dose reduction.

⑤Whether the same adverse event occurs again after re-exposure to the same drug.

9.2.4.2 Judgment Results of Interrelationships

The relationship between adverse events and investigational product is evaluated according to the judgment basis of the interrelationship (see Section 9.2.4.1): definitely related, possibly related, possibly unrelated, definitely unrelated and indeterminable (Table 7).

(1) Definitely related: The type of adverse event has been identified as a side effect of the drug that must occur and cannot be explained by other reasons, such as concomitant drugs or concomitant diseases. The time of onset of an adverse event strongly suggests a causal relationship, such as a response to withdrawal and re-administration.

(2) Possibly related: The occurrence of adverse events may be caused by the

investigational drug. The occurrence of adverse events cannot rule out whether it may be caused by other factors, such as concomitant drugs or concurrent diseases. The adverse event occurs in a reasonable temporal sequence with the use of the investigational drug, and causal relationship between the event and the investigational drug cannot be ruled out.

(3) Unlikely related: The occurrence of adverse events is likely related to other factors, such as concomitant drugs or concomitant diseases. The timing of the event suggests that it is unlikely to be causally related to the use of the study drug.

(4) Definitely unrelated: There is no correlation between adverse events and the use of drugs.

(5) Unable to judge: the existing information is either contradictory or insufficient to judge the correlation between adverse events and drugs.

Table 7 Relationship between adverse events and investigational product

Judgment results	Judgment basis				
	①	②	③	④	⑤
Definitely related	+	+	−	+	+
Possibly related	+	+	+	±	?
Unlikely related	+	−	±	±	?
Definitely unrelated	−	−	+	−	−
Unable to judge	?	?	?	?	?

9.2.4.3 Incidence of adverse reactions

The investigator should make every effort to determine the relationship of adverse events (including serious adverse events) to the drug. If the judgment results are definitely related, possibly related and indeterminable, these three results will be considered as adverse drug reactions; the number of adverse reactions is counted according to the sum of the number of cases with these three results, and the incidence of adverse reactions is calculated within the scope of all the test cases with available adverse reaction evaluation.

9.3 Non-Serious Adverse Events of Special Interest

9.3.1 Determination of Non-Serious Adverse Events of Special Interest

Non-serious adverse events of special interest (AESI): It refers to elevation of

ALT or AST ≥ 10 times ULN combined with elevation of TBIL ≥ 2 times ULN (DBIL ≥ 35% TBIL); or clinical jaundice; and suspected transmission of pathogens caused by the investigational product.

9.3.2 Reporting of Non-Serious Adverse Events of Special Interest

Upon awareness of an AESI, the Investigator must collect and record relevant information in a timely manner and notify the Sponsor and/or CRO within 48 hours after awareness.

9.4 Serious Adverse Events

9.4.1 Determination of Serious Adverse Events

SAEs include:

(1) Leading to death;

(2) Life threatening;

(3) Causing congenital abnormalities or birth defects;

(4) Causing significant or permanent human disability or organ function damage;

(5) Leading to hospitalization or prolongation of hospitalization;

(6) Other important medical events (after medical judgment, it may cause harm to subjects or require medical or surgical treatment to avoid the occurrence of the above conditions);

Some events that require hospitalization or prolong hospitalization may not be considered as SAEs, including: hospitalization for other reasons than adverse events, such as administrative/social/welfare admission, hospitalization for collection of blood sample for PK analysis, pre-specified admission before enrollment (such as hospitalization for screening examination, but excluding conditions requiring early admission due to aggravation of original disease), emergency stay for observation for no more than 24 hours; or hospitalization for predefined surgery or other treatment or examination purpose before the study.

9.4.2 Reporting of Serious Adverse Events

After being informed of the occurrence of SAE, the investigator must complete the SAE Report Form as required within 24 hours, and report to the Drug Study Supervision Department, Department of Drug and Cosmetics Registration, CFDA, the Hospital Authority of the National Health and Family Planning Commission, the Ethics Committee of the site, the provincial drug regulatory authority in the place where the site and the sponsor are located, and notify the sponsor and/or CRO.

9.5 Handling of Adverse Events

9.5.1 Sponsor Responsibilities

(1) Provide legal and economic guarantees to investigators in accordance with GCP requirements, except for those caused by medical accidents;

(2) Provide the corresponding treatment and compensation or economic compensation for the adverse events that may be related to the trial or the investigational drug;

(3) Adverse events that occur rapidly with the investigator;

(4) Timely notifying the investigators to the relevant units for cooperation;

(5) Provide the corresponding drug R & D data as considered necessary by the investigator;

(6) Other matters requiring the assistance of the sponsor.

9.5.2 Investigator Responsibilities

(1) Take necessary and reasonable medical measures for subjects to ensure the safety of subjects;

(2) Judge the relationship between adverse events and investigational drug;

(3) Recording and follow-up of adverse events;

(4) Timely notify relevant units and institutions of the information in accordance with GCP requirements.

9.5.3 Follow-up of Adverse Events

The follow-up of adverse events is not only conducted during the trial, but also the unresolved adverse events (including laboratory abnormalities) at the end of the trial or early withdrawal of subjects must be followed up until one of the following conditions is met:

(1) Event resolution;

(2) The event is stable;

(3) The event returns to the baseline level;

(4) The event can be attributed to drugs other than the test drug or unrelated to the study;

(5) When more information is impossible to obtain (the subject refuses to provide more information, or the subject is lost to follow-up, or the subject has died);

Before the end of follow-up, the investigator may take necessary and reasonable medical measures according to relevant regulations to ensure the safety and rights and

interests of the subjects.

10. data management and statistical analysis

10.1 Data Safety Monitoring Committee

The Data Safety Monitoring Committee (DMC) assists the investigators in monitoring safety data. The DMC consisted of investigators, biostatisticians, independent clinical scientists, representatives from the sponsor, etc. The DMC will develop and implement a safety data review plan.

10.2 Data Management

An electronic data capture (EDC) system was used for data management in this clinical study. The data management unit undertaking this study is responsible for establishing the database. The data manager builds the database according to the study protocol, and at the same time sets logic check for data validity, so as to check the data. The observation records of each enrolled case (including drop-out cases) must be timely, completely, accurately and normatively recorded in the eCRF. Completed eCRFs must be reviewed and signed (electronically) by the investigator and data management performed by the clinical trial data manager.

The data manager checked the data and inquired the investigator about the doubts through the EDC system. The data manager checked and modified the data according to the investigator's answers and issued the doubts again when necessary. After all data queries are resolved, the "clean" data are exported and transferred to the statistical analyst. The principal investigator, sponsor and statistical analyst review the data, finalize the statistical plan, lock the database and perform the statistical analysis according to the statistical analysis plan.

10.3 Statistical Analysis

10.3.1 Statistical Analysis Datasets

(1) Full Analysis Set (FAS) population

All patients who were screened as eligible and took the study drug at least once and had data for post-dose evaluation at least once. The FAS was the primary analysis set.

(2) Per-Protocol Set (PPS) population

The collection of cases that meet the inclusion criteria, do not meet the exclusion criteria and complete the treatment plan, that is, to analyze the cases that meet the trial

protocol, have good compliance and complete the content specified in the CRF (PP analysis). The PP analysis was primarily used for efficacy measures.

(3) Safety Set (SS) Population

Received at least one treatment with actual data recorded for safety measures. Missing safety values should not be carried forward; some excluded cases that can be evaluated are included, such as those with age exceeding the inclusion criteria, but excluding those whose use of prohibited drugs makes safety judgment impossible. The incidence of adverse reactions takes the number of cases in the safety set as the denominator.

10.3.2 Statistical Analysis Plan

General Principles:

All statistical tests were performed using the test, and a P value of less than or equal to 0.05 was considered statistically significant for the tested difference, and a confidence interval of 95% was used.

Baseline data were analyzed by the full analysis set, and all efficacy measures were analyzed by the full analysis set and per protocol set; safety analysis was performed using the safety analysis set.

This clinical study is a single-arm superiority study, and the superiority hypothesis tests are:

$H0: \pi_{test\ group} - 75\% \leqslant 0$

$H1: \pi_{Test\ Group} - 75\% > 0$

A = 0.025

The 95% confidence interval for the proportion of subjects achieving SVR12 was calculated using the binomial distribution, and superiority was considered established if the lower bound of the 95% confidence interval for the proportion of subjects achieving SVR12 was greater than 75%.

10.3.2.1 Analysis of Subjects

(1) List the total number of included subjects and the number of completed subjects in each site, and determine three analysis sets (FAS, PPS and SS).

(2) List the dropouts and excluded cases and their reasons.

10.3.2.2 Demographic data and baseline analysis

Descriptive statistics of demographic data and other baseline characteristics:

Continuous variables will be calculated by their number of cases, mean, standard

deviation, median, minimum and maximum.

Frequency and proportion were calculated for count and grade data.

Baseline parameters (including demographic data, medical history, history of other diseases, physical examination, vital signs, etc.) will be statistically described.

10.3.2.3 Efficacy Analysis

10.3.2.3.1 Analysis of Primary Efficacy Indicators

To count the proportion of subjects achieving SVR12:

The proportion of subjects achieving SVR12 will be calculated according to the definition of SVR12 in this protocol. The binomial distribution will be used to calculate the 95% confidence interval, and the superiority will be judged based on this.

10.3.2.3.2 Analysis of Secondary Efficacy Indicators

(1) Statistics RVR4:

The rate of subjects achieving RVR4 values will be calculated based on the definition of RVR4 in this protocol, with 95% confidence intervals calculated using the binomial distribution.

(2) Statistics SVR4:

The proportion of subjects achieving SVR4 will be calculated according to the definition of SVR4 in this protocol, and 95% confidence interval will be calculated using binomial distribution.

(3) Statistics SVR24:

The proportion of subjects achieving SVR24 will be calculated according to the definition of SVR24 in this protocol, and 95% confidence interval will be calculated using binomial distribution.

(4) Statistics of virological response rate at each visit:

Virologic response rates were calculated by visit as specified in this protocol, and 95% confidence intervals were calculated using the binomial distribution.

(5) Statistics of the logarithmic difference between HCV RNA at each visit and baseline value:

Calculate the difference between the log value of HCV RNA at each visit and the log value at baseline as specified in this protocol.

(6) Statistics of the recurrence rate after the end of treatment.

Recurrence rates will be calculated as specified in this protocol and 95% confidence intervals will be calculated using the binomial distribution.

(7) Drug resistance analysis

Collect blood samples from subjects according to the trial procedures. Samples for drug resistance monitoring studies were selected for phenotypic and/or sequence analysis based on HCV RNA test results.

10.3.2.4 Safety Analysis

(1) Coding of adverse events and concomitant medication

AEs were classified and coded using MedDRA by system organ class and preferred term.

Concomitant medications were coded using WHO DD.

(2) Calculate the incidence of adverse events and adverse reactions:

Frequency and frequency of adverse events and adverse reactions will be listed by system, and percentage will be calculated.

Detailed listing of cases of each adverse event.

Detailed listing of cases of each adverse reaction.

Number and conversion rate of vital signs and physical examination, laboratory indicators and ECG "normal to abnormal" or "abnormal intensification" after the trial.

Cases and clinical interpretations of abnormal vital signs and physical examinations, laboratory parameters, and electrocardiograms were listed.

10.3.3 Interim Analysis

An interim analysis meeting drug registration requirements will be completed when 12-week follow-up data or early termination data are available for all subjects.

11. Risk control of clinical study

In addition to the following, the Sponsor has developed a more comprehensive and detailed "Risk Management Plan for ASC08 Tablets" to be used as an attachment to this clinical trial protocol in order to better identify, analyze and manage various risks that may be encountered during the clinical use of ASC08 Tablets.

11.1 Main risks

In previous clinical trials of ASC08/r in combination with PEG-IFN α and RBV in CHC, the identified risks were neutropenia, anemia, gastrointestinal side effects, and drug interactions.

11.2 Risk control measures for clinical study

11.2.1 Neutropenia

Subjects with grade 4 neutropenia, investigators can take appropriate measures: (1)

PEG-IFNα dose reduction or discontinuation; (2) with other treatment measures, such as the use of G-CSF treatment. If the intervention is ineffective (neutrophil count continues to decrease), the subject is withdrawn from the trial and followed up to the outcome as specified in the protocol; medical care and appropriate care is provided to the subject during the follow-up period.

11.2.2 Anemia

(1) Subjects with HB < 110 g/L (female) or < 120 g/L (male) and any risk of anemia at baseline were excluded during the screening period;

(2) HB changes were monitored during the treatment and post-treatment follow-up periods, and subjects experienced severe HB reduction (HB < 85 g/L), and investigators could take appropriate measures: (1) RBV dose reduction or discontinuation; (2) treatment with other therapeutic measures, such as EPO therapy. If the intervention was ineffective (HB continued to decrease), the subject was withdrawn from the trial and followed up to the outcome specified in the protocol; medical care and appropriate care was provided to the subject during the follow-up period.

11.2.3 Gastrointestinal Adverse Reactions

Gastrointestinal adverse reactions were observed during clinical studies. The investigator will grade the gastrointestinal adverse reactions and take corresponding treatment measures according to different grades to help the subjects recover.

11.2.4 Drug Interactions

ASC08 is a substrate of the following transporters: OATP1B1, OATP1B3, Pgp. It is also a strong inhibitor of OATPs and UGT1A1, but not an inducer of UGT1. Drugs that inhibit OATPs or Pgp may affect the exposure of ASC08. ASC08 may also affect the exposure of other drugs that are substrates of OATPs and UGT1A1.

ASC08 is metabolized by CYP3A4. CYP3A4 inhibitors or inducers may alter the metabolism of ASC08. CYP3A4 inducers include rifampin, rifambutine, phenobarbital, phenytoin, carbamazepine, and St. John's Wort. Strong inhibitors of CYP3A4 include ketoconazole and ritonavir. In addition, certain foods, such as grapefruit and Seville oranges, inhibit CYP3A4. However, when ASC08 was co-administered with RTV, CYP3A4 was almost completely inhibited, and the effect of other CYP3A inhibitors was minimal.

For drugs that should not be used concomitantly or should be restricted or used with caution during this clinical study, see "5.2 Concomitant Medications".

11.2.5 Elevated ALT

In the phase II clinical trial ATLAS study, ACTG grade 4 ALT elevation occurred in the 600 mg and 900 mg ASC08 tablets groups. However, none of the subsequent clinical studies with ASC08 intensified with RTV had grade 4 ALT elevations during treatment. ALT changes will also be observed during this clinical study.

Subjects with grade 4 ALT elevation, as well as subjects with grade 3 ALT elevation combined with total bilirubin > 2 × ULN (DBIL ≥ 35% TBIL) or grade 3 ALT elevation combined with INR > 1.5 should discontinue the study drug treatment and withdraw from the trial, be followed up to the outcome specified in this trial protocol, and provide medical care and appropriate treatment for the subjects when necessary.

11.2.6 Adverse Reactions of Combination Drugs

During this clinical study, RTV, PEG-IFN α , and RBV used in combination with ASC08 Tablets may have adverse reactions. The investigators should inquire, observe and record the known adverse reactions of these three drugs and other safety issues of concern according to the contents of the package inserts of RTV, PEG-IFN α and RBV, and take corresponding treatment measures.

11.2.7 Monitoring of safety indicators

The vital signs, blood and urine routine, blood biochemistry, coagulation function, ECG and other safety indicators of the subjects are monitored during the screening period, treatment period and post-treatment follow-up period. For the safety problems occurred, the investigator should give the subjects appropriate treatment according to the requirements of the trial protocol and the clinical medical principles to protect the interests of the subjects.

11.2.8 Remedial Measures for Combination Failure

During this clinical study, subjects who have failed combination therapy as defined by the protocol (including viral breakthrough, partial response, non-response, and relapse) will continue to be offered PEG-IFN α and RBV for up to 48 weeks as rescue therapy, and the specific rescue therapy regimen and implementation of this therapy regimen will be decided by the investigator according to the actual situation of the subjects.

11.2.9 Investigator Training

Relevant knowledge training was provided to investigators participating in the trial

during this clinical study to ensure that all investigators had a full understanding of risk factors and management measures.

12. Quality control and quality assurance of clinical trials

12.1 Clinical Trial Site and Study Personnel

Before the trial, the sponsor and/or CRO should confirm that the study site has been qualified to participate in the trial, including the qualification of drug clinical trial institution approved by CFDA, various inspection equipment related to the trial, sufficient number of subjects, etc. Standard operating procedures were established for all study processes in this trial, and standard operating procedures and quality control procedures for test indicators were established. The investigators participating in the clinical trial must have received the training related to the clinical trial and have the professional background and ability to carry out the clinical trial.

12.2 Clinical Monitoring

The trained monitor will call and conduct on-site monitoring on the study sites during the study progress, mainly to control the study progress and study quality.

The monitor must ensure that the clinical facilities of the participating institution meet the requirements, ensure that the investigators follow the trial protocol and accurately record the trial results, and ensure that each subject participating in the trial signs the informed consent form. The monitor regularly makes on-site monitoring visits, checks the trial data, checks the storage and use of the investigational drug, pays attention to adverse events, understands the completion of medical records and eCRFs, and makes timely corrections to the errors and omissions found during the monitoring process, which shall be recorded in writing.

12.3 Clinical Audits

According to the requirements of GCP, the study site must also accept the audit of clinical trial by the auditor appointed by the sponsor. The auditors conduct systematic inspection of clinical trial-related activities and documents to evaluate whether the trial is conducted in accordance with the trial protocol, standard operating procedures and relevant regulatory requirements, and whether the trial data are recorded in a timely, true, accurate and complete manner. The audit does not directly involve the personnel conducting the clinical trial.

13. Ethics

13.1 Ethics Committee

The study protocol, informed consent form, subject diary card and other study data to be reviewed should be reviewed and approved by the Ethics Committee of the study site before the start of the study. The clinical study can only be initiated after the approval document is obtained. The above changes can only be implemented after approved by the Ethics Committee.

13.2 Guidance on GCP

The study must be carried out in accordance with the guidelines of China GCP (2003 Edition), Declaration of Helsinki (2013 Edition) and ICH-GCP (2002 Edition), so as to provide effective guarantee for protecting the rights, safety and interests of the subjects and ensure the reliability of clinical trial data.

13.3 Informed Consent Form

Before the subjects are included in this trial, the investigator must fully introduce to the subjects or their legal guardians or agents the purpose, procedures, possible benefits and risks of this clinical trial, other alternative treatments, and the rights and obligations of the subjects in accordance with the Declaration of Helsinki; and shall let the subjects know that they have the right to withdraw from this trial at any time, without causing any damage to their personal interests. Each subject or his/her legal guardian or representative must sign an informed consent prior to enrollment. It was the responsibility of the investigator to have each subject obtain a copy of the signed informed consent form prior to study entry and to retain a copy of the signed informed consent form for the study file.

13.4 Confidentiality of Subject Information

Study personnel must protect the privacy of clinical trial subjects. During the clinical trial, except for the necessary documents (such as informed consent form), only letters, numbers and/or codes can be used to identify subjects in other study documents, rather than the real names of subjects. The investigator must properly keep the record documents of subject code, name and address. The investigator must maintain strict confidentiality on documents that identify the subject.

14. Trial management

14.1 Ethics Management

Before the clinical study is initiated, the investigator should provide the clinical

trial protocol, CRF, informed consent form and other documents to the Ethics Committee, so as to obtain the approval document for the implementation of clinical study through ethical review. All changes to the clinical trial protocol shall be maintained as protocol supplements. Any amendments to the study protocol and informed consent form should be submitted to the ethics committee for approval before implementation.

During the clinical study, any issues related to the safety of the clinical study, such as changes to the clinical study protocol or patient information sheet and serious adverse reactions during the clinical study, must be reported to the Ethics Committee in a timely manner. The end or early termination of the clinical study must also be reported to the Ethics Committee.

The information on subject recruitment shall be released during the clinical trial. No matter which method is adopted, the recruitment can be implemented only after the approval of the Ethics Committee is obtained.

14.2 Training

Training of study personnel: The principal investigator must ensure that all personnel participating in this clinical trial receive the training required for this trial. Before this trial is officially started, the study site must hold a kick-off meeting to provide a unified training for the personnel participating in the trial to ensure that the trial is conducted in accordance with the protocol and GCP. The main contents of training include: the development of investigational drug, the introduction of preliminary research results; the detailed explanation of protocol content; the explanation of informed consent form and the precautions when signing; the recording and reporting of serious adverse events and other adverse events; and the precautions for filling in CRF. During the course of this trial, the sponsor and the principal investigator may decide on the method and content of re-training based on the actual situation.

Training of subjects: The investigator should explain the trial protocol and requirements to the subjects in detail from signing the ICF, and inform the subjects of some important examination, medication or precautions for return visit by phone before return visit (including the return of investigational drug, return of diary card, etc.), so as to ensure that the subjects follow the trial protocol.

14.3 Protocol Deviations and Violations

This clinical trial is conducted in accordance with the clinical trial protocol approved by the Ethics Committee and the GCP regulations.

In the process of clinical trials, the phenomenon of deviation from the trial protocol due to some reasons occurs, for example: (1) the subject does not meet the inclusion criteria, but is included in the trial; (2) the subject does not sign the informed consent form, or the subject only signs the informed consent form after participating in the trial; (3) the blood sample coagulation for clinical test leads to missing test; (4) some laboratory tests are performed that are not approved by the Ethics Committee; (5) the subject is not followed up within the time window specified in the protocol; (6) the investigator fails to confirm whether the subject meets the requirements, so that the subject can use the drug; (7) the subject fails to use the drug on time or omits the drug; (8) the investigator issues the wrong test drug or uses the wrong drug dose; (9) the serious adverse event is missed or not reported in time; (10) the subject uses the prohibited drug, etc. During the clinical trial, in order to ensure the safety and health of subjects in emergencies, the investigator may make a decision not to comply with the provisions of the trial protocol to implement emergency intervention measures.

The investigator should record in detail the discovery time, occurrence time and reason, occurrence process and treatment of the event of deviation and violation of trial protocol, and archive them for review. In the event of an emergency, accident, or error that results in a significant deviation from, or violation of the protocol, the Investigator should promptly notify the Clinical Monitor or Sponsor so that a decision can be made as soon as possible regarding the subject's continued participation in the clinical trial. The investigator and the clinical monitor should take appropriate measures to deal with the deviation and protocol violation. For the clinical trial data generated due to deviation and violation of the trial protocol, the handling measures shall be discussed and decided when reviewing the trial data.

14.4 Data Tracking and Verification

The investigator must ensure that the eCRFs are completed in a timely, standardized, complete, and accurate manner. Only one subject's data will be recorded on each eCRF. All the data or text filled in incorrectly may not be altered arbitrarily, nor may the original record content be masked, and must be modified as required. All subjects who have signed the informed consent form to participate in this trial,

regardless of whether they complete the trial or not, must keep their eCRFs.

The investigator must cooperate with the CRA and auditors to view and review the data in this clinical trial so as to confirm the authenticity, completeness and accuracy of the original data and understand the actual progress of the study.

14.5 Replacement of Study Sites

The study site should only be replaced in case of reasons such as slow enrollment of subjects, poor compliance with the study protocol and/or GCP, and should not be replaced due to drug-related adverse reactions in the trial. Site substitutions must be documented.

14.6 Study Termination and Closure

14.6.1 Study Termination

The Sponsor reserves the right to discontinue the study site at any time to continue the study. The investigator may also request to terminate the trial, but appropriate reasons should be given in advance and agreed by the sponsor. Reasons for discontinuation from the trial may include failure of the investigator to comply with the trial protocol, operating procedures or GCP requirements, drug safety issues, insufficient subjects, etc.

14.6.2 End of Study

The completion of the last visit of the last subject during the course of this clinical trial is considered the end of the clinical observation process for this clinical study. Only when the study site completes the clinical trial summary report and transfers it to the sponsor can this clinical study be considered as completed.

15. Data storage and information use

15.1 Storage of Materials

After completing the data entry and verification as required, the original case report forms shall be archived and stored in the order of number and filled in the retrieval catalogue for reference. Electronic data files, including databases, inspection procedures, analysis procedures, analysis results, codebook and description files, shall be stored by classification, and multiple backups shall be stored on different disks or recording media, and properly kept to prevent damage. All the original files shall be preserved according to the time limit specified in Good Clinical Practice for Drugs.

In order to ensure the evaluation by China Food and Drug Administration and the

sponsor, the study site should retain all study data, including all original signed informed consent forms, all subject screening and inclusion records, all CRFs, drug storage and use records, inpatient records and examination records, etc., in accordance with relevant national regulations. The preservation period of all the study data shall be at least 5 years; upon the expiry of the preservation period, the study site shall contact the sponsor to decide the processing method of the study data and dispose of it by itself.

The ownership of all the data of this clinical trial belongs to the sponsor. Without the written consent of the sponsor, the study site and/or investigator should not transfer to other units or individuals in any form.

15.2 Use of Information

All unpublished information provided by the Sponsor to the Study Site and/or the Investigator, including but not limited to information related to the study drug, business information of the Sponsor (such as patent situation, formula, production process, basic research data, previous clinical data and prescription data), and any information derived from the trial and containing the benefit of copyright protection, shall be kept confidential and proprietary to the Sponsor. Except for the information that must be informed in obtaining the ICF signed by subjects who are willing to participate in the trial, the Study Site and the Investigator must keep such information confidential and use such information only for the completion of this clinical study instead of using such information for other purposes, without the written authorization of the Sponsor.

The Study Site and the Investigator shall understand that the scientific or medical information obtained in this clinical trial may be of commercial value to the Sponsor or may be used by the Sponsor for further drug development, and thus the Study Site and the Investigator are obliged to provide the Sponsor with all the information obtained from this trial.

The sponsor has the right to publicly release the data and information related to this study without the consent of the study site and/or investigator. If the Study Site and/or the Investigator wishes to release trial-related information to the public, the consent of the Sponsor shall be obtained in advance, and the information to be published shall be provided to the Sponsor for review and approval 60 days prior to submission or presentation before public release. The signature of the public release

information related to this study shall be determined by the Sponsor through negotiation with the Study Site and the Investigator. Prior to publication of the overall clinical study results of a multi-center clinical study, the information from each study site may not be published separately.

Main responsibilities assumed by all parties

16.1 Principal Investigator Responsibilities

(1) The investigator should agree with the sponsor on the trial protocol and sign it, and report it to the Ethics Committee for review and approval before implementation.

(2) The investigator must read and understand the contents of the trial protocol in detail and strictly follow the protocol.

(3) The investigator should understand and be familiar with the nature, effect, efficacy and safety of the investigational drug (including the relevant data of the preclinical study of the drug), and should also master all the new information related to the drug found during the clinical trial.

(4) Investigators must conduct clinical trials in medical institutions with good medical facilities, laboratory equipment and personnel allocation. Such institutions should have all the facilities for dealing with emergencies to ensure the safety of subjects; laboratory test results should be accurate and reliable.

(5) The investigator shall obtain the consent of the medical institution or competent unit where he/she is located, and ensure that there is sufficient time to be responsible for and complete the clinical trial within the time limit specified in the protocol.

(6) The investigator shall explain the materials, provisions and responsibilities of the trial to all the personnel participating in the clinical trial, so as to ensure that a sufficient number of subjects who meet the trial protocol enter the clinical trial.

(7) The investigator should explain the details of the trial approved by the ethics committee to the subjects and obtain the informed consent signed by the subjects.

(8) The investigator is responsible for making medical decisions related to the clinical trial to ensure that the subjects receive appropriate treatment when adverse events occur during the trial.

(9) The investigator is obliged to take necessary measures to ensure the safety of subjects, and record them. When a serious adverse event occurs during the clinical

trial, the investigator should immediately take appropriate therapeutic measures for the subject, and report to the national drug regulatory authority, the sponsor and the Ethics Committee with his/her name and date signed on the report.

(10) The investigator should ensure that the data are truthfully, accurately, completely, standardized, timely and legally recorded in the medical records and case report forms.

(11) The investigator should accept the monitoring and audit of the clinical monitor and/or auditor appointed by the sponsor as well as the audit and inspection of the national drug regulatory authority to ensure the quality of the clinical trial.

(12) The investigator shall negotiate with the sponsor on the cost of clinical trial, and specify it in the contract. During the clinical trial, the investigator shall not charge the subject any fees necessary for the trial. Upon completion of the clinical trial, the investigator must prepare, sign and date the final report, and then submit it to the sponsor.

16.2 Main Responsibilities of Sponsor

(1) The sponsor should obtain the approval of China Food and Drug Administration before carrying out the clinical trial.

(2) The sponsor is responsible for initiating and applying for clinical trials and providing trial funds.

(3) The sponsor provides the investigator's brochure, which includes the pharmaceutical, toxicological, pharmacological and clinical (including previous and ongoing trials) data and data of the investigational drug.

(4) The sponsor and the investigator agree on the clinical trial protocol and sign the trial protocol and contract agreed by the two parties.

(5) The sponsor provides the investigator with investigational drugs that are easily identified, correctly coded and labeled with special labels, and ensures that the quality is qualified. Investigational medicinal products should be appropriately packaged as specified in the trial protocol and stored under validated conditions. The sponsor shall establish management system and record system for investigational drugs.

(6) The sponsor shall appoint a qualified clinical research associate and auditor, who shall be accepted by the investigator.

(7) Sponsors shall establish a quality control and quality assurance system for

clinical trials, and may organize the audit of clinical trials to ensure the quality.

(8) The sponsor and the investigator should quickly study the serious adverse events occurred, take necessary measures to ensure the safety and rights and interests of subjects, and timely report to the national drug regulatory authorities.

(9) The sponsor shall be responsible for submitting the final report of the trial to China Food and Drug Administration.

(10) The sponsor shall provide necessary guarantee for the subjects participating in the clinical trial, and bear the cost of treatment and corresponding economic compensation for the subjects with damage or death related to the trial. Except for the medical negligence, the Sponsor shall provide guarantee for the Investigator both legally and economically.

17. Expected progress of the trial

This clinical trial will be carried out after the approval of the Ethics Committee is obtained, the investigational drug is in place, and the cooperation agreement is signed. The trial period is about 15 months.

18. References

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(19) Quantitative systematic review report on the clinical efficacy of pegylated interferon combined with ribavirin in the treatment of hepatitis C in Asian population. September 2014.
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Appendix 1 Liver Biopsy Scores

Liver biopsy results must be scored as described below. Metavir score ≤ 3 was classified as non-cirrhotic.

METAVIR Fibrosis Score:

Score 0: No fibrosis

1 point: Stellate enlargement of portal tract but without septa formation

2 points: Enlargement of portal tract with rare septa formation

3 points: Numerous septa without cirrhosis

4 points: Cirrhosis

Appendix 2 Dose Modification Principles

For subjects who must have their dose adjusted due to moderate and severe adverse reactions, including clinical manifestations and/or laboratory abnormalities, PEG-IFNα and RBV therapy should follow the principles described below for dose adjustment. Gradual increase or return to the initial dose may be considered as adverse effects abate.

If PEG-IFN α and/or RBV dose adjustment is required, subjects should undergo hematological parameters every 1 week or every 2 weeks; investigators should promptly assess subjects for AEs (especially neutropenia, anemia, and thrombocytopenia) and take appropriate management measures (including PEG-IFN α and/or RBV dose adjustment and other necessary medical measures) until the AE resolves or maintains a stable state.

1. Hematological parameters

(1) PEG-IFN α

Dose reduction should be considered when absolute neutrophil count (ANC) is less than 0.75 × 109/L; temporary discontinuation should be considered when ANC is less than 0.50 × 109/L, and treatment can be resumed until ANC recovers to greater than 1.0 × 109/L. Re-treatment should be started with 90 micrograms and neutrophil counts should be monitored.

When PLT is less than 50 × 109/L, PEG-IFNα dose should be reduced to 90 μg; when PLT is less than 25 × 109/L, drug withdrawal should be considered (Table 8).

If PEG-IFNα is not tolerated, treatment with ASC08/r + RBV can be continued.

(2) RBV

The subject has no significant cardiovascular disease and presents HB < 100 g/L and ≥ 85 g/L; or when the subject has stable cardiovascular disease and any 4 HB drops ≥ 20 g/L during treatment, RBV should be reduced to 600 mg/day. Restoration to the original dose is not recommended.

RBV should be withheld in the following circumstances: the subject has no significant cardiovascular disease and HB does drop below 85 g/L; or the subject has stable cardiovascular disease and HB persists below 120 g/L after 4 weeks of dose reduction. RBV 600 mg/day may be resumed when normal values are restored and further increased to 800 mg/day at the discretion of the investigator, but return to the original dose is not recommended (Table 8).

The dose of RBV may be tapered according to the severity of the AE (Table 9). If intolerant to RBV, treatment with ASC08/r + PEG-IFNα can be continued.

Table 8 Dose Modifications Based on Hematologic Therapy

PEG-IFN α Dose Modification		
ANC	< 0.75 × 109/L	PEG-IFN α was reduced to 135 μg.
	< 0.50 × 109/L	Withhold PEG-IFN α until ANC ⩾ 1.0 × 109/L, initiate treatment at 90 μg and monitor for changes in ANC.
PLT	< 50.0 × 109/L, > 25.0 × 109/L	PEG-IFN α was reduced to 90 μg.
	< 25.0 × 109/L	PEG-IFN α therapy was stopped and PLT changes were monitored at a frequency of 1 ~ 2 times/week.
RBV Dose Modification		
HB (without heart disease)	< 100 g/L, ≥ 85 g/L	Reduce RBV dose to 1000 mg (body weight ⩾ 75 kg), or 800 mg (body weight < 75 kg).
	< 85 g/L	RBV therapy was suspended.
HB (stable cardiac disease)	Any decrease ≥ 20 g/L	RBV was reduced to 800 mg (body weight ⩾ 75 kg), or 600 mg (body weight < 75 kg).
	Dose reduction for 4 weeks is still < 120 g/L	RBV therapy was suspended.

Table 9 RBV Dose Modification Levels

Dose	Weight ≥ 75 kg	Weight < 75 kg
Full Dose	1200 mg/day a.m. (: 600 mg; p.m.: 600 mg)	1000 mg/day a.m. (: 500 mg; p.m.: 500 mg)
Level 1	1000 mg/day a.m. (: 500 mg; p.m.: 500 mg)	800 mg/day a.m. (: 400 mg; p.m.: 400 mg)
2nd level	800 mg/day a.m. (: 400 mg; p.m.: 400 mg)	600 mg/day a.m. (: 300 mg; p.m.: 300 mg)

2. ALT

Liver function often fluctuates in patients with chronic hepatitis. Increases in ALT occur after treatment with PEG-IFNα, including in patients with improved viral response. A dose reduction to 135 μg should be considered when patients with hepatitis C present with persistent elevations of ALT up to 10-fold and TBIL more than 2 ULN. After dose reduction, if ALT elevation persists, or bilirubin elevation or hepatic decompensation occurs, immediate discontinuation should be considered.

Appendix 3 NCI CTCAE (v4.03)

Common toxicity grades

Adverse events	Grading				
	1	2	3	4	5
Blood/lymphatic system					
Anemia	Hemoglobin (Hgb) < LLN - 100 g/L	Hgb from 80 to 100 g/L	Hgb < 80 g/L	Life-threatening; urgent treatment indicated	Death
Febrile neutropenia	-	-	Absolute neutrophil count (ANC) < 1.0 × 109/L with body temperature > 38.3℃ or body temperature 38℃ for more than 1 hour	Life-threatening; urgent treatment indicated	Death
Leukopenia	< LLN-3.0 × 109/L	< 3.0-2.0 × 109/L	< 2.0-1.0 × 109/L	< 1.0 × 109/L	-
Neutropenia	< LLN-1.5 × 109/L	< 1.5-1.0 × 109/L	< 1.0-0.5 × 109/L	< 0.5 × 109/L	-
Thrombocytopenia	< LLN- 75.0 × 109/L	< 75.0-50.0 × 109/L	< 50.0 - 25.0 × 109/L	< 25.0 × 109/L	-
Lymph node pain	Mild pain	Moderate pain; interference with instrumental activities of daily living	Severe pain; interfere with personal activities of daily living	-	-
Blood/lymphatic system (Others)	Asymptomatic or mild symptoms; no treatment required	Moderate; minimal, local, or noninvasive treatment; influence age-appropriate instrumental sexual activity	Severe or significant clinical symptoms, but not life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; interfering with personal activities of daily living	Life-threatening; urgent treatment indicated	Death
Coagulation function					
Activated partial thromboplastin time (Aptt)	> 1-1.5 x ULN	> 1.5-2.5 x ULN	> 2.5 x ULN; bleeding	-	-

Adverse events	Grading				
	1	2	3	4	5
Fibrinogen decreased	< 1.0 - 0.75 x lower limit of normal or < 25% decrease from baseline	< 0.75 - 0.5 x lower limit of normal or 25% - < 50% decrease from baseline	< 0.5 - 0.25 x lower limit of normal or 50 - < 75% decrease from baseline	< 0.25 x lower limit of normal or 75% decrease from baseline, or absolute value < 50 mg/Dl	-
Metabolism and malnutrition					
Anorexia	Decreased appetite without change in eating habits	Change in food intake without weight loss or malnutrition; oral nutritional supplementation required	Significant weight loss or symptoms of malnutrition (e.g., inadequate caloric intake); requiring nasogastric or total parenteral nutrition	Life-threatening; urgent treatment indicated	-
Dehydration	Increased fluid intake; dry mucous membranes; inadequate filling of cutaneous vessels	Infusion required < 24 hours	Requires infusion or hospitalization	Life-threatening; urgent treatment indicated	Death
TBIL	> ULN-1.5x ULN	> 1.5-3.0x ULN	> 3.0-10.0 × ULN	> 10.0Xuln	-
ALT	> ULN - 3.0 × ULN	> 3.0-5.0 × ULN	> 5.0-20.0 × ULN	> 20 × ULN	-
AST	> ULN - 3.0 × ULN	> 3.0-5.0 × ULN	> 5.0-20.0 × ULN	> 20 × ULN	-
GGT	> ULN - 2.5 × ULN	> 2.5-5.0 × ULN	> 5.0-20.0 × ULN	> 20 × ULN	-
ALP	> ULN - 2.5 × ULN	> 2.5-5.0 × ULN	> 5.0-20.0 × ULN	> 20 × ULN	-
Hypercholesterolemia	> ULN- 300 mg/Dl; > ULN-7.75 mmol/L	> 300-400 mg/Dl; > 7.75-10.34 mmol/L	> 400-500 g/Dl; > 10.34-12.92 mmol/L	> 500 mg/Dl; > 12.92 mmol/L	-
Hyperglycaemia	Fasting glucose concentration > ULN - 160 mg/dL; fasting glucose concentration > ULN - 8.9 mmol/L	Fasting glucose concentration > 160-250 mg/Dl; fasting glucose concentration > 8.9-13.9 mmol/L	> 250-500 mg/Dl; > 13.9-27.8 mmol/L; hospitalization indicated	> 500 mg/Dl; > 27.8 mmol/L; life-threatening	Death
Hypoalbuminemia	< LLN-3.0 g/Dl	< 3.0-2.0 g/Dl	< 2.0 g/Dl	Life-threatening; urgent treatment indicated	Death
Hypocalcemia	< LLN-8.0 mg/Dl; < LLN-2.0 mmol/L	< 8.0-7.0 mg/Dl; < 2.0-1.75 mmol/L; Symptomatic	< 7.0-6.0 mg/Dl; < 1.75-1.5 mmol/L; Requires hospitalization	< 6.0 mg/Dl; < 1.5 mmol/L; Life Threatening	Death
Hyponatremia	< LLN - 130 mmol/L	-	< 130-120 mmol/L	< 120 mmol/L;	Deat

Adverse events	Grading				
	1	2	3	4	5
				Life Threatening	h
Hypokalemia	< LLN - 3.0 mmol/L	< LLN - 3.0 mmol/L; symptomatic; treatment required	< 3.0-2.5 mmol/L; hospitalization indicated	< 2.5 mmol/L; life-threatening	Deat h
Alimentary tract					
Oral mucositis	Asymptomatic or mild symptoms; no treatment required	Moderate pain; does not interfere with food intake; requires dietary modification	Severe pain; affecting eating in panic	Life-threatening; urgent treatment indicated	Death
Nausea	Loss of appetite, but no change in eating habits	Reduced food intake without significant weight loss, dehydration, or malnutrition	Insufficient intake of energy or water; nasogastric feeding required; total parenteral nutrition or hospitalization required	Life-threatening; urgent treatment indicated	-
Vomiting	1-2 episodes in 24 hours (5 minutes apart)	3-5 episodes in 24 hours (5 minutes apart)	More than 6 episodes within 24 hours (5 minutes apart); required nasogastric feeding; total parenteral nutrition or hospitalization	Life-threatening; urgent treatment indicated	Death
Diarrhea	< 4 stools/day increase from pretreatment; mild increase in ostomy output	4-6 stools/day more than pretreatment; moderate increase in ostomy output	Increase in stool frequency ≥ 7 stools/day from pretreatment; fecal incontinence; severe increase in ostomy output; interference with personal activities of daily living	Life-threatening; urgent treatment indicated	Death
Constipation	Occasional or intermittent symptoms; occasional need for stool softeners, laxatives, dietary modification, or enemas	Persistent symptoms, regular use of laxatives or enemas; interference with instrumental activities of daily living	Obstinate constipation requiring manual dredging; influence on personal activities of daily living	Life-threatening; urgent treatment indicated	Death
Gastrointestinal haemorrhage	Mild; no treatment required	Moderate; requires medical treatment or minor hemostatic	Requirement for transfusion, radiology, endoscopic or	Life-threatening; urgent treatment indicated	Death

Adverse events	Grading				
	1	2	3	4	5
		treatment	elective surgery		
Gastrointestinal perforation	-	Symptomatic; medical treatment indicated	Severe symptoms; elective surgery indicated	Life-threatening; urgent treatment indicated	Death
Renal/Urinary					
Acute kidney injury	Increase in creatinine level of greater than 0.3 mg/dl; or between 1.5 and 2.0 times the baseline	Creatinine 2-3 fold above baseline	Creatinine greater than 3 x baseline or greater than 4.0 mg/dl; hospitalization indicated	Life-threatening; requiring dialysis	Death
Chronic kidney injury	Glomerular filtration rate or creatinine clearance less than 60ml/min/1.73 m2, proteinuria 2 +; urine protein greater than 0.5	Glomerular filtration rate or creatinine clearance 59-30 ml/min/1.73 m2	Glomerular filtration rate or creatinine clearance 29-15 ml/min/1.73 m2	Glomerular filtration rate or creatinine clearance Rate less than 15 ml/min/1.73 m2; requiring dialysis or transplant	Death
Renal hemorrhage	Mild symptoms, intervention not indicated	Analgesic use requiring hematocrit monitoring	Requires transfusion, radiology, hospitalization; requires elective radiology, endoscopy, or surgery	Life-threatening; urgent radiation required Medical or surgical treatment	Death
Creatinine	> ULN-1.5 × ULN; > 1 — 1.5 times of baseline value;	> 1.5-3.0 × ULN; > 1.5 — 3.0 times baseline value	> 3.0-6.0 × ULN; > 3.0 times baseline value;	> 6.0 × ULN	Death
Proteinuria	Proteinuria 1 +, 24 hour urine protein less than 1.0g	Adults: proteinuria 2 +, 24-hour urine protein 1.0-3.4g, children: urine (protein/creatinine) ratio 0.5-1.9	Adults: 24-hour urine protein 3.5g, children: urine protein/creatinine ratio greater than 1.9	-	-
Haematuria	Asymptomatic, clinical observations or diagnostic findings only, no treatment required	Mild symptoms requiring urinary catheter or bladder cleansing; interference with instrumental activities of daily living	Extensive hematuria requiring transfusion, intravenous administration, or hospitalization; elective endoscopic, radiation, or surgical intervention indicated;	Life-threatening; urgent radiological or surgical intervention indicated	Death

Adverse events	Grading				
	1	2	3	4	5
			influence on personal activities of daily living		
Renal and urinary disorders (other)	Asymptomatic or mild symptoms, clinical observations or diagnostic observations only; intervention not indicated	Moderate symptoms; local or noninvasive intervention indicated; interference with instrumental activities of daily living	Severe or significant clinical symptoms not life-threatening; hospitalization or prolongation of hospitalization indicated; influence on personal activities of daily living	Life-threatening; urgent treatment indicated	Death
Respiratory					
Cough	Mild symptoms; require over the counter treatment	Moderate symptoms; clinical drug therapy indicated; interference with instrumental activities of daily living	Severe symptoms; influence personal activities of daily living	-	-
Dyspnea	Shortness of breath with moderate activity	Shortness of breath with minimal activity; instrumental activities of daily living affected	Shortness of breath at rest; influence personal activities of daily living	Life-threatening; urgent treatment indicated	Death
Epistaxis	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated (cotton wool packing, hemostasis, topical vasoconstrictor)	Need for transfusion, radiotherapy, endoscopy, surgery (hemostasis at bleeding site)	Life-threatening; urgent treatment indicated	Death
Pneumonia	Asymptomatic; clinical examination or diagnostic finding only; intervention not indicated	Symptomatic; intervention indicated; instrumental activities of daily living affected	Severe symptoms; influence personal activities of daily living; require oxygen inhalation	Life-threatening respiratory disorder; urgent treatment indicated (tracheostomy or Cannula)	Death
Cardiac/Cardiovascular					
Acute coronary syndrome	-	Symptomatic, progressive angina; normal cardiac enzymes; hemodynamically stable	Symptomatic, unstable angina with/or acute myocardial infarction, abnormal cardiac enzymes, hemodynamically stable	Symptomatic, unstable angina with/or acute myocardial infarction, abnormal cardiac enzymes, hemodynamic instability	Death

Adverse events	Grading				
	1	2	3	4	5
Hypertension	Prehypertension (systolic blood pressure between 120 and 139 mmHg, diastolic blood pressure between 80 and 89 mmHg)	Stage I hypertension (systolic blood pressure 140-159 mmHg, diastolic blood pressure 90-99 mmHg); medical intervention indicated; recurrent or persistent (greater than or equal to 24 hours); symptomatic increase in systolic blood pressure greater than 20 mmHg or to greater than 140/90 mmHg after previous normal blood pressure; medical treatment indicated. Pediatrics: Repeated or persistent (greater than or equal to 24 hours) blood pressure above the upper limit of normal; requiring treatment.	Stage II hypertension (systolic blood pressure greater than or equal to 160 mmHg, diastolic blood pressure greater than or equal to 100 mmHg); medical intervention indicated; polypharmacy indicated; Pediatrics: Same as adults	Life-threatening (eg, malignant hypertension, transient or persistent neurologic impairment, hypertensive crisis); urgent intervention indicated; Pediatrics: Same as adults	Death
Thromboembolic events	Venous thrombosis (e.g., superficial)	Venous thrombosis (e.g. uncomplicated deep vein thrombosis) requiring medical intervention	Thrombus (e.g. uncomplicated pulmonary embolism (venous), non-embolic cardiovascular thrombosis (arterial)) requiring medical intervention	Life-threatening (e.g., pulmonary embolism, cerebrovascular event, insufficient arterial supply); hemodynamic or neurological dysfunction; urgent treatment indicated	Death
Myocardial infarction	-	Asymptomatic, minimally abnormal cardiac enzymes, no regional absence, no evidence of ischemic ECG changes	Severe symptoms; myocardial enzyme changes; haemodynamic stability; ECG changes consistent with the diagnosis of myocardial infarction	Life-threatening; hemodynamic imbalance	Death

Adverse events	Grading				
	1	2	3	4	5
Left ventricular systolic dysfunction	-	-	- Symptoms associated with decreased heart rate and response to treatment	Refractory or uncontrolled heart failure due to a reduced score; requiring ventricular assist device, intravenous vasopressor therapy, or heart transplantation	Death
Cardiac troponin I (cTnI) increased	Above the upper limit of normal, below the level defined by the manufacturer for the diagnosis of myocardial infarction	-	Achieve the level defined by the manufacturer for myocardial infarction	-	-
Cardiac troponin T (cTnT) increased	Above the upper limit of normal, below the level defined by the manufacturer for the diagnosis of myocardial infarction	-	Achieve the level defined by the manufacturer for myocardial infarction	-	-
QT prolongation	QTc 450-480 ms	QTc 481-500 ms	QTc 501 ms on at least two ECGs	QTc ≥ 501 or change from baseline > 60 ms and signs/symptoms of Torsade de Pointes or severe arrhythmia	-
Decrease in score	-	Resting EF 40-50%; 10-19% below baseline	Resting EF 20-39%; > 20% below baseline	Resting score (EF) < 20%	-
Nervous system					
Ataxia	Asymptomatic; clinical symptoms or diagnostic findings only; intervention not indicated	Moderate symptoms; interference with instrumental activities of daily living	Severe symptoms; influence personal activities of daily living; mechanical assistance required	-	-
Cognitive impairment	Mild cognitive impairment; no influence on work/life/study; no need for special educational services/devices	Moderate cognitive impairment; work/life/study related, but independent; short term care by specialized staff	Severe cognitive impairment; significant impact on work/life/study	-	-

Adverse events	Grading				
	1	2	3	4	5
Headache	Mild headache	Moderate headache; affecting instrumental days Regular life activities	Severe headache; personal everyday Activities of life	-	-
Vertigo	Mild instability or movement sensation	Moderately unstable; affecting instrumental activities of daily living	Severe instability; influence personal activities of daily living	-	-
Other					
Hypothyroidism	Asymptomatic; clinical exam or diagnostic findings only; no treatment required	Symptomatic; thyroid hormone replacement therapy; instrumental activities of daily living affected	Serious; influence on personal activities of daily living; hospitalization indicated	Serious; influence on personal activities of daily living; hospitalization indicated	Death
Adrenal insufficiency	Asymptomatic; clinical exam or diagnostic findings only; no treatment required	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening; urgent treatment indicated	Death
Insomnia	Mild difficulty sleeping, staying asleep or waking up early	Moderate difficulty sleeping, staying asleep or waking up early	Severe difficulty sleeping, staying asleep or waking up early	-	-
Alopecia	Hair loss is not more than 50%, there is no difference in the distance, but it can be seen in the near. Hair loss needs to be concealed by changing the hair style, but no wig or wig block is needed to conceal it	Hair loss greater than 50%, significant symptoms, need for a wig or wig block, psychologically influential	-	-	-
Hand-foot syndrome	Slight painless skin changes or dermatitis (e.g. erythema, edema, hyperkeratosis)	Painful skin changes (e.g. flaking, blistering, bleeding, swelling, hyperkeratosis); interference with instrumental activities of daily living	Severe skin changes (flaking, blistering, bleeding, edema, hyperkeratosis) with pain; influence personal activities of daily living	-	-
Pain (not due to tumor)	Mild pain	Moderate pain; interference with instrumental activities of	Severe pain; influence personal activities of daily living	-	-

Adverse events	Grading				
	1	2	3	4	5
		daily living			

Appendix 4 Test Flow

		Screening Period	Treatment Period 11						Post-Treatment Follow-up Period		
Number of visits		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Visit time	Day	- 28-1	1	8	15	29	57	85	113	169	253
	Week	- 4-0		1	2	4	8	12	16	24	36
Window (day)			± 0	± 0	± 1	± 1	± 2	± 2	± 7	± 7	± 7
Signed informed consent		×									
Check inclusion/exclusion criteria		×									
Demographic data		×									
Past medical/medication history		×									
Vital Signs		×	× 10	×	×	×	×	×	×	×	×
Physical Exam 1		×	× 10	×	×	×	×	×	×	×	×
BMI		×									
Anti-HAV (IgM)		×									
HBsAg		×									
Anti-HEV (IgM)		×									
Anti-HIV		×									
Anti-HCV		×									
Fundoscopy		×									

FibroScan Scan 2	×									
Liver biopsy 3	×									
HCV Genotyping 4	×									
IL28B Genotyping 4	×									
HCV RNA4	×	× 10	×	×	×	×	×	×	×	×

TEST PROCEDURES (Continued)

		Screening Period	Treatment Period 10						Post-Treatment Follow-up Period		
Number of visits		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Visit time	Day	- 28-1	1	8	15	29	57	85	113	169	253
	Week	- 4-0		1	2	4	8	12	16	24	36
Window (day)			± 0	± 0	± 1	± 1	± 2	± 2	± 7	± 7	± 7
Drug Resistance Surveillance 4		×	× 10	×	×	×	×	×	×	×	×
Blood routine 5		×	× 10	×	×	×	×	×	×	×	×
Urinalysis 5		×	× 10	×	×	×	×	×	×	×	×
Blood chemistry 5		×	× 10	×	×	×	×	×	×	×	×
Blood electrolytes 5		×	× 10					×			
Coagulation 5		×	× 10			×	×	×			
Thyroid Function 6		×	× 10			×	×	×			
HbA1c7		×									
Immunological examination		×									
AFP		×									
Color Doppler		×									

Ultrasound										
ECG	×	× 10			×	×	×			
Pregnancy test 8	×	× 10			×	×	×	×	×	×
Dispense drug9		×		×	×	×				
Recovered Drug 9				×	×	×	×			
Issue diary	×	×		×	×	×	×	×	×	
Recycling diary		×		×	×	×	×	×	×	×
Record concomitant medication	×	×	×	×	×	×	×	×	×	×
Recording AEs	×	×	×	×	×	×	×	×	×	×

1. The height of the subject is measured only during the screening period, and may not be measured during the treatment period and post-treatment follow-up period.

2. If the subject has been examined at the study site within 1 month before screening, the examination may not be performed at the screening period.

3. Only perform this examination when necessary according to the inclusion criteria; this project completes the pathological examination at the study site; and the Metavir score for the pathological specimen is completed at the central laboratory.

4. For this project, blood samples will be collected at the study site and tested at the central laboratory.

5. These tests may not be performed at Visit 2 if they were performed within 3 days before Visit 2.

6. Only TSH, T3 and T4 are measured at screening, and only TSH is measured at baseline and during treatment.

7. Test this only in diabetic patients.

8. Only for women of childbearing potential.

9. Parosin can be distributed, recovered, and destroyed together with ASC08 tablets, RTV, and RBV, or separately. Only one dose of Pegasys ® can be dispensed at V2 and V3, respectively; multiple doses of Pegasys ® can be dispensed at visits during the remaining treatment periods.

10. It should be completed before the first dose in the morning of the same day as the baseline.

11. The first dose in the morning of each visit should be administered after completion of fasting (at least 8 hours) blood sample collection.