DNDi
Drugs for Neglected Diseases *initiative*

CLINICAL TRIAL PROTOCOL

Open label phase II/III, multicenter, trial to assess the efficacy, safety, tolerance, and pharmacokinetics of sofosbuvir plus ravidasvir in HCV (+/- HIV) chronically infected adults with no or compensated cirrhosis in Thailand and Malaysia

Short title	Strategic transformation of the market of HCV treatments (STORM-C-1)
Name of product(s)	Sofosbuvir 400 mg tablet manufactured by European Egyptian Pharmaceutical Industries (EEPI), Egypt Ravidasvir 200 mg tablet manufactured by Doppel Farmaceutici, Italy
Drug Class	HCV Direct Acting Agents Antivirals (DAAs) Sofosbuvir (SOF): NS5 B polymerase nucleotide inhibitor Ravidasvir (RDV, formerly PPI-668): NS5 A replication complex inhibitor
Phase	Phase II/III
Indication	Chronic Hepatitis C infection [+/- HIV co-infection]
Clinical Trial Protocol Number	DNDi-SOF/RDV-01-HCV
EudraCT	Not applicable
Co-Sponsors	Drugs for Neglected Diseases *initiative* (DNDi) Ministry of Health Malaysia Ministry of Public Health Thailand National Science and Technology Development Agency (NSTDA) Thailand
National Coordinating Investigator	[redacted]
Clinical Trial Protocol Version / Date	Final version 8.0 dated 18 March 2020

CONTACT DETAILS

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Medically qualified DNDi Officer

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2. Name and title of the Investigators who are responsible for conducting the trial :
The full list of investigators and sites contact details are provided in Appendix I.

3. Names and addresses of the clinical laboratories and other medical and/or technical departments and/or Institutions involved in the trial

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Responsible for initiation, management and financing.

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h) Hair samples analysis

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Abbreviations and Glossary of Terms

Acronyms

AE	adverse event
AIDS	acquired Immune deficiency syndrome
ALT	alanine aminotransferase (also SGPT)
APRI	Aspartate aminotransferase [AST]–to-Platelet Ratio Index
ARV	Anti retro viral
ART	Anti retro viral therapy
AST	aspartate aminotransferase (also SGOT)
AUC	area under the curve
BOC	boceprevir
BMI	body mass index
cART	combined Anti retro viral therapy
CBC	complete blood count
CFR	Code of Federal Regulations (USA)
CIOMS	Council for International Organisation of Medical Sciences
CRA	clinical research associate
CRF	case report form
CTIL	Clinical Trial Import Licence
CTP	Child-Turcotte-Pugh score
C_{max}	maximum observed concentration of drug
CYP	cytochrome P
DAA	direct acting antiviral
DAIDS	division of Aids (National institute of Health)
DCV	Daclatasvir
DCA	Drug control authority
DBS	dried blood spots
DNDi	Drug for Neglected Disease *initiative*
DSMB	Data safety monitoring board
EAE	Expedited Adverse Event
ECG	electrocardiogram
EEPI	European Egyptian Pharmaceutical Industries
EMA	European Medicines Agency
EOT	End-of-Treatment
EVR	Early Virologic Response
F0 to F4	Metavir Liver fibrosis scores 0 to 4
FAS	Full Analysis Set
FIB-4	a liver fibrosis index based on age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet (PLT) count.
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GT	genotype (viral)
HBV	Hepatitis B virus
HCV	hepatitis C virus
HCC	Hepatocellular Carcinoma

HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IFN	interferon
IDU	Injection Drug Users
IL28	interleukine 28
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRIS	Immune reconstitution inflammatory syndrome
IQA	immunology quality assurance
IQR	interquartile range
IRB	institutional review board
ITT	intention-to-treat
Kpa	kilopascal
LFT	liver function test
LLOQ	lower limit of quantification
LSM	liver stiffness measurement
MELD	Model for End Stage Liver Disease score NDA
MSF	Médecins sans Frontières
MSM	Men who have sex with men
NDA	New Drug Application
NAFLD	Non-alcoholic fatty liver disease
NNRTI	non-nucleoside reverse transcriptase inhibitor
NPRA	National Pharmaceutical Regulatory Agency
OTC	over the counter
PEG	pegylated interferon
PK	pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PPS	Per Protocol Set
PT-INR	prothrombin time-international normalized ratio
PWID	People Who Inject Drugs
PWUD	People who use Drugs
QoL	quality of life
qd, bid, tid	Once a day, twice a day, three times a day (dosing)
RAV	viral resistance associated variants
RBV	ribavirin
RDV	Ravidasvir
RNA	Ribonucleic Acid
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SOC	Standard of Care
SOF	Sofosbuvir
STORM-C-1	Strategic transformation of the market of HCV treatments

SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	sustained virologic response
SVR12	sustained virologic response 12 weeks after end of treatment (EOT)
TEAE	Treatment Emergent Adverse Event
TFDA	Thailand FDA
TVR	telaprevir
ULN	upper limit of the normal range
VL	Viral load

Protocol synopsis

Title: Open label phase II/III, multicenter, trial to assess the efficacy, safety, tolerance, and pharmacokinetics of sofosbuvir plus ravidasvir in HCV (+/- HIV) chronically infected adults with no or compensated cirrhosis in Thailand and Malaysia

Short title: Strategic transformation of the market of HCV treatments (STORM-C-1)

Countries*:* Malaysia and Thailand

Co-Sponsors: Drugs for Neglected Diseases *initiative* (DND*i*)
Ministry of Health Malaysia
Ministry of Public Health Thailand
National Science and Technology Development Agency (NSTDA) Thailand

Study centers in Malaysia*:*

Department of Hepatology, Hospital Selayang
Department of Medicine/Infectious Disease, Hospital Sungai Buloh
Department of Medicine/Gastroenterology, Hospital Ampang
Department of Medicine/Gastroenterology, Hospital Sultanah Bahiyah
Department of Medicine/Gastroenterology, Hospital Tengku Ampuan Afzan Hospital (Stage 1 only)
Department of Medicine/Gastroenterology, University Malaya Medical Centre (Stage 1 only)
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Study centers in Thailand*:*

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Internal Medicine unit, Medical Department, Nakornping Hospital, Chiang Mai
Internal Medicine, Bamrasnaradura Infectious Diseases Institute, Nonthaburi
King Chulalongkorn Memorial Hospital/HIV-NAT, Pathum Wan, Bangkok

Study duration:
Stage 1:
Actual first enrollment: October 2016 in Malaysia, April 2017 in Thailand
Actual last visit completed (Follow-up visit Week 24): April 2018
Stage 2:
Actual first enrollment: January 2019 in Malaysia, August 2019 in Thailand
Estimated last visit completed (end of long term follow-up): up to Q4 2023

Clinical Phase*:* Phase II/III

Study Objectives:
Primary Objective
- To assess the efficacy of 12 weeks sofosbuvir-ravidasvir (SOF-RDV) in subjects with chronic HCV infection and no cirrhosis (Metavir F0 to F3), and 24 weeks SOF-RDV in subjects with compensated cirrhosis (Metavir F4 and CTP class A), 12 weeks after the end of study treatment.

Secondary Objective
- To assess the efficacy of 12 weeks SOF-RDV in subjects with chronic HCV infection and no cirrhosis and 24 weeks SOF-RDV in subjects with compensated cirrhosis at 4 and 24 weeks after the end of study treatment.

- To assess the safety of 12 weeks SOF-RDV in subjects with chronic HCV infection and no cirrhosis, and 24 weeks SOF-RDV in subjects with compensated cirrhosis.
- To study the pharmacokinetics of SOF and RDV, evaluate potential drug-drug interactions with antiretrovirals and, as needed, interactions with concomitant prescribed or non-prescribed drugs.
- To describe subjects demographic, clinical and biological characteristics and their relationship with SVR12.
- To assess subjects quality of life before and after therapy.
- To evaluate the presence of viral resistance-associated variants (RAVs) to SOF-RDV at the time of failure or at first point after failure when viral load is sufficient to get a positive result in patients with virological failure and their persistence until 1 year after treatment cessation or the initiation of an alternative HCV therapy.

Exploratory objective

- To evaluate the effect of drug use, as determined by hair analysis on safety and efficacy
- To assess the occurence of drug use in virological failures
- To evaluate the change in HCV RNA values over time during the treatment period

Study Endpoints:

Primary endpoint

- SVR12, as evidenced by HCV RNA level less than the lower limit of quantification (LLOQ).

Secondary endpoints

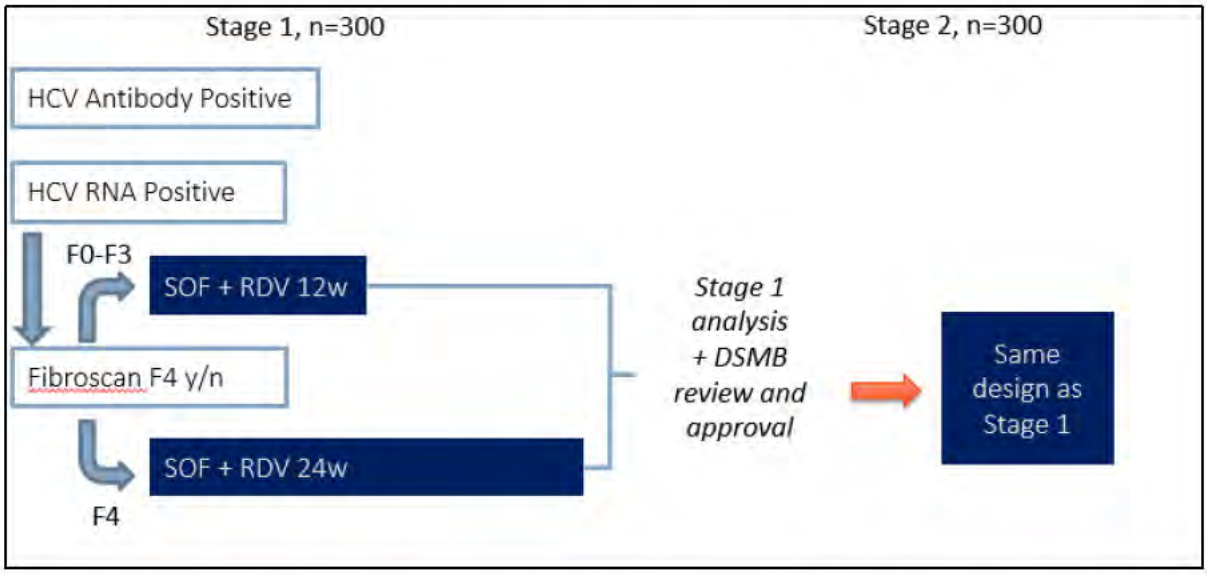
- Sustained virologic response at 4 and 24 weeks post treatment completion (SVR4 and SVR24), as evidenced by HCV RNA level less than the lower limit of quantification.
- Among subjects not achieving SVR12:
  - Occurrence of on-treatment virologic failure, defined as HCV RNA ≥ LLOQ at the end of the treatment period.
  - Occurrence of virologic breakthrough, defined as either confirmed ≥ 1 log10 IU/mL increase in HCV RNA from nadir while on treatment or confirmed HCV RNA ≥ LLOQ if HCV RNA previously declined to < LLOQ while on treatment.
  - Occurrence of virologic relapse, defined as HCV RNA < LLOQ at the end of the treatment period but HCV RNA ≥ LLOQ during the post-treatment period.
  - Occurrence of non-virologic failure, defined as any failure that does not meet the above virologic failure criteria (e.g. adverse event, lost to follow-up).
- Safety endpoints:
  - Occurrence of premature treatment discontinuation and occurrence of premature study discontinuation (overall and by reason for premature discontinuation).
  - Time to premature treatment discontinuation and time to premature study discontinuation.
  - Occurrence of the following events (overall, by system organ class and by severity): Treatment Emergent Adverse Event (TEAE), TEAE considered to be at least possibly related to at least one of the study drugs, TEAE leading to premature treatment discontinuation, TE laboratory abnormality, grade 3/4 TEAE, TE serious adverse event (SAE) and death.
  - Time to first TEAE, time to first grade 3/4 TEAE and time to first TE SAE.
- PK parameters of ravidasvir (and sofosbuvir if needed): Cmax, Tmax, predose (C0), C24, Cmin, AUC0-24, and apparent oral clearance (CL/F).
- Baseline factors associated with SVR12 outcome.
- Change in the PROQOL-HCV domain scores from treatment initiation to 12 weeks after treatment completion.
- Baseline HCV NS5A sequences and changes from treatment initiation in subjects not achieving SVR12.

Exploratory endpoints

- Above-described efficacy and safety endpoints in the subgroup of subjects who use drugs.

- Number and proportion of subjects who use drugs among those with a virological failure.
- Change in HCV RNA values from treatment initiation to treatment completion.

Study design



This is a Phase II/III, multicenter, multi-country trial to assess the efficacy, safety, tolerance, and pharmacokinetics of sofosbuvir plus ravidasvir (SOF-RDV) for the treatment of HCV infection, across genotypes 1,2,3,6, among non-cirrhotic and cirrhotic with CTP class A[1], interferon/ribavirin naïve or experienced, HCV mono-infected and HCV/HIV co-infected subjects.

It will also study the pharmacokinetics of RDV and, in HCV/HIV co-infected subjects, possible drug-drug interactions with antiretrovirals.

The treatment duration will be 12 weeks for subjects with no cirrhosis (Metavir F0 to F3) and 24 weeks for subjects with compensated cirrhosis (Metavir F4, CTP class A).

The study is performed in two stages:

- Stage 1 with a target of 300 subjects to enroll. Stage 1 will provide preliminary evidence of the efficacy, safety and pharmacokinetics of SOF-RDV in all subgroups.
  A separate stratum of the stage 1 will be defined aiming at enrolling up to 150 additional PWID (people self-declared as being active injection drug users or with recent injection drug use or for whom active injection drug use cannot be ruled out).
  Efficacy and safety results from Stage 1 will be reviewed and approved by the independent Data and Safety Monitoring Board (DSMB) which provide the recommendation to proceed with the stage 2.
- Stage 2 with a target of 300 subjects to enroll. Stage 2 aims to supplement Stage 1 results and provide additional information on the performance of SOF-RDV in the main genotypes found in Malaysia and Thailand. People self-declared as being active injection drug users will not be enrolled.

The overall target will be 600 enrolled subjects.

Study drugs

Sofosbuvir (SOF or Grateziano®)

- 400 mg tablet orally once daily with food (in the morning) for 12 weeks for subjects Metavir stage F0-F3
- 400 mg tablet orally once daily with food (in the morning) for 24 weeks for subjects Metavir stage F4 CTP class A

Ravidasvir (RDV, formerly PPI-668)

- 200 mg tablet orally once daily with food (in the morning) for 12 weeks for subjects Metavir stage F0-F3
- 200 mg tablet orally once daily with food (in the morning) for 24 weeks for subjects Metavir stage F4 CTP class A

Eligibility

Subjects with chronic hepatitis C infection of all HCV genotypes, with/without HIV co-infection and with no (Metavir F0-F3) or compensated liver cirrhosis (Metavir F4 with CTP class A), regardless of the source of infection.

Inclusion Criteria

- Evidence of chronic HCV infection, defined as:
  - Positive anti-HCV antibody **or** detectable HCV RNA **or** HCV genotype at least 6 months before screening **and** HCV viral load $\geq 10^4$ IU/mL at the time of screening
  - In subjects without documented HCV test results 6 months before screening, chronic hepatitis C infection can be assumed if risk exposures occurred ≥ 6 months prior to screening and HCV viral load is $\geq 10^4$ IU/mL at the time of screening.
- Willing and able to provide written informed consent.
- Men and women age ≥ 18 years and < 70 years.
- Body Mass Index (BMI) of 18 to 35 kg/ m^2.
- Intention to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments.
- Women with a negative pregnancy test at screening and baseline.
- Women of child bearing potential who accept a highly effective contraceptive method from at least 2 weeks prior to study day 1 until 1-month post-treatment. A woman is of non-child bearing potential if she (a) reached natural menopause determined retrospectively after 12 months of amenorrhea without any other obvious medical cause or (b) had procedures like bilateral tubal ligation or hysterectomy or bilateral oophorectomy.
- Subjects who are compliant in an opioid substitution maintenance program (e.g. with methadone or buprenorphine) may be included as long as there is no concern about study medications adherence and interaction or compliance to study schedules.
- Inclusion criteria related to HIV/HCV co-infected patients:
  - HIV/HCV co-infected patients receiving cART fulfilling the below criteria are eligible for the study:
    - Antiretroviral therapy should have been initiated at least 6 months prior to screening [i]
    - Patient has to have been on the same protocol-approved ARV regimen for ≥ 8 weeks prior to screening and is expected to continue the current ARV regimen through the end of study.
    - HIV ARVs: agents allowed in this study should be administered per the prescribing information in the package insert
    - Screening HIV RNA < 50 copies/mL[ii]
    - Screening CD4 cell count ≥ 100 cells/uL
  - HIV/HCV co-infected patients not receiving cART: Screening CD4 cell count must be ≥ 500 cells/uL

[i] To avoid he possibility of Immune reconstitution inflammatory syndrome - IRIS

[ii] This would allow us to properly evaluate the risk of virological failure during therapy

Exclusion criteria

- Decompensated cirrhosis defined as:
  Evidence of advanced stage liver cirrhosis and Child-Turcotte-Pugh (CTP) Class B or C or CTP score >6) or current/past history of decompensation including ascites, variceal bleeding, spontaneous bacterial peritonitis, or hepatic encephalopathy.
- Hepatocellular carcinoma: for all patients with cirrhosis, hepatocellular carcinoma (HCC), should be excluded by liver imaging within 6 months prior to screening, and this must continue periodically as in routine HCC surveillance.
- Laboratory exclusion criteria:
  - cirrhotic subjects with albumin < 2.8 g/dL
  - direct bilirubin > 3xULN
  - AST, ALT > 10xULN
  - Low neutrophil count (≤599 cells/mm^3), hemoglobin (<9.0 g/dL for male, <8.5 g/dL for female), platelets (<50000 cells/mm^3) classified as ≥ Grade 3
- Patients with serum creatinine > 1.5 ULN or end stage renal disease[2]
- Hepatitis B co-infection (HBsAg positive)
- Pregnancy, as documented by positive pregnancy tests at screening or baseline
- Breastfeeding
- Subjects currently receiving (or unable to stop the use for at least 1 week prior to receiving the first dose of study drug) any medications or herbal supplements known to be potent inhibitors or moderate inducers of cytochrome P450 (CYP) 3A4 or potent inducers of P-glycoprotein. This includes subjects who are on amiodarone or other contraindicated/excluded drugs (see section 9.3).
- Participation in other clinical trials within 3 months
- Any clinically significant findings or unstable condition during the screening, medical history or physical examination that, in the investigator's opinion, would compromise participation in this study as per standard guidelines and local practice.[iii] This could include patients with poorly controlled hypertension, asthma, diabetes, or other life-threatening conditions.
- Current or history of use within the preceding 6 months of immunosuppressive or immune-modulating agents. Corticosteroid used to treat any medical condition are allowed if systemic for not more than 2 weeks or if topical.
- History of solid organ or bone marrow transplantation.
- Any prior NS5A inhibitors therapy.[iv]
- Patients with significant cardiovascular conditions including:
  - myocardial infarction within the previous 6 months or
  - heart failure NYHA class III or IV
  - history of Torsade de pointes
  - third degree heart block
  - QTcF (Fridericia) value ≥ 450 milliseconds at Baseline.
  - Severe sinus bradycardia with a rate of under 50 beats per minute
  - A sinus bradycardia with third degree atrioventricular block or with Mobitz II AV block
- Use of medications associated with QT prolongation concurrently or within the 30 days prior to Screening Visit, including: macrolides, antiarrhythmic agents, azoles, fluoroquinolones, and tricyclic anti-depressants. Commonly used and essential medications for this study population like methadone and/or efavirenz is allowed as long as the QTcF value at baseline is < 450 milliseconds.
- Self-reporting active injection drug use at screening (only for stage 2).

[iii] Management of clinical/biological findings are detailed in the Manual of Operations

[iv] Note: Prior Interferon based therapy is allowed but will be one of the important stratification criteria. It is anticipated that this category will become irrelevant in the future as interferon based therapy is phased out.

- Exclusion criteria related to HIV/HCV co-infected patients:
  - HIV/HCV co-infected patients not yet on stable antiretroviral therapy or for whom ART treatment initiation maybe scheduled during the study period.

Timing of assessments:

Eligibility visit

The eligibility visit can be performed the same day than the screening visit for patients already diagnosed as HCV chronically infected.

Informed consent for enrollment in the study will be obtained during this visit.

Screening visit

The eligibility visit can be performed the same day than the screening visit for patients already diagnosed as HCV chronically infected.

Screening evaluations must occur prior to the subject starting any study medications, treatments, or interventions. In addition to data being collected on subjects who will enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured at site on the CRF and then entered into the study database.

Day 1 visit: Study treatment initiation

Treatment initiation will follow thorough explanation of the treatment schedule --which differ according to fibrosis staging--, and of the importance of adherence to therapy as well as study visits.

On treatment visits

After treatment initiation, on treatment visits will be schedule at week-1, week-4, week-8 and week-12 for non-cirrhotic subjects. Cirrhotic subjects will have additional on treatment visits at week 16, week 20 and week 24.

Visit at week 1 will have a window of ± 3 days. Visits at Weeks 4, 8, 12, 16, 20 and 24 have a window of ± 7 days.

On treatment visits will focus on recording vital signs, inquiring about new signs and symptoms, adherence to therapy, concomitant medications and symptom targeted clinical examination. Study drugs will be dispensed every 4 weeks until end of therapy (12 weeks for subjects without cirrhosis, or 24 weeks for cirrhotic subjects).

Follow-up visits: SVR4, SVR 12, SVR 24 and end of study visit

HCV viral load will be performed for all the patients on plasma taken at week 4 post-treatment visit (SVR4). HCV viral load will be performed for all the patient on plasma taken at the week 12 post-treatment visit (SVR12).

This final visit will focus on assessing SVR 24 weeks after treatment discontinuation. Post-treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data.

Long term Follow-up visits

A series of long-term follow-up visits will be implemented retrospectively for stage 1 (only for newly consented patients with virological failure) and for stage 2.

A representative subset of the cured patients (i.e achieving SVR 12) will be followed up for one year after end of treatment to assess durability of response. One additional follow-up visit will be scheduled 12 months after the end of treatment visit

All patients with virological failure at SVR 12 or SVR 24 will be followed up for three years after end of treatment or until they receive another treatment for HCV, whichever comes first. Five additional follow-up visits will be scheduled one year, 18 months, 2 years, 30 months and 3 years after the end of treatment visit.

Statistical Analysis

A comprehensive analysis of the study results will be performed at the end of Stage 1 and an interim Clinical Study Report will be released. An analogous analysis will be performed at the end of stage 2 with data from stage 1 + stage 2 and a final Clinical Study Report will be released.

The final Statistical Analysis Plan (SAP) will be submitted and approved by the DSMB prior to the database lock for the final study analysis (stage 1 + stage 2).

Descriptive statistics

Participant's characteristics at baseline and over time will be tabulated. Categorical variables will be described using frequencies and proportions, and discrete and continuous variables using means (standard deviations), medians (25^{th}; 75^{th} percentiles) and ranges (minimum-maximum).

Efficacy

The efficacy of SOF-RDV will be evaluated overall and for each of the pre-specified subgroups: presence/absence of cirrhosis, genotype, prior/no prior therapy, and HIV/no HIV co-infection.

Non-virological failures (including deaths and lost to follow-ups), on-treatment virological failures and virological relapses, will be considered as failures. Reinfections are not considered as failures.

Time-to-event endpoints will be estimated using the Kaplan-Meier method. Changes in continuous variables from baseline will be assessed using Wilcoxon signed-rank test.

In exploratory analyses, multivariable logistic regression models and Cox proportional hazards regression models may be used to evaluate risk factors associated with binary and time-to-event endpoints, respectively.

Safety

Adverse events will be described during the study period, until 24 weeks after treatment discontinuation. AEs and Medical History will be coded using MedDRA and tabulated by severity / DAIDS AE grading table version 2/ November 2014. Causality of AEs for each sudy drug will also be tabulated.

The number and percentage of subjects who experienced each of the safety events listed as secondary endpoints will be presented overall, by assigned treatment duration and by key subgroup. In addition, the number and percentage of subjects who experienced these events will be summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT) and presented overall and by assigned treatment duration.

Safety and tolerance of the study agents will be evaluated by summarizing the number and percentage of subjects with documented Grade 3 or higher adverse events; each summary will be conducted overall and by assigned treatment duration. The proportion of subjects experiencing Grade 3+ adverse events will be presented overall and by assigned treatment duration, with these proportions bounded by exact 95% confidence intervals; this will also be done for the proportions of subjects with Grade 3+ intensity adverse events which have been judged to be at least possibly related (possibly/probably/definitely related) to treatment.

Serious Adverse Events will be described by individual narratives based on the SAE reports provided by the site investigators.

Pharmacokinetics

In stage 1, the pharmacokinetics of RDV will be evaluated using an intensive PK schedule for a small proportion of the subjects enrolled in selected sites to establish the PK model and by sparse PK data collection for the others. Twenty-five evaluable intensive PK evaluations will provide sufficient precision in the PK parameter estimates to use as initial estimates in the population model.

The population PK (sparse PK) model built using these parameters has allowed in stage 1 and will allow in stage 2, with a small number of samples collected in all the other subjects at variable times after drug intake, the estimation of the population pharmacokinetic parameters of the drugs as well

as inter-patient variability. This approach enables the evaluation of the role of factors such as antiretroviral co-treatments and patient's characteristics (e.g., BMI, sex, etc.).

1. Background

1.1. Background

HCV infection and disease

Hepatitis C is an inflammatory liver disease caused by infection with the hepatitis C virus (HCV). HCV is transmitted parenterally through exchange of body fluids, mostly through exposure to contaminated blood.

About 71 million people are chronically infected with HCV in the world[3] and more than 399 000 people are estimated to die from HCV-related liver diseases each year. Dramatic increases in the numbers of cases of decompensated cirrhosis, hepatocellular carcinoma (HCC), and HCV-related deaths are predicted as the infected population ages. However, most of the ~71 million infected patients are unaware of their infection status. Furthermore, access to treatment remains beyond reach in most developing countries where the burden of disease is the greatest, and no vaccine is available. More than 463 000 persons are estimated to be chronically infected with HCV in Thailand and 382 000 in Malaysia[4].

The incubation period for hepatitis C infection lasts from 2 weeks to 6 months. Approximately 15% to 20% of people clear the infection. While they have developed HCV-specific antibodies, after a few months HCV RNA can no longer be detected in their blood. However, about 80–85 % of newly infected persons develop chronic infection: HCV infects their liver cells and can cause severe inflammation of the liver with long-term complications. About 60–70% of chronically infected people develop chronic liver disease; 5–20% develop cirrhosis within the first two decades of infection and 5% liver cancer[5]. In addition to liver disease, HCV persistent infection is associated with chronic fatigue, diabetes, depression, cryoglobulinemia, and kidney disease[6].

HCV is an enveloped, single stranded, positive sense RNA virus, and a member of the *Flaviviridae* family[7]. The genome of HCV is highly mutable, leading to great genetic variability. Due to the high genetic heterogeneity of HCV, it is classified by phylogenetic methods into 6 major genotypes (GT 1 to 6). Disease expression and response to therapy may vary according to the genotype, e.g., genotype 3 is associated with more steatosis. In Thailand, 47.8% of HCV infections are genotype 3, 17.4 % genotype 1 and 34.8% genotype 6. In Malaysia, 62.3% of HCV infections are genotype 3, 35.8% genotype 1, 0.4% genotype 6, 1.5% for the other genotypes[8].

HIV-HCV and other co-infections

About 2.3 million people of the estimated 36.7 million living with HIV globally have serological evidence of past or present HCV infection[9].

HIV hastens the progression of HCV-related liver disease, and more than triples the risk for liver disease, liver failure, and liver-related death from HCV[10] [11] [12] [13].

HBV/HCV coinfection is not rare[14]. Persons with HBV/HCV coinfection and detectable viremia of both viruses are at increased risk for disease progression, decompensated liver disease, and the development of hepatocellular carcinoma[15]. HBV/HCV co-infected individuals are susceptible to a process called viral interference wherein one virus may interfere with the replication of the other virus[16] [17] and therapy should be undertaken with caution[17].

HCV Diagnosis

Diagnosis of acute HCV infection is often missed because the majority of infected people are asymptomatic in the early stages. The presence of antibodies against the hepatitis C virus indicates that a person has been infected by HCV, however infection may have spontaneously cleared. Diagnosis of chronic infection is made when HCV RNA is identified in a person with evidence of HCV infection for more than 6 months (anti-HCV antibodies, or evidence of hepatitis C virus). Specialized tests are then needed to evaluate patients for liver disease, including cirrhosis and liver cancer[19] [20].

Assessment of the degree of liver fibrosis and cirrhosis

Efficacy of therapy and decisions regarding treatment management for HCV are based on a patient's degree of liver fibrosis. Patients with less advanced fibrosis respond better to HCV treatment, with a higher sustained cure rates.

The Metavir classification system, based on liver biopsy histological results, recognizes five disease stages from F0 (No fibrosis), to F1 (Portal fibrosis without septa), F2 (Portal fibrosis with septa), F3 (Numerous septa without cirrhosis) and F4 (Cirrhosis).

A variety of non-invasive fibrosis tests based on blood indices and imaging techniques are now available, which are more suitable for public health use. These include serum tests such as the APRI, or FIB4 scores, which use indirect markers of fibrosis such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and platelet count, tests that should be available at all clinics treating patients with HCV. Techniques based on ultrasound technology, in particular transient elastography performed by FibroScan, accurately assess the degree of fibrosis and cirrhosis by measuring liver stiffness. FibroScan is progressively replacing liver biopsy[21].

The Child-Turcotte-Pugh (CTP) score has been used successfully for assessing the prognosis of patients with cirrhosis[22][23][24]. It includes the presence and severity of ascites and encephalopathy, prolongation of prothrombin time and the levels of albumin and bilirubin. Patients with score 5-6 are categorized as CTP class A, with 7-9 as class B and > 9 as class C[v] (see Figure 1).

Figure 1: Child-Turcotte-Pugh (CTP) classification of the severity of cirrhosis

	Points		
	1	2	3
Encephalopathy	None	Grade 1-2 (or precitant-induced)	Grade 3-4 (or chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
PT (sec prolonged) or INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3

CTP score is obtained by adding the score for each parameter

CTP class: A = 5-6 points
B = 7-9 points
C = 10-15 points

Hepatitis C treatment

The goal of HCV therapy is the cure of infection, or Sustained Virological Response (SVR[25]) and the elimination or, if liver fibrosis is advanced, the reduction of its long term complications[26].

Therapy of chronic hepatitis C has evolved from interferon α (IFNα) monotherapy in 1986[27]to the use of pegylated IFNα (pegIFNα), together with ribavirin (RBV). However, IFN and pegIFNα cause severe side effects, including fever, flu-like illness, depression, anorexia, anaemia and lymphopenia, and these problems are exacerbated by ribavirin[28][29]. Many patients cannot complete their treatment course[30].

[v] Bilirubin cut-offs in SI units- < 34 umol/l, 34-50, > 50; Albumin in SI units > 35g/l, 28-35 g/l, < 28g/l

The availability of Direct Acting Antivirals (DAAs) which directly interfere with HCV viral replication, has dramatically improved the efficacy of therapy[31][32].

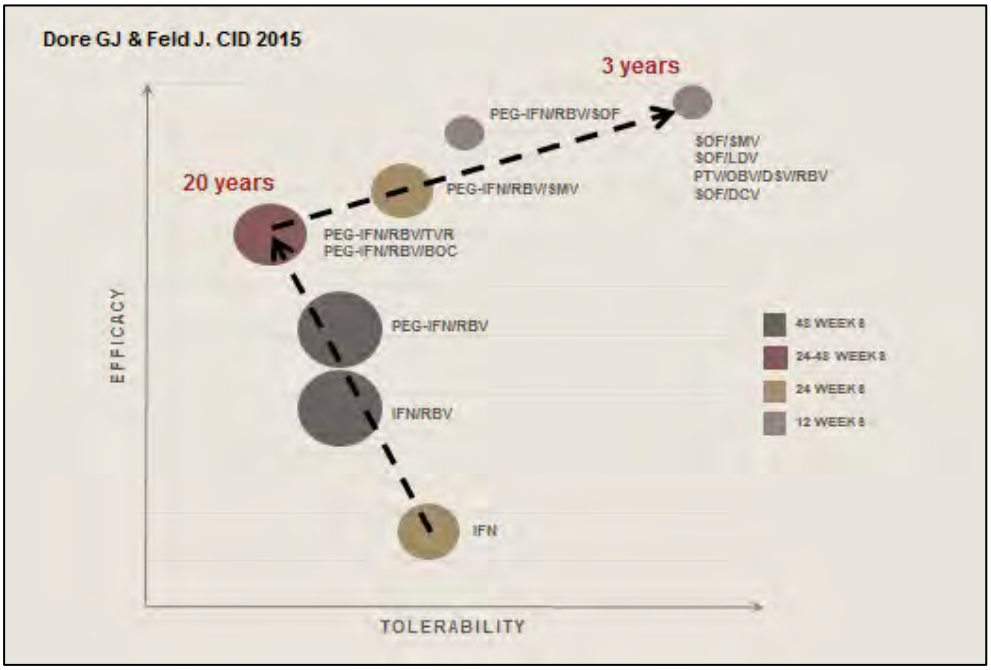
Since 2011, the use of first generation DAAs (boceprevir and telaprevir) in GT 1 HCV, started to transform the treatment of HCV with cure rates around 70%. However, the side effects of these protease inhibitors associated with peginterferon and ribavirin were worse than those of peginterferon and ribavirin alone. Response rates among the patients with cirrhosis remained relatively low and HCV antiviral resistance developed in most patients who failed to respond to treatment[33].

Direct-acting antivirals (DAAs) target viral proteins of the hepatitis C virus (HCV) which are critical for viral replication, resulting in the four classes of antivirals currently approved: nonstructural protein 3 (NS3) protease inhibitors (PI), NS5A inhibitors, NS5B nucleot(s)ide polymerase inhibitors and NS5B non-nucleot(s)ide polymerase inhibitors[34][35][36].

Since late 2013, five single-component DAAs and six fixed-dose combinations have received regulatory approval from at least one stringent regulatory authority. DAAs eliminate HCV from the body by preventing the virus from multiplying.

Within a few years, extremely efficacious, highly tolerable, simple once daily oral treatment regimens of short-duration (6-12 weeks) have become available (see Figure 2) [37]. In more than 95% of cases, they cure individuals of HCV, usually within 8–12 weeks[38][39].

Figure 2: Hepatitis C virus therapeutic development: in pursuit of "perfectovir"



1.2. Delivering the promises of the new DAAs in low and middle income countries

Countries that have achieved significant price reductions or that can procure DAAs at affordable prices now have to seize the opportunity and scale up treatment more rapidly as low prices alone do not guarantee access. This requires dealing with other challenges, including expanding screening and diagnostic services, and strengthening procurement and distribution systems for HCV medicines, promoting service delivery models that can reach those populations most affected, and integrating HCV testing and treatment into national health benefit packages to be delivered by public health services[40].

In the HCV context, a public health approach not only aims at identifying and treating those with advanced fibrosis at immediate need for therapy, before they develop cirrhosis decompensation and liver cancer, but also at extending therapy and prevention to all those infected in order to

prevent the long term morbidity and mortality associated with HCV as well as preventing further transmission to others. Now, the difficult task remains for countries to independently prioritise the cure of a curable disease and finance the cost of a cost-effective therapy to make elimination possible[41].

Since HCV has no known natural non-human reservoir and is now curable, control or elimination of HCV has become a possibility. However, significant barriers exist; some universal for all endemic countries regardless of wealth, some particularly severe in low and middle income countries[42].

However, pharmaceutical companies have historically priced their drugs in the developed countries based on what the market is willing to bear. Although this has been accepted practice, the exorbitant pricing of HCV therapies has led to serious consideration of price controls, even in the United States, which historically has avoided interfering in the market economy[43].

Globally, the number of people who initiated DAA-based treatment for HCV rose between 2015 and 2016, from approximately 1 million to 1.5 million. A small number of countries were responsible for the bulk of that increase. Egypt and Pakistan accounted for about half of all people who started DAA treatment in 2016.There was encouraging progress also in countries as diverse as Australia, Brazil, China, France, Georgia, Mongolia, Morocco, Rwanda and Spain[44].

High drug cost is probably the most significant barrier to overcome[45]. HCV DAA therapies could be produced as generics at a fraction of the current costs[46].

Drugs for Neglected Diseases *initiative* (DNDi) aims to deliver a safe, effective, and easy-to-use direct-acting antiviral regimen, to be used as an affordable combination in a diverse population of people living with HCV thus paving the way for a public health approach to HCV.

DNDi is a collaborative, patients' needs-driven, non-profit R&D organization that is developing new treatments for neglected diseases. To overcome the barriers which prevent the vast majority of people with HCV from accessing the extraordinary powerful and well tolerated drug combinations which have been recently discovered, DNDi has decided to enter the HCV field and to develop, in partnership with key affected countries, a for-patient HCV drug development strategy.

DNDi's strategy is complementary and synergistic to other efforts aimed at improving access to HCV education, surveillance, screening, testing and linkage to care and prevention. It consists of accelerating the development of drug candidates already in the pipeline independent from the for-profit efforts led by the pharmaceutical industry. It focuses on the creation of a short, affordable, easy-to-use, highly efficacious and safe, all-oral pan-genotypic regimen that will enable countries to implement a public health approach to the HCV epidemic[47].

2. Study rationale

2.1. Ravidasvir for HCV infection

Ravidasvir (formerly PPI-668)[48] is a NS5A inhibitor, which exhibits potent inhibition of HCV replication in HCV replicon assays. Its activity is additive to synergistic in replicon assays when combined with other HCV antiviral agents. HCV variants with reduced susceptibility to RDV remain fully susceptible to other classes of HCV inhibitors, and ravidasvir inhibits replication of variant HCV replicons encoding resistance mutations for the other major classes of HCV DAAs.

Ravidasvir has a favourable in vitro metabolic stability profile, consistent oral bioavailability, and a favourable preclinical pharmacology and toxicology profile. Distribution to liver, an important target organ for antiviral efficacy, is higher than to plasma. Biliary excretion of unchanged ravidasvir appears to be the primary route of elimination of the absorbed dose, while renal excretion of the drug appeared negligible.

2.2. Clinical Experience with Ravidasvir

The Investigator brochure is the reference document for all clinical studies completed with Ravidasvir[49].

The sofosbuvir and ravidasvir combination has shown to be highly efficacious and safe in the Phase 3 study performed in patients infected by HCV genotype 4 in Egypt (PPI-668-202 protocol).

However, there were no data existing in patients from Thailand and Malaysia where prevalent genotypes are genotype 3, 1 and to a lesser extent 6.

Ongoing SOF - RDV phase II/III clinical trial in Thailand and Malaysia STORM-C-1 (as per current protocol)

The Malaysian Ministry of Health and the Thai Ministry of Public Health together with DNDi and Pharco, the pharmaceutical company developing ravidasvir, decided to launch an open label phase II/III, multicenter, trial to assess the efficacy, safety, tolerance, and pharmacokinetics of sofosbuvir plus ravidasvir in HCV (+/- HIV) chronically infected adults with no or compensated cirrhosis in Thailand and Malaysia (DNDi-SOF/RDV-01-HCV[50]; ClinicalTrials.gov Identifier: NCT02961426[51]).

This on-going study hypothesizes that sofosbuvir plus ravidasvir constitutes a pan-genotypic, potent and safe regimen which can be used in decentralized public health settings under the supervision of appropriately trained health care professionals.

2.3. Risks and benefits assessment

Risks and benefits are discussed in various sections of this protocol. We provide here a summary of the risks and benefits to be taken into consideration.

These risks and benefits can be grouped around 3 general questions:

- What are the risks/benefits of being treated for HCV chronic infection?
- What are the risks/benefits of the new modern treatments of HCV chronic infection compared to previous treatments?
- What are the risks/benefits of participating in this specific trial using the sofosbuvir-ravidasvir combination?

What are the risks/benefits of being treated for HCV chronic infection?

HCV chronic infection affects around 71 million persons worldwide. HCV infects liver cells and causes chronic inflammation of the liver with long-term complications: 60–70% of chronically infected people develop chronic liver disease, 5–20% will develop cirrhosis and 1–5% will die from cirrhosis or liver cancer.

In addition to liver manifestations, there are multiple extrahepatic clinical manifestations attributable to Hepatitis C Infection: Arthralgia, neuropathy, nephropathy, glomerulonephritis, livedo reticularis, lichen planus, and cold agglutinin disease. HCV chronic infection has been shown to be associated with diabetes, hypertension, and chronic fatigue; it also increases the risks of psychiatric diseases such as depression[53].

HIV/HCV co-infection is very frequent. HIV hastens progression of HCV-related liver disease, and more than triples the risk of liver-related death[54].

Current therapies with DAAs result in a cure for more than 95% of the patients, therefore when treated early (before the onset of liver cirrhosis) the expected benefits of therapy, are the prevention of the most severe manifestations of HCV, cirrhosis and cancer, but also of all the non-hepatic manifestations. Cure after the onset of liver cirrhosis is still beneficial with reduction of the risk of liver cancer and of worsening of liver cirrhosis. Studies also shown a reduction in all causes mortality and of the need for liver transplantation[55].

Patients with decompensated cirrhosis represent specific challenges for DAA treatment. Some trials have provided evidence that DAA therapy can be used for the treatment of decompensated liver cirrhosis patients and pretransplant and posttransplant liver cirrhosis patients. SVR12 rates are reported to be lower at 80% to 90% in CPT class B and C patients with or without previous liver

transplantation; pretransplant DAA therapy can achieve a relatively high rate (70%) of SVR after transplantation[56].

Decompensated cirrhotic patients will not be enrolled in this study.

What are the risks/benefits of the new modern treatments of HCV chronic infection, compared with previous treatments?

The efficacy, safety and tolerability of the therapy of chronic hepatitis C has evolved from interferon α (IFNα) monotherapy to the use of pegylated IFNα together with ribavirin. It is most often the only treatment available, although its efficacy is mediocre –40% to 70%-- depending on the genotype, liver cirrhosis and genetic constitution[57].

Side effects of pegIFN plus ribavirin are numerous. Common side effects of pegIFN include flu-like illness, depression, anorexia, anaemia and lymphopenia, and these problems are exacerbated by ribavirin. The risk of these complications is so high that many patients are ineligible for therapy. Treatment therefore needs to be delivered by a multidisciplinary team. The rate for treatment discontinuation is as high as 36%, half of which are due to adverse events[58].

The use of boceprevir (BOC) or telaprevir (TVR), the first two potent direct-acting antiviral agents (DAA) approved, in addition to pegIFN plus ribavirin, has, for some genotypes, considerably improved efficacy, but side effects of triple therapy are worse than those of pegIFN and ribavirin alone, response rates among the patients with cirrhosis remain relatively low and drug resistance develops in most patients who have not had a response to treatment[59].

The use of second generation dual DAAs has completely modified the situation: these treatments are prescribed for a short duration and are extremely well tolerated, safe and efficacious. In an analysis of data from a large prospective study of patients with HCV-associated compensated or decompensated cirrhosis, it has been found that SVR to DAA treatment reduced the incidence of HCC over a mean follow-up of 14 months[60].

Today, although the risk/benefit ratio is clearly in favour of modern therapies, pegIFNα together with ribavirin remains the standard of care in Thailand[61], essentially for economic reasons as the price of DAAs put them out of reach of public funded medical services as well as, for most people, of privately funded individual care.

What are the risks/benefits of participating in this specific trial using the sofosbuvir-ravidasvir (SOF-RDV) combination?

Participation to any trial includes risks and benefits:

Among risks are those inherent to an experimental treatment or procedure. In a well-controlled phase 3 study in Egypt (PPI-668-202 protocol), sofosbuvir plus ravidasvir has shown excellent efficacy, close to 100% in GT4 cirrhotic and non-cirrhotic patients[62].

In the Stage 1 of the present study, sofosbuvir plus ravidasvir yielded very high efficacy results in Malaysia and Thailand, in HCV GT1, 3 and 6 infected patients, cirrhotic and non cirrhotic, HIV/HCV coinfected, in treatment naïve and experienced patients.

Side effects of sofosbuvir and ravidasvir are rare and are the same as those reported for similar combinations. They have been listed in the informed consent form for participation in the study.

Ravidasvir in combination with sofosbuvir has been shown to be safe in phase 3 trials. The most frequently reported adverse reactions were fatigue, headache, and nausea. No Grade 3 or 4 adverse reactions were reported (reported cases of bradycardia were associated with sofosbuvir).

The effect of sofosbuvir plus ravidasvir on an unborn child is not known. Therefore, women who are able to become pregnant will be given a pregnancy test to confirm they are not pregnant at screening and will be asked to use highly effective birth control methods. Also breastfeeding women will not be enrolled as study drugs may be transferred in breast milk.

Other risks include those of study procedures, which are essentially blood draws. Other study assessments are non-invasive.

Benefits of participation to the trial also include HCV diagnosis and thorough evaluation of damages to the liver and extrahepatic manifestations, most of which may not have been diagnosed. Subjects will be carefully followed during and after therapy.

3. Study Objectives and Endpoints

3.1. Study Objectives

3.1.1. Primary Objective

- To assess the efficacy of 12 weeks sofosbuvir-ravidasvir (SOF-RDV) in subjects with chronic HCV infection and no cirrhosis (Metavir F0 to F3), and 24 weeks SOF-RDV in subjects with compensated cirrhosis (Metavir F4 and CTP class A), 12 weeks after the end of study treatment.

3.1.2. Secondary Objectives

- To assess the efficacy of 12 weeks SOF-RDV in subjects with chronic HCV infection and no cirrhosis and 24 weeks SOF-RDV in subjects with compensated cirrhosis at 4 and 24 weeks after the end of study treatment.
- To assess the safety of 12 weeks SOF-RDV in subjects with chronic HCV infection and no cirrhosis, and 24 weeks SOF-RDV in subjects with compensated cirrhosis.
- To study the pharmacokinetics of SOF and RDV, evaluate potential drug-drug interactions with antiretrovirals and, as needed, interactions with concomitant prescribed or non-prescribed drugs.
- To describe the subjects' demographic, clinical and biological characteristics and their relationship with SVR12.
- To assess the subjects' quality of life before and after therapy.
- To evaluate the presence of viral resistance-associated variants (RAVs) to SOF-RDV at the time of failure or at first point after failure when viral load is sufficient to get a positive result in patients with virological failure and their persistence until 1 year after treatment cessation or the initiation of an alternative HCV therapy.

3.1.3. Exploratory objective

- To evaluate the effect of drug use, as determined by hair analysis on safety and efficacy.
- To assess the occurence of drug use in virological failures.
- To evaluate the change in HCV RNA values over time during the treatment period.

3.2. Study Endpoints

3.2.1. Primary endpoint

- SVR12, as evidenced by HCV RNA level less than the lower limit of quantification (LLOQ).

3.2.2. Secondary endpoints

- Sustained virologic response at 4 and 24 weeks post treatment completion (SVR4 and SVR24), as evidenced by HCV RNA level less than the lower limit of quantification.
- Among subjects not achieving SVR12:
  - Occurrence of on-treatment virologic failure, defined as HCV RNA ≥ LLOQ at the end of the treatment period.
  - Occurrence of virologic breakthrough, defined as either confirmed ≥ 1 log10 IU/mL increase in HCV RNA from nadir while on treatment or confirmed HCV RNA ≥ LLOQ if HCV RNA previously declined to < LLOQ while on treatment.
  - Occurrence of virologic relapse, defined as HCV RNA < LLOQ at the end of the treatment period but HCV RNA ≥ LLOQ during the post-treatment period.

  - Occurrence of non-virologic failure, defined as any failure that does not meet the above virologic failure criteria (e.g. adverse event, lost to follow-up).
- Safety endpoints:
  - Occurrence of premature treatment discontinuation and occurrence of premature study discontinuation (overall and by reason for premature discontinuation).
  - Time to premature treatment discontinuation and time to premature study discontinuation.
  - Occurrence of the following events (overall, by system organ class and by severity): Treatment Emergent Adverse Event (TEAE), TEAE considered to be at least possibly related to at least one of the study drugs, TEAE leading to premature treatment discontinuation, TE laboratory abnormality, grade 3/4 TEAE, TE serious adverse event (SAE) and death.
  - Time to first TEAE, time to first grade 3/4 TEAE and time to first TE SAE.
- PK parameters of ravidasvir (and sofosbuvir if needed): Cmax, Tmax, predose (C0), C24, Cmin, AUC0-24, and apparent oral clearance (CL/F).
- Baseline factors associated with SVR12 outcome.
- Change in the PROQOL-HCV domain scores from treatment initiation to 12 weeks after treatment completion.
- Baseline HCV NS5A sequences and changes from treatment initiation in subjects not achieving SVR12.

3.2.3. Exploratory endpoints

- Above-described efficacy and safety endpoints in the subgroup of subjects who use drugs.
- Number and proportion of subjects who use drugs among those with a virological failure.
- Change in HCV RNA values from treatment initiation to treatment completion.

4. Study Design

4.1. Overall study design

This is a Phase II/III, multicenter, multi-country, trial to assess the efficacy, safety, tolerance, and pharmacokinetics of sofosbuvir plus ravidasvir (SOF-RDV) for the treatment of HCV infection, across genotypes 1,2,3,6, among non-cirrhotic and cirrhotic with CTP class A[52], interferon/ribavirin naïve or experienced, HCV mono-infected and HCV/HIV co-infected subjects.

The treatment duration will be 12 weeks for subjects with no cirrhosis (Metavir F0 to F3) and 24 weeks for subjects with compensated cirrhosis (Metavir F4, CTP class A).

It will also study the pharmacokinetics of RDV and, in HCV/HIV co-infected subjects, possible drug-drug interactions with antiretrovirals.

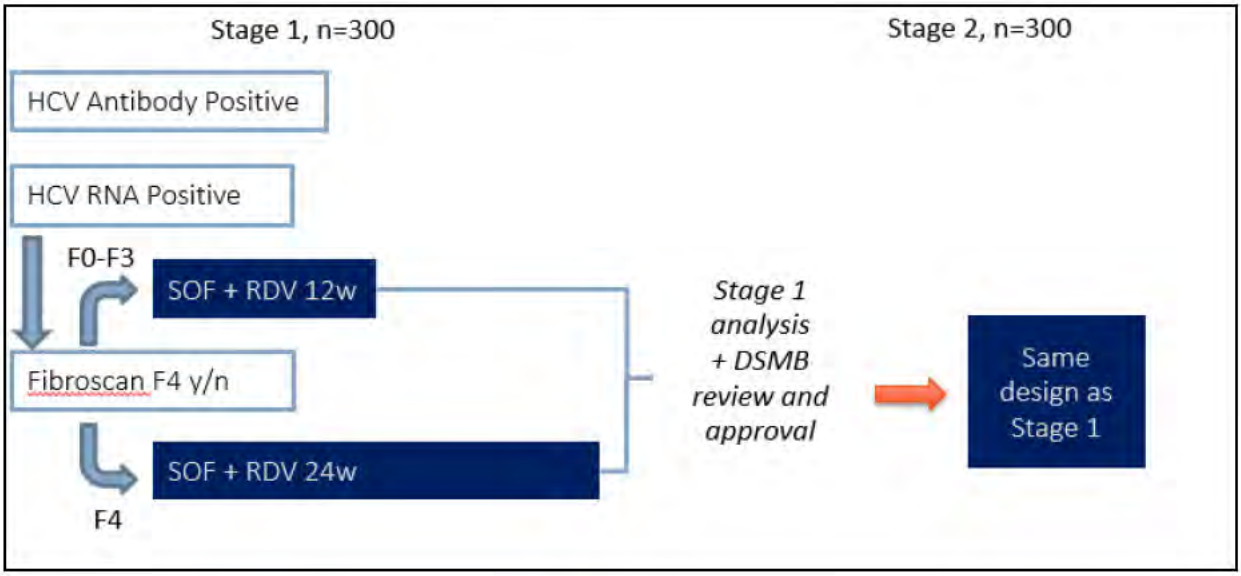
The study is performed in two stages:

- Stage 1 with a target of 300 subjects enrolled. Stage 1 will provide preliminary evidence of the efficacy, safety, tolerance and pharmacokinetics of SOF-RDV in all subgroups.
  A separate stratum of the stage 1 will be defined aiming at enrolling up to 150 additional PWID (people self-declared as being active injection drug users or with recent injection drug use or for whom active injection drug use cannot be ruled out).
  Efficacy and safety results from Stage 1 will be reviewed and approved by the independent Data and Safety Monitoring Board (DSMB) which provide the recommendation to proceed with the stage 2.
- Stage 2 with a target of 300 subjects enrolled. Stage 2 aims to supplement Stage 1 results and provide additional information on the performance of SOF-RDV in the main

genotypes found in Malaysia and Thailand. People self-declared as being active injection drug users will not be enrolled.

The overall target will be 600 enrolled subjects.

4.2. Schematic diagram of study design



4.3. Study duration and duration of subject participation

Study duration for the subject:

12/24 weeks on-treatment for non-cirrhotic/cirrhotic patient

+ 24 weeks post-treatment follow-up

Total = 36/48 weeks for non-cirrhotic/cirrhotic patient

+ additional long term follow-up of 6 months for subset of cured patients: total of about 16/19 months for such non-cirrhotic/cirrhotic patients

or

+ additional long term follow-up of 30 months for all patients with virological failure: total of about 40/43 months for such non-cirrhotic/cirrhotic patients

Study duration stage 1:

Actual first enrollment: October 2016 in Malaysia, April 2017 in Thailand

Actual last visit completed (Follow-up visit Week 24): April 2018

Study duration stage 2:

Actual first enrollment: January 2019 in Malaysia, August 2019 in Thailand

Estimated last visit completed (end of long term follow-up): up to Q4 2023

5. Selection of subjects

5.1. Eligibility

Subjects with chronic hepatitis C infection of all HCV genotypes, with/without HIV co-infection and with no (Metavir F0-F3) or compensated liver cirrhosis (Metavir F4 with CTP class A), regardless of the source of infection.

5.2. Inclusion Criteria

- Evidence of chronic HCV infection, defined as:
  - Positive anti-HCV antibody **or** detectable HCV RNA **or** HCV genotype at least 6 months before screening **and** HCV viral load ≥10^4 IU/mL at the time of screening
  - In subjects without documented HCV test results 6 months before screening, chronic hepatitis C infection can be assumed if risk exposures occurred ≥ 6 months prior to screening and HCV viral load is ≥10^4 IU/mL at the time of screening.
- Willing and able to provide written informed consent.
- Men and women age ≥ 18 years and < 70 years.
- Body Mass Index (BMI) of 18 to 35 kg/ m^2.
- Intention to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments.
- Women with a negative pregnancy test at screening and baseline.
- Women of child bearing potential who accept a highly effective contraceptive method from at least 2 weeks prior to study day 1 until 1-month post-treatment. A woman is of non-child bearing potential if she (a) reached natural menopause determined retrospectively after 12 months of amenorrhea without any other obvious medical cause or (b) had procedures like bilateral tubal ligation or hysterectomy or bilateral oophorectomy.
- Subjects who are compliant in an opioid substitution maintenance program (e.g. with methadone or buprenorphine) may be included as long as there is no concern about study medications adherence and interaction or compliance to study schedules.
- Inclusion criteria related to HIV/HCV co-infected patients:
  - HIV/HCV co-infected patients receiving cART fulfilling the below criteria are eligible for the study:
    - Antiretroviral therapy (ART) should have been initiated at least 6 months prior to screening[vi]
    - Patient has to have been on the same protocol-approved ARV regimen for ≥ 8 weeks prior to screening and is expected to continue the current ARV regimen through the end of study.
    - HIV ARVs: agents allowed in this study should be administered per the prescribing information in the package insert
    - Screening HIV RNA < 50 copies/mL[vii]
    - Screening CD4 cell count ≥ 100 cells/uL
  - HIV/HCV co-infected patients not receiving cART: Screening CD4 cell count must be ≥ 500 cells/uL (new WHO recommendations are to treat virtually all people with HIV.

5.3. Exclusion Criteria

- Decompensated cirrhosis defined as:
  Evidence of advanced stage liver cirrhosis and Child-Turcotte-Pugh (CTP) Class B or C or CTP score >6) or current/past history of decompensation including ascites, variceal bleeding, spontaneous bacterial peritonitis, or hepatic encephalopathy.
- Hepatocellular carcinoma: for all patients with cirrhosis, hepatocellular carcinoma (HCC), should be excluded by liver imaging within 6 months prior to screening, and this must continue periodically as in routine HCC surveillance.
- Laboratory exclusion criteria:
  - cirrhotic subjects with albumin < 2.8 g/dL

[vi] To avoid the possibility of Immune reconstitution inflammatory syndrome - IRIS

[vii] This would allow us to properly evaluate the risk of virological failure during herapy

  - direct bilirubin > 3xULN
  - AST, ALT > 10xULN
  - Low neutrophil count (≤599 cells/mm^3), hemoglobin (<9.0 g/dL for male, <8.5 g/dL for female), platelets (<50000 cells/mm^3) classified as ≥ Grade 3
- Patients with serum creatinine > 1.5 ULN or end stage renal disease[63]
- Hepatitis B co-infection (HBsAg positive)
- Pregnancy, as documented by positive pregnancy tests at screening or baseline
- Breastfeeding
- Subjects currently receiving or unable to stop the use for at least 1 week prior to receiving the first dose of study drug any medications or herbal supplements known to be potent inhibitors or moderate inducers of cytochrome P450 (CYP) 3A4 or potent inducers of P-glycoprotein. This includes subjects who are on amiodarone or other contraindicated /excluded drugs (see section 9.3).
- Participation in other clinical trials within 3 months
- Any clinically significant findings or unstable condition during the screening, medical history or physical examination that, in the investigator's opinion, would compromise participation in this study as per standard guidelines and local practice.[viii] This could include patients with poorly controlled hypertension, asthma, diabetes, or other life-threatening conditions.
- Current or history of use within the preceding 6 months of immunosuppressive or immune-modulating agents. Corticosteroid used to treat any medical condition are allowed if systemic for not more than 2 weeks or if topical.
- History of solid organ or bone marrow transplantation.
- Any prior NS5A inhibitors therapy.[ix]
- Patients with significant cardiovascular conditions including:
  - myocardial infarction within the previous 6 months or
  - heart failure NYHA class III or IV
  - history of Torsade de pointes
  - third degree heart block
  - QTcF (Fridericia) value ≥ 450 milliseconds at Baseline.
  - severe sinus bradycardia with a rate of under 50 beats per minute
  - A sinus bradycardia with third degree atrioventricular block or with Mobitz II AV block
- Use of medications associated with QT prolongation concurrently or within the 30 days prior to Screening Visit, including: macrolides, antiarrhythmic agents, azoles, fluoroquinolones, and tricyclic anti-depressants. Commonly used and essential medications for this study population like methadone and/or efavirenz is allowed as long as the QTcF value at baseline is < 450 milliseconds.
- Self-reporting active injection drug use at screening (only for stage 2).
- Exclusion criteria related to HIV/HCV co-infected patients:
  - HIV/HCV co-infected patients not yet on stable antiretroviral therapy or for whom ART treatment initiation maybe scheduled during the study period.

6. Subject withdrawal & drop-out

Subjects who wish to terminate their participation can withdraw from the study at any time without jeopardizing their standard medical care or possible participation in future research studies. They should be counselled about the potential consequences and risks of antiviral therapy interruption.

Also, a study site co-investigator may decide to end a subject's participation in the study if, in his/her own judgment, such a participation would be detrimental to a subject's well-being.

[viii] Management of clinical/biological findings are detailed in the Manual of Operations

[ix] Note: Prior Interferon based therapy is allowed but will be one of the important stratification criteria. It is anticipated that this category will become irrelevant in the future as interferon based therapy is phased out.

The study may also be discontinued at any time by the Ethics Committee, sponsor or other country specific governmental agencies as part of their duties to ensure that research participants' wellbeing is protected, in particular if new data modified the risk/benefit balance of the study.

6.1. Withdrawal criteria and procedures

Subjects should notify the investigator of their decision to withdraw consent in writing, whenever possible. Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures (end of treatment, 4 weeks, 12 and 24 weeks post treatment visits). The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information.

Withdrawal of consent should be documented in the medical records and the appropriate CRF: this includes withdrawal from receiving study treatment only, or also from study procedures and/or post-treatment study follow-up. As far as possible, all attempts should be made to understand and document the reasons for withdrawal (except if the patient is not in agreement to share the reasons).

6.2. Subject replacement policy

Subjects who have taken at least 1 dose of study treatment and withdraw from the study will not be replaced.

6.3. Screening failures

Reasons for screening failures will be documented and reported in a consolidated listing in the clinical study reports.

For screening failure patients, safety events and updates must be recorded in CRFs using the AE or SAE forms (as appropriate) until the date the subject was determined to be a screening failure. It is therefore important to ensure that the date of screening failure is recorded (i.e. medical records, log maintained by site or study team…).

6.4. Lost to Follow-Up

Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented attempts over a period of 2 months (phone calls, emails, mail letter, or home visit if applicable) or if the subject misses both Follow-up Weeks 12 and 24 visits despite reasonable attemps to reach him/her. All reasonable efforts will be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. All attempts will be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. In the event that vital status needs to be confirmed from non-medical source, publicly available information may be used only in accordance with local law.

7. Schedule of Events

7.1. Schedule of visits and Study Assessments for non-cirrhotic patients

Evaluations / study procedures / study visit [1]	**Eligibility** (45 days to day -1)	**Screening** (30 days to day -1)	**Day 1**	**On-Treatment Study Visits 12 weeks**				**Follow-up visit wk. 4 (SVR4)** (-1 day and +7 days)	**Follow-up visit wk. 12 (SVR12)** (-1 day and +28 days)	**Follow-up wk.24 (SVR24)** (-3 days and +28 days)	**Long term Follow-up visits**[13] (-28 days and +28 days)
				Treatment Visit Wk. 1 +/- 3days	**Treatment Visit wk. 4** +/- 7days	**Treatment Visit wk. 8** +/- 7days	**Treatment Visit W12 (End of Treatment or premature discontinuation) +/- 7days**				
Information, counselling	X[2]	X									
Informed consent	X										
Inclusion/exclusion criteria & demography		X									
HCV, HBsAg, HIV	X										
Medical history, full clinical examination[3] Height Weight		X									
Symptom directed assessment			X	X	X	X	X	X	X	X	X
Concomitant medication review		X	X	X	X	X	X	X	X	X	
AE review			X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X		
Fibroscan[4]		X									X[4]
12 leads ECG		X		X			X	X[14]			
Hematology (full blood count)		X	X		X	X	X	X	X		X
Chemistry (alkaline phosphatase, serum albumin, direct/total bilirubin, ALT/ AST, serum creatinine)		X	X		X	X	X	X	X	X[12]	X
Fasting blood sugar (glucose)		X									
Coagulation (PT, INR)		X								X	
Urinalysis		X							X		
Urine pregnancy tests[5]		X	X	X	X	X	X	X			
HCV RNA	X			X[6]	X[6]	X[6]	X[6]	X[6a]	X[6]	X	X
HIV RNA[7]		X							X		
CD4 count[7]		X							X		
HCV genotype		X									X
Stored Plasma and DBS[8]	X	X	X	X	X	X	X	X	X	X	X

Evaluations / study procedures / study visit [1]	**Eligibility** (45 days to day -1)	**Screening** (30 days to day -1)	**Day 1**	**On-Treatment Study Visits 12 weeks**				**Follow-up visit wk. 4 (SVR4)** (-1 day and +7 days)	**Follow-up visit wk. 12 (SVR12)** (-1 day and +28 days)	**Follow-up wk.24 (SVR24)** (-3 days and +28 days)	**Long term Follow-up visits**[13] (-28 days and +28 days)
				Treatment Visit Wk. 1 +/- 3days	**Treatment Visit wk. 4** +/- 7days	**Treatment Visit wk. 8** +/- 7days	**Treatment Visit W12 (End of Treatment or premature discontinuation) +/- 7days**				
Resistance testing[9]		X									
PK Intensive Sampling (stage 1 only)[10]					X						
PK sparse sampling[11]					X	X	X				
Predose ARV PK sample for subjects on ART			X								
Hair sampling		X					X				
Adherence				X	X	X	X				
Study Drug Dispensing			X		X	X					
PROQOL-HCV			X			X			X		

[1] Eligibility and screening can be done on the same day for already HCV diagnosed subjects
[2] For subjects tested for the first time for HCV, extensive information and counselling perform HCV serology and confirm HCV chronic infection.
[3] At screening a full clinical assessment is required. On other visits-a symptom directed assessment is required
[4] Fibroscan will be conducted only at screening visit or baseline FibroScan within 12 months to screening maybe use to assign treatment duration. A Fibroscan can also performed at all long term follow-up visits (until one year after end of treatment for patients cured and until 3 years after end of treatment for non-cured patients- see details of assessments in section 13.5.2)
[5] Urine pregnancy test to be done for women of child bearing age
[6] For stage 1, HCV RNA will be performed on stored samples if SVR12 is not achieved or on any patient at any time if needed. For stage 2, HCV RNA will be performed on all samples on an ongoing basis at each treatment visit.
[6a] Will be performed on stored samples for all patients
[7] For HIV positive cases only (HIV monitoring (CD4 and viral load) is part of the standard of care for HIV subjects enrolled in the study. Closer follow-up performed upon clinical judgment of the principal investigator will be paid by the study).
[8] Tests to be performed retrospectively on stored samples if needed: HCV genotyping, HCV sequencing, HCV resistance testing RAV, sparse drug levels on therapy and IL28B gene. IL28B will be tested systematically and at baseline only on stored samples.
[9] Samples obtained at screening will be tested retrospectively for NS5A Resistance testing for all patients and for NS5B Resistance testing for treatment failures. For virological failures, NS5A and NS5B Resistance testing will be performed at first point after failure when viral load is sufficient to get a positive result (test can be performed retrospectively on stored samples if needed, see note 8)
[10] During stage 1 only, intensive PK (Predose, 1, 2, 3, 4, 6, 8, 24 hours post dose) in 25 mono-infected patients in selected sites.
[11] Sparse PK sampling: a) at W4: 2 samples (Predose, 2-4 hours post dose); b) W8: 1 sample (at any time post dose within 24 hours); c) W12: 2 samples (2 hours apart between 6-26 hours' post-dose)
[12] Serum creatinine not required for SVR24 only.
[13] A series of long-term follow-up visits will be implemented retrospectively for stage 1 for all patients with virological failure at SVR 12 or SVR 24 and for stage 2 for a representative subset of the cured patients (i.e achieving SVR 12) and for all patients with virological failure at SVR 12 or SVR 24 (see section 13.5.2).
[14] ECG at SVR4 visit will be performed only on patients showing ECG abnormalities at end of treatment visit.

7.2. Schedule of visits and Study Assessments for cirrhotic patients

Evaluations / study procedures / study visit [1]	**Eligibility** (45 days to day -1)	**Screening period** (within 30 days to day -1)	**Day 1**	**On-Treatment Study Visits 24 Weeks**					**Follow-up visit wk. 4 (SVR4)** (-1 day and +7 days)	**Follow-up visit wk. 12 (SVR12)** (-1 day and +28 days)	**Follow-up W24 (SVR24)** (-3days and +28 days)	**Long term FU visits**[14] (-28 days and +28 days)
				Treatment Visit wk. 1 +/- 3days	**Treatment Visit wk. 4** +/- 7days	**Treatment Visit wk. 8** +/- 7days	**Treatment Visit Wks 12, 16 ,20** +/- 7days	**Treatment Visit wk. 24 (END of Treatment Premature discontinuation)** +/- 7days				
Information, counseling	X[2]	X										
Informed consent	X											
Inclusion/exclusion criteria & demography		X										
Medical history, full clinical examination[3] Height/Weight		X										
HCV, HBsAg, HIV	X											
CTP score[5]		X	X	X	X	X	X	X	X	X	X	X
Symptom directed assessment			X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X		
Conc. medication review		X	X	X	X	X	X	X	X	X	X	
AE review			X	X	X	X	X	X	X	X	X	X
Fibroscan [4]		X					Wk:12 only			X	X	X[4]
12 leads ECG		X		X				X	X[15]			
Hematology (full blood count)		X	X		X	X	X	X	X	X		X
Chemistry (alkaline phosphatase, serum albumin, direct/total bilirubin, ALT/ AST, serum creatinine)		X	X		X	X	X	X	X	X	X[13]	X
Fasting blood sugar (glucose)		X										
Coagulation Markers (PT, INR)[5]		X	X		X	X	X	X	X	X	X	X[5]
Urinalysis		X								X		
Urine pregnancy tests[6]		X	X	X	X	X	X	X	X			
HCV RNA	X			X[7]	X[7]	X[7]	X[7]	X[7]	X[7a]	X[7]	X	X
HIV RNA[8]		X								X		
CD4 count[8]		X								X		
HCV genotype		X										X
Resistance testing [9]		X										

Evaluations / study procedures / study visit [1]	**Eligibility** (45 days to day -1)	**Screening period** (within 30 days to day -1)	**Day 1**	**On-Treatment Study Visits 24 Weeks**					**Follow-up visit wk. 4 (SVR4)** (-1 day and +7 days)	**Follow-up visit wk. 12 (SVR12)** (-1 day and +28 days)	**Follow-up W24 (SVR24)** (-3days and +28 days)	**Long term FU visits**[14] (-28 days and +28 days)
				Treatment Visit wk. 1 +/- 3days	**Treatment Visit wk. 4** +/- 7days	**Treatment Visit wk. 8** +/- 7days	**Treatment Visit Wks 12, 16 ,20** +/- 7days	**Treatment Visit wk. 24 (END of Treatment Premature discontinuation)** +/- 7days				
Stored Plasma and DBS [10]	X	X	X	X	X	X	X	X	X	X	X	X
Intensive PK Sampling (stage 1 only)[11]					X							
PK sparse sampling[12]					X	X	X					
Predose ARV PK sample for subjects on ART			X									
Hair sampling		X						X				
Adherence				X	X	X	X	X				
Study Drug Dispensing			X		X	X	X					
PROQOL-HCV			X			X				X		

[1] Eligibility and screening can be done on the same day for already HCV diagnosed subjects
[2] For subjects tested for the first time for HCV, extensive information and counselling perform HCV serology and confirm HCV chronic infection.
[3] At screening a full clinical assessment is required and the signs or symptoms of hepatic decompensation must be documented. On other visits-a symptom directed assessment is required. In addition, for the cirrhotic group features of decompensation like ascites or hepatic encephalopathy need to be assessed and the CTP score calculated.
[4] Fibroscan can be conducted at Screening visit or baseline FibroScan within 12 months to screening maybe use to assign treatment duration. A repeat FibroScan will be done at treatment W12 and W12 and W24 post treatment visits. A F broscan can also performed at all long term follow-up visits (until one year after end of treatment for patients cured and until 3 years after end of treatment for non-cured patients- see details of assessments in section 13.5.2).
[5] CTP and coagulation tests are applicable to cirrhotic patients only and score based on the CTP score chart provided. Cirrhotic patients must continue their HCC surveillance program and any finding of HCC is suspected/confirmed to report as AE. A coagulation test can also performed at all long term follow-up visits (until one year after end of treatment for patients cured and until 3 years after end of treatment for non-cured patients- see details of assessments in section 13.5.2)
[6] Urine pregnancy test to be done for women of child bearing age
[7] For stage 1, HCV RNA will be performed on stored samples if SVR12 is not achieved or on any patient at any time if needed. For stage 2, HCV RNA will be performed on all samples on an ongoing basis at each treatment visit.
[7a] Will be performed on stored samples for all patients
[8] For HIV positive cases only (HIV monitoring (CD4 and viral load) is part of the standard of care for HIV subjects enrolled in the study. Closer follow-up performed upon clinical judgment of the principal investigator will be paid by the study).
[9] Samples obtained at screening will be tested retrospectively for NS5A Resistance testing for all patients and for NS5B Resistance testing for treatment failures . For virological failures, NS5A and NS5B Resistance testing will be performed at first point after failure when viral load is sufficient to get a positive result (test can be performed retrospectively on stored samples if needed, see note 10)
[10]Tests to be performed retrospectively on stored samples if needed: HCV genotyping, HCV sequencing, HCV resistance testing RAV, sparse drug levels on therapy and IL28B gene. IL28B will be tested systematically and at baseline only on stored samples.
[11] In stage 1 only, intensive PK (Predose, 1, 2, 3, 4, 6, 8, 24 hours post dose) in 25 mono-infected patients in selected sites
[12] Sparse PK sampling: a) at W4: 2 samples (Predose, 2-4 hours post dose); b) W8: 1 sample (at any time post dose within 24 hours); c) W12: 2 samples (2 hours apart between 6-26 hours' post-dose)
[13] Serum creatinine not required for SVR24 only.
[14] A series of long-term follow-up visits will be implemented retrospectively for stage 1 for all patients with virological failure at SVR 12 or SVR 24 and for stage 2 for a representative subset of the cured patients (i.e achieving SVR 12) and for all patients with virological failure at SVR 12 or SVR 24 (see section 13.5.2).
[15] ECG at SVR4 visit will be performed only on patients showing ECG abnormalities at end of treatment visit

8. Enrolment procedures

All relevant medical and non-medical conditions must be taken into consideration when deciding whether this protocol is suitable for a particular subject. Any questions regarding a subject's eligibility should be discussed with DNDi prior to subject's enrollment. Prior to any clinical procedures and evaluations, written signed informed consent must be obtained.

Screening and enrolment must be completed within a maximum of 30 days.

Procedures completed during Screening visit are described in section 7.

No restrictions will be imposed on the number of subjects in each subgroup (genotype and cirrhotic status) in stage 1. Additional subjects will be enrolled in stage 2 in order to reach ideally 50 subjects per subgroup (30 for GT2) when combining both stages. If recruitment of some subgroups proves very slow, recruitment will be adjusted in other sub-groups to achieve the target of 300 subjects for stage 2 within a reasonable timeframe. This is most likely to apply to genotype 2.

9. Study Treatment

9.1. Description of study drug

Sofosbuvir (SOF, Grateziano®)

- 400 mg tablet orally once daily with food (in the morning) for 12 weeks for subjects with liver fibrosis Metavir stage F0-F3
- 400 mg tablet orally once daily with food (in the morning) for 24 weeks for subjects with Metavir stage F4, CTP Class A

Ravidasvir (RDV or PPI-668)

- 200 mg tablet orally once daily with food (in the morning) for 12 weeks for subjects with Metavir stage F0-F3
- 200 mg tablet orally once daily with food (in the morning) for 24 weeks for subjects with Metavir stage F4, CTP Class A

Sofosbuvir and Ravidasvir are to be taken orally with meals. Participants will be told to swallow tablets whole and not to chew or crush these tablets due the unpleasant taste of the active substance.

Missed dose: If it is within 18 hours of the normal time, participants should be instructed to take the tablet as soon as possible and then participants should take the next dose at the usual time. If it is after 18 hours of the normal time, the dose should be skipped and the next dose taken at the usual time. Participants should be instructed not to take a double dose.

In case patient vomits: The instructions below should be advised:
1. In the event of vomit occur, subject should contact site team immediately for further advice.
2. To re-dose SOF and RDV again if vomiting happened within 2 hours post dose. Else, take the next dose as usual.
3. If vomiting happened 2 times or more, within 2 hours post dose, no re-dosing is required. (maximum number of re-dosing that can be done is only 1 time, within the same dose interval).
Adverse event has to be reported accordingly as per described in section 15.2.

9.2. Investigational product supply and handling

9.2.1. Supply, packaging and labelling

Formulations of study-supplied medications

Generic name Abbreviation	Formulation	Storage
Sofosbuvir SOF	400 mg film-coated tablets	Do not store above 30°C
Ravidasvir RDV	200 mg tablets	Do not store above 30°C

This is an open label study. After study approval from Independent Ethics Committees and regulatory authorities, the sponsor will supply study drugs under controlled temperature conditions and the labels will follow country requirements (in particular product name, composition, and batch number/Lot No. /Lot, expiry date and storage instructions and identification of the clinical trial). After receipt at clinical site, the study drugs will be verified for packs sealed condition and adequacy of information provided by the Sponsor.

9.2.2. Dispensing

Sofosbuvir and ravidasvir will be supplied in treatment bottles of 28 tablets each for 4 weeks treatment. Drugs will be dispensed to each subject at the following visits by authorized site personnel:

- For non-cirrhotic subjects: study visit at day 1 (2 bottles), week 4 (third bottle)
- For cirrhotic subjects: study visit at day 1 (2 bottles), week 4 (1 bottle) and week 8 (1 bottle), week 12 (1 bottle) and week 16 (last bottle)

9.2.3. Accountability

Subjects will be reminded to complete every day their patient diary card to record each drug intake and to come back at the next visit with their empty bottles and completed patient diary card.

Study-specific forms will be used for accountability of the study medication. Appropriate records concerning receipt, use, returns, loss and any other disposition of the study medication will be maintained by Investigators or their delegates on site, under the supervision of the Principal Investigator. Study monitors will check accountability of the study medication during on-site monitoring visits.

At each investigational site, study medication must be stored in a locked room, or a locked cabinet if no specific room is available, with access restricted to the authorized study personnel.

The study medication must not be used for purposes other than specified in the protocol.

9.2.4. Storage

Prior to dispensing, all study medications must be kept at room temperature (not above 30°C) in a locked cabinet that can be accessed only by the appropriate study personnel. Temperature will be recored regularly to ensure appropriate storage conditions They cannot be used for purposes other than this study.

9.3. Concomitant and or prohibited medication/treatment

Investigators must refer to the most updated list in www.hep_druginteractions.org for information on drug-drug interaction as well as the manual of investigator and study drugs investigator's brochure for contraindicated/excluded co-medications.

Sofosbuvir in combination with another direct acting antiviral (DAA) when co-administered with Amiodarone (a medicine used to treat certain heart problems), particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may cause serious symptomatic bradycardia such as near-fainting or fainting, dizziness or light-headedness, malaise, weakness, excessive tiredness, shortness of breath, chest pain, confusion or memory problems[64]. Subjects on amiodarone are excluded from this study.

Patients treated with medications associated with QT prolongation concurrently or within the 30 days prior to Screening Visit, including: macrolides, antiarrhythmic agents, azoles,

fluoroquinolones, and tricyclic anti-depressants are excluded from the study. Commonly used and essential medications for this study population like methadone and/or efavirenz is allowed as long as the QTcF value at baseline is < 450 milliseconds. A QTcF value increase up to 500 milliseconds during study conduct is accepted.

HIV/HCV co-infected patients not yet on stable antiretroviral therapy or for whom ART treatment initiation maybe scheduled during the study period are excluded from the study.

The following treatments are prohibited and should be discontinued at least one week prior to Day 1 of study drugs administration:

- Strong inhibitors of CYP3A4 are prohibited, including, but not limited to: ketoconazole, troleandomycin, itraconazole, voriconazole, mibefradil, clarithromycin, telithromycin, grapefruit juice and grapefruit-containing products, Seville oranges, juices and products that contain Seville oranges, conivaptan, nefazodone, etc;
- Strong CYP3A4 inducers are prohibited, including but not limited to: rifampin, rifabutin, rifapentin, dexamethasone, phenytoin, carbamazepine, phenobarbital, St John's wort, etc;
- CYP3A substrates with narrow therapeutic index are prohibited, including but not limited to alfentanil, cisapride, dihydroergotamine, ergotamine, fentanyl, pimozide, and quinidine;
- Strong P-gp inhibitors are prohibited (eg, ketoconazole, indinavir, lapatinib, quinidine, amiodarone, ranolazine, erythromycin, clarithromycin, and azithromycin (azithromycin will be allowed for a duration of 7 days or less or once weekly);
- P-gp inducers are prohibited, including but not limited to, avasimibe, carbamazepine, oxcarbazepine, phenytoin, rifampin, rifabutin, rifapentine, St John’s wort, and boosted tipranavir.

The following treatments should be **used with caution** during dosing with RDV and SOF.

- Substrates of OATP1B1 and OTAP1B3 (eg, glyburide, bosentan, rosuvastatin, pravastatin, and pitavastatin);
- Substrates of BCRP (eg, rosuvastatin);
- P-gp substrates with a narrow therapeutic index (eg, digoxin) at the lowest efficacious dose with appropriate monitoring (eg, therapeutic drug monitoring).

The complete list of currently used medications, including over-the counter and alternative/herbal medications, will be recorded at the screening/entry visit and all subsequent visits. To minimize the risk of adverse effects due to drug-drug interaction the investigator should limit concomitant use of drugs to those that are absolutely needed by the patient.

The investigator may consider the following steps in the management of drugs with potential interaction with the study medications e.g.:

(i) stop a drug, such as a statin, for the period of study treatment
(ii) replace the drug with an alternative product without a drug interaction in the same therapeutic class
(iii) adapt the dose of non-study medications (change of dose of study medications is not allowed) with a clear monitoring plan.

These changes must be discussed with the study team and documented in the source documents and concomitant medication case report form. Use of discontinued or dose-adjusted concomitant medications can resume as prior to change 2 weeks after the last dose of study treatments.

During the course of the study, should there be a clinical indication for any additional medication including medication given to treat an adverse event related to the study drug, the name of the drug, the dosage, and the route, date and time of administration will be recorded in the CRF. Whenever

a concomitant medication is initiated or a dose changed, investigators must review the concomitant medication's and study drug's most recent package insert and Investigator's Brochure to obtain the most current information on drug interactions, contraindications, and precautions.

Note: specific training will be provided at site in order to avoid use of contra-indicated drugs and to deal with possible adverse reactions. Study personnel will be advised on checking for drug-drug interaction using the current and updated version of www.hep_druginteractions.org.

Although in a drug-drug interaction study (PPI-668-ravidasvir 102 protocol), no clinically significant interaction was observed between ravidasvir and standard doses of either midazolam or omeprazole, suggesting that ravidasvir does not cause clinically significant inhibition of CYP3A4 or 2C19 and although ravidasvir showed no appreciable interactions with other CYP isoforms, in liver microsome assays *in vitro*, the protocol applies to SOF-RDV the same precautions used for SOF and DCV (a drug whose profile is similar to that of RDV).

9.4. Other Restrictions and Precautions

- Medications with known or potential anti-HCV activity other than the assigned study treatment are prohibited from study treatment initiation until 12 weeks' post-treatment.
- Use of any medication or herbal product not prescribed by the investigator or a licensed physician is prohibited.
- Methadone and buprenorphine can be used with caution.

  Long-term treatment (≥ 2 weeks) with agents that are immunosuppressive, or have a high risk for nephrotoxicity or hepatotoxicity, should be discussed with the study team.

9.5. Contraception methods

Since the safety of DAAs during pregnancy is not known and results indicated a teratogenic potential for ravidasvir (PPI-668) in rabbits at doses of 100mg/kg/day or more, women of child bearing potential must use a highly effective contraceptive method from at least 2 weeks before treatment initiation and until 1 month after the last dose of study medications. Highly effective acceptable methods of contraception include intrauterine device (IUD), intrauterine hormone-releasing system (IUS), hormonal contraceptives, bilateral tubal occlusion, vasectomised partner and sexual abstinence. Pregnant women will be excluded during screening evaluations.

9.6. Assessment of adherence

This study will use a combination of two measures of adherence:

1. Subject diary card
2. Pill count

At each study visit, adherence will be assessed by pill count. Study drug and dosing diary will be reconciled at all on-treatment visits by the site staff/investigator in order to monitor the subject's adherence with the study drug regimen.

Subjects must be instructed to bring back all bottles of study drugs in the original container at each study visits.

9.7. Discontinuation and interruption of treatment

Treatment may be discontinued:

- upon request of the subject, following counselling on the potential consequences and risks of antiviral discontinuation
- upon request of the primary care provider if s/he thinks that the it is no longer in the best interest of the subject,
- if, after discussion with the study team, the investigator judges that the subject is at significant risk of failing to comply with the provisions of the protocol thus compromising the validity of the study results,

- in case of HCV virological failure,
- in occurrence of serious adverse events deemed to be related to the study drugs or possibly interfering with therapy and upon consultation with the DSMB. Patient's follow-up will continue as follow-up visits in protocol and unscheduled visits are allowed as decided by investigators.
- upon recommendation of the Data and Safety Monitoring Board (DSMB) and,
- at the discretion of the IRB, relevant regulatory agency, any other government agency as part of their duties to protect the welfare of subjects

The study team must be informed, as soon as possible, when a subject comes off study treatment due to an AE. Restart of treatment after any interruption must be discussed and agreed on a case by case basis with the investigator and agreed with the sponsor.

Subjects who prematurely discontinue study treatment (i.e., prior to completion of their assigned dosing period) will complete all end of treatment evaluations, will remain on study and complete all post treatment visits, except if they have withdrawn consent.

If applicable, additional unscheduled post-treatment safety follow-up will be determined by the site investigator.

In stage 2, the following treatment stop criteria[65] will apply for any patient from stage 2 study with:

- ALT/AST > 8x ULN
- ALT/AST remains > 5x ULN over 2 wks
- ALT/AST > 3x ULN & T Bili > 2x ULN or INR > 1.5
- ALT/AST > 3x ULN with symptoms (e.g. fatigue, nausea and vomiting, right upper quadrant of abdomen pain, fever, rash) or eosinophilia

Generally, rechallenge of subjects with significant ALT/AST elevations (>5xULN) should not be attempted. If such subjects are rechallenged, they should be followed closely. Rechallenge can be considered if the subject has shown important benefit from the drug and other options are not available or if substantial accumulated data with the test drug do not show a potential for severe injury. The subject should be made aware of the potential risk, and consent to the rechallenge, and the institutional review board consulted.

A DSMB meeting will be set up in case one patient meets any of the above listed criteria, which is considered as a major safety signal.

10. Baseline Assessments

10.1. Information

Information and education materials will be used to raise awareness about HCV, the short and long term morbidity associated with chronic infection as well as the availability of short, highly effective, interferon/ribavirin free treatment courses with cure rates above 90%. Each site will develop its recruitment scheme according to locally relevant risk factors.

10.2. Counseling

Interested subjects will receive further information and counseling about HCV, co-infections, the implications of a positive test, as well as the practical details of the study. Consenting subjects will be tested for HCV serology, and if positive serology for HCV RNA. An appointment will be made to discuss the results and implications of this eligibility phase.

10.3. HCV testing

A quantitative HCV RNA viral load is essential to confirm that subjects with a positive HCV antibody test have chronic HCV infection, and establish pre-treatment baseline viral load levels.
Blood sample for HCV RNA PCR testing will be collected, processed, and shipped to the designated laboratory.

Results will be reported within 2 weeks after specimen receipt. Additional plasma will be stored to allow confirmatory tests: genotyping, viral load, presence of prescribed or non-prescribed drugs.

HCV chronic infection confirmation and initial evaluations

HCV RNA positive patients will be further explained the study process including baseline evaluations, the need for referral to the academic/dedicated site for liver fibrosis staging or on-site appointment for fibrosis staging depending on availability of the Fibroscan equipment and/or the results of APRI score, nature and duration of treatment dependent on the presence/absence liver cirrhosis and potential side-effects. They will also be explained all study clinical and biological procedures up through the end of the study visit (i.e. post-treatment follow-up Week 24 or end of long term follow-up for subset of cured patients or patients with virological failure).

10.4. Medical history

Medical history will focus on:

- Risk factors for HCV acquisition including injection drug use (IDU), receipt of a blood/blood products transfusion prior to universal HCV infection screening for blood donation, needle stick injury, tattooing, body piercing, mother-to- child transmission, sexual transmission among men who have sex with men (MSM), particularly men with HIV infection.
- Psychiatric History: Patients with HCV infection have a higher incidence of psychiatric illness compared with the general population; inadequately treated psychiatric illness represent a barrier to successful HCV therapy.
- Medical Comorbidities / extrahepatic manifestations: all medical history need to be documented in particular diabetes, any diagnosis of kidney disease (nephropathy, glomerulonephritis), thyroid disease, skin disease (livedo reticularis, lichen planus, and cold agglutinin disease), arthralgia, neuropathy or non-alcoholic fatty liver disease (NAFLD).
- Coinfections: Hepatitis B virus (HBV), and human immunodeficiency virus (HIV).
- Complications of liver Disease: ascites including diuretic controlled ascites, hepatic encephalopathy, jaundice, hepatocellular carcinoma or variceal bleeding. CTP scoring will be performed.
- Prior Treatment for Hepatitis C.
- Documentation of the types of treatment received previously and types of response i.e:
    1. non responders (HCV RNA detected at the end of treatment) or
    2. relapsers (HCV RNA not detected at the end of treatment but detected at any time within 24 weeks post treatment or
    3. Treatment discontinuation due to lack of EVR (HCV RNA < 1 log drop at week 12 on-treatment) or
    4. Premature discontinuation due to intolerable adverse effects.

A complete medication (including prescribed medications, OTC, supplements and herbal medications or drinks) history must be assessed, including start and stop dates. Any allergies to any medications and their formulations must be documented. Potential drug-drug interactions should be checked with the current updated *www.hep druginteractions.org* (see section 9.3).

10.5. Physical examination

A full physical examination will be performed at Screening. It will focus on clinical signs and symptoms which strongly suggest the presence of cirrhosis, such as palmar erythema, spider nevi, dilated abdominal wall veins, ascites, asterixis, gynecomastia, and loss of body or pubic hair.

A symptom targeted physical examination will be performed at day 1 and at all subsequent visits. It should include vital signs (oral temperature, pulse, and respiratory rate, and resting blood pressure)

and is to be driven by any previously identified or new signs or symptoms including diagnoses that the subject has experienced since the last visit.

10.6. ECG

Patients taking beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia.

A 12 leads ECG will be performed at Screening and at week 1. It will also be performed at any time there is symptom suggestive of a cardiac event or signs of irregular heart beat or bradycardia. Patients will be referred to a cardiologist in case of unclear anomaly. Also, patients will be instructed to consult immediately in case of malaise, dizziness, light headedness, fainting spell, bradycardia or irregular heartbeat. An ECG will be repeated at the end of the treatment (resp. week 12 or week 24) and at SVR4 visit on patients showing ECG abnormalities at end of treatment visit.

Descriptive statistics for change from baseline to the end-of-study visit will be provided for each ECG parameter. ECG results will be reviewed for clinically notable abnormalities ("clinically significant"). Subjects exhibiting clinically notable ECG abnormalities (after re-test) will be listed. AEs will be recorded for clinically notable abnormalities that are considered clinically significant in the judgment of the Investigator.

QTcF value at baseline is < 450 milliseconds. A QTcF value increase up to 500 milliseconds during study conduct is accepted.

10.7. Baseline Laboratory Tests

- Complete blood count: white blood cell (WBC), red blood cell (RBC), hemoglobin, hematocrit, platelets, absolute neutrophil, absolute lymphocyte
- Renal function: serum creatinine
- Hepatic Inflammation: Alanine aminotransferase (ALT) and aspartate aminotransferase (AST).
- Hepatobiliary Disease: Bilirubin direct/total, alkaline phosphatase.
- Hepatic Function: Serum albumin
- Glucose (Fasting)
- Coagulation: prothrombin time (PT), International Normalized Ratio (INR).
- Coinfections: Hepatitis B surface antigen, HIV antibody.
- HCV Genotype: Hepatitis C virus exists as one of six distinct genotypes with different clinical characteristics and treatment response rates. Determining HCV genotype does not need to be performed real-time but will be important to establish treatment efficacy across genotypes in particular genotype 1, 3 and 6 which are most prevalent in Thailand and Malaysia.
- Genotype is provisionally determined at screening and confirmed definitively by sequencing of baseline samples. Sequencing will be performed at final analysis on all failures in order to exclude the possibility of reinfection during the study.
- Baseline NS5A Resistance testing is done of all subjects. Results are not expected to be available before treatment initiation.
- Urinalysis.

10.7.1. Additional Laboratory evaluations for HIV co-infected subjects

A documented plasma HIV-1 RNA level must be noted at screening (within 30 days) in those who are anti-HIV positive from a laboratory that has certification. On-study HIV-1 RNA should be performed at a certified laboratory using an approved assay with a lower limit cut-off ≤ 50 copies/mL.

Screening and end of study CD4+ cell count may be done by any laboratory that possesses certification (Immunology Quality Assurance (IQA) Program).

10.7.2. Resistance testing for virological failures

NS5A and NS5B resistance testing will be performed for all virological failures. Patients with detectable resistance-associated substitutions (RAS) will be reassessed for RAS 1 year after treatment cessation or at initiation of alternative HCV therapies. These subjects will receive specific counselling and be asked to provide consent for this extended follow-up.

10.8. Fibrosis staging

Following initial evaluation, subjects will be referred for fibrosis staging. Depending on the site organization, staging may be performed on site or at the closest center with the required equipment. Also, based on clinical or biological score results, investigators may decide to refer the subject for hepatologist's advice as cirrhotic subject not only need immediate therapy but also to be scheduled for hepatitis cancer screening and monitoring.

Fibrosis Stage Metavir F1-2-3-4 will be determined by transient elastography (FibroScan[66][67][68]) and secondarily using the APRI score.

Transient elastography, an ultrasound based technique, measures the stiffness of the liver, which is well correlated with the fibrosis stage assessed by liver biopsy. It has been extensively used as a noninvasive method for detection of cirrhosis in patients with chronic liver disease[69].

In addition, to further characterize patients enrolled in this study, the APRI score will be calculated: the AST to platelets ratio index (APRI score) will be calculated at baseline as it has been shown to predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C[70].

For therapy, the study population will be stratified according to fibrosis stage i.e. Metavir F4 or < F4 based on the results of transient elastography. After completion of the study, the performances of various fibrosis scores will be evaluated against transient elastography which will be considered as the gold standard. Indeed, one of the study objectives is to assess the potential for scaling up HCV therapy in primary health care settings and such scale-up will have to rely on biological tests readily available such as those used to calculate the APRI or the FIB4 scores or similar scores.

Definition of stage of fibrosis for this study:

Absence of cirrhosis is defined as any one of the following:

- Liver biopsy performed within 24 months of screening of this study showing absence of cirrhosis.
- Fibroscan performed within 12 months of screening or anytime between screening and treatment initiation with a result $\leq$ 12.5 KPa with M probe or ≤ 10 KPa with XL probe.

Cirrhosis is defined as follows:

- Liver biopsy performed prior to screening of this study showing cirrhosis (Metavir F4 or Modified HAI F6)
- Fibroscan performed within 12 months of screening or anytime between screening and treatment initiation with a result > 12.5 KPa with M probe or > 10 KPa with XL probe.

Fibroscan and APRI score (at screening) are done on all subjects. Fibroscan should be performed within 12 months of screening or anytime between screening and treatment initiation. The final valid Fibroscan result will be used to determine the subject study treatment duration.

A valid fibroscan reading is one done with at least 3 hours fasting and an examination will be considered successful if there were ten valid measurements, and reliable if the interquartile range (IQR)/median for liver stiffness measurement (LSM) was ≤ 30%, or the LSM was < 7.1 kPa when the IQR/median for LSM was > 30% (Boursier, Hepatology 2013). The XL probe will be used in patients with unsuccessful or unreliable liver stiffness measurement using the M probe.

The Fibroscan is the reference method for fibrosis assessment. However, in case of failure to get a reliable Fibroscan reading, liver biopsy results or APRI score will be used to diagnose fibrosis. In the

absence of reliable Fibroscan the APRI score will be calculated. An APRI score of > 2 indicates cirrhosis.

10.9. Hair sampling

Hair analysis has proved to be a suitable method to detect chronic or acute abuse of many drugs such as opiates, cocaine, amphetamines and many others.

Additional measures will be taken to pseudonomize the hair analysis data to maintain confidentiality of information about illicit drug use.

Hair samples will be collected at baseline and at end of treatment for all subjects where possible.

These samples will be used to evaluate the effect of drug use on safety and efficacy and to assess drug use in subjects who fail to meet the primary study endpoint (SVR12).

10.10. Quality of life assessment

The PROQOL- HCV quality of life questionnaire is a questionnaire specific to the evaluation of the quality of life in relation with HCV infection. It has been validated in many countries and is translated in different languages.

10.11. Pharmacogenomic assessment

IL28B genotyping is assessed at screening visit only and retrospectively tested from stored plasma to determine its association to treatment response to DAAs.

11. Assessment of efficacy

- Percentage of participants with Sustained Virologic Response at 12 Weeks after end of study drug treatment (SVR12).
    - Where SVR12 results are missing, SVR24 results, if available, will be used.
    - Where SVR12 results are missing, SVR4 results cannot be used to impute outcome.

  Participants will be considered to have achieved SVR12 if HCV RNA is less than the lower limit of quantification (12 IU/mL or 15 IU/mL depending on the laboratory where HCV RNA is done[x]) at 12 weeks after the end of treatment.

Categorisation of failures is defined as follows:

- On-Treatment Virologic Failure: HCV RNA ≥ LLOQ at the end of treatment. For example, can include patients who experienced virologic breakthrough (confirmed or unconfirmed) or met an on-treatment virologic futility rule.
- Virologic Breakthrough: Subcategory of On-Treatment Virologic Failure. Confirmed ≥ 1 log10 IU/mL HCV RNA on-treatment increase from nadir, or confirmed increase in HCV RNA ≥ LLOQ if HCV RNA previously declined to < LLOQ (detected or not detected).

x

Country	Laboratory	Assay (*Machine*) used for HCV RNA	Lower limit of quantification	Sites	Visits
Stage 1					
Malaysia	Hospital Kuala Lumpur	Real-Time PCR (COBAS AmpliPrep (CAP) & TaqMan48 (CTM) system)	15 IU/mL	All sites in Malaysia	All visits
Thailand	HIVNAT AIDS Research Centre	Real-Time PCR (Abbott m2000 system)	12 IU/mL	Site 10 (Thailand)	Screening visit only
	Ramathibodi Hospital	Real-Time PCR (Roche COBAS AmpliPrep/COBAS TaqMan system)	15 IU/mL	Site 9 (Thailand)	Screening visit only
	AMS Clinical Service Center	Real-Time PCR (Roche COBAS AmpliPrep/COBAS TaqMan system)	15 IU/mL	Sites 7 & 8 (Thailand)	Screening visit only
	IRD-PHPT Research Group	Real-Time PCR (Abbott m2000 system)	12 IU/mL	All sites in Thailand	All visits except screening visit
Stage 2					
Malaysia	IMR	Real-Time PCR (COBAS 4800 system)	15 IU/mL	All sites in Malaysia	All visits
Thailand	IRD-PHPT Research Group	Real-Time PCR (Abbott m2000 system)	12 IU/mL	All sites in Thailand	All visits

- Virologic Relapse: HCV RNA < LLOQ at end of treatment, but HCV RNA quantifiable (≥ LLOQ) during follow-up; can include patients who experienced late virologic relapse who also achieved primary SVR endpoint.
- Nonvirologic Failure: Did not achieve SVR and did not meet any virologic failure criteria (e.g., adverse event, lost to follow-up).

- Percentage of participants with Sustained Virologic Response at 4 weeks and 24 weeks after end of study drug Treatment (SVR4 and SVR24) will be evaluated in order to provide a comprehensive view of the timecourse of reduction in viral load.
  - Where SVR4 results are missing, SVR12 results, if available, will be used.
  - Where SVR4 and SVR12 results are missing, SVR24 results, if available, will be used.
  - Where SVR24 results are missing, SVR4 or SVR12 results cannot be used to impute outcome.
- Percentage of participants with Alanine Aminotransferase (ALT) normalization normalization (defined as ALT > ULN at baseline and ALT ≤ ULN at a later visit) and of participants with Aspartate Aminotransferase (AST) normalization (defined as AST > ULN at baseline and AST ≤ ULN at a later visit)
- Change from baseline of Quality of life (QoL) measured by PROQOL-HCV questionnaire.
- Change from baseline of HCV NS5A and NS5B sequences in virological failures
  - Sequencing of the HCV non-structural protein 5A (NS5A) and 5B (NS5B) genes will be done retrospectively to identify pre-existing polymorphisms and characterize emerging HCV viral variants.

12. PK assessments

Intensive PK study will beperformed in stage 1 only.
Sparse PK samples collection, ARV data and hair samples will be collected in both stages.

12.1. Ravidasvir Pharmacokinetic (PK) assessments

12.1.1. Intensive PK study

In stage 1, in selected centres, intensive PK sampling: 0 (pre-dose), 1, 2, 3, 4, 6, 8 and 24 hours' post-dose at Week 4 will be performed in 25 HCV mono-infected patients receiving ravidasvir 200 mg, once daily in the morning. The steady-state pharmacokinetic parameters of ravidasvir, AUC_{0-24}, Cmax, Tmax, Cmin, predose (C0), C24, apparent oral clearance (CL/F) and apparent volume of distribution (Vd/F) will be determined using a non-compartmental analysis. Subjects will be asked to fast at least 6 hours prior to the intensive PK sampling visit and until 2 hours after dosing at site.

12.1.2. Sparse PK samples collection

In both stage 1 and stage 2, population PK parameters using sparse sampling is estimated on other subjects using non-linear mixed effects regression. Exact timing of drug intake as well as relationship with food intake is recorded for all blood draws.

Two blood samples will be collected at week 4 (pre-dose and 2-4 hours post dose), 1 blood sample at week 8 (collected at any time point post-dose within 24 hours) and 2 samples at week 12 (preferably 2 hours apart between 6 and 26 hours' post-dose). Exact timing of drug intake as well as relationship with food intake will be recorded for all blood draws. Subjects were will be asked to fast at least 6 hours prior to the intensive PK sampling visit and until 2 hours after dosing at site.

The intensive and sparse PK samples for ravidasvir will be combined and population PK parameters will be estimated using non-linear mixed effects regression.

12.2. Pharmacokinetic (PK) assessments of DAAs and Antiretroviral Drugs

12.2.1. Sparse PK samples collection in HCV/HIV coinfected patients for potential drug-drug interaction detection

The presence of concomitant Antiretroviral (ARV) medications will be coded as a binary variable (e.g. one variable per ARV drug) to estimate population PK parameters in the presence of the covariate i.e. to determine the fractional change due to the presence of the concomitant ARV drug(s).

Ravidasvir pharmacokinetics

The impact of co-administered antiretroviral drugs on ravidasvir PK parameters is investigated using a population pharmacokinetic approach (morning trough concentration and other available sparse samples). HCV mono-infected subjects (except those in the intensive PK study) and HIV/HCV co-infected patients receiving an NNRTIs (e.g. efavirenz, nevirapine) or PI (e.g. lopinavir/ritonavir or atazanavir/ritonavir) will have sparse PK sampling performed.

Antiretroviral Pharmacokinetics for HIV co-infected subjects

As part of the planned sparse PK sampling for ravidasvir, antiretroviral trough concentrations will be determined in the pre-dose sample collected at week 4. In addition, for all the subjects on ART a single plasma sample (e.g. trough or mid-dose) will also be collected at study entry prior to initiating the HCV treatment. The analysis of ARV trough concentrations will be descriptive and mean concentrations will be compared to historical ranges reported in adults and the recommended cut-off concentrations for virologic efficacy.

Potential for other drug-drug interactions

Stored blood samples may be used to assess blood levels of concomitant medications

13. Timing of assessments

13.1. Eligibility visit

Potential participants will be recruited at participating study sites.

The eligibility visit can be performed the same day than the screening visit for patients already diagnosed as HCV chronically infected.

Informed consent for enrollment in the study will be obtained during this visit.

The assessments performed at eligibility visit are detailed in section 7 Schedule of events.

13.2. Screening visit

The eligibility visit can be performed the same day than the screening visit for patients already diagnosed as HCV chronically infected.

The assessments performed at screening visit are detailed in section 7 Schedule of events.

Screening evaluations must occur prior to the subject starting any study medications, treatments, or interventions. In addition to data being collected on subjects who will enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured at site on the CRF and then entered into the study database.

13.3. Day 1 visit: Study treatment initiation

Treatment initiation will follow thorough explanation of the treatment schedule, which differ according to fibrosis staging, and of the importance of adherence to therapy as well as study visits.

Subjects will be reminded of the importance of informing the team of any concomitant treatment, and reporting of new signs and symptoms. Subjects will be asked to avoid use over the counter medications, herbal preparations as medications/drinks/soup and consult the research team as needed.

13.4. On treatment visits

After treatment initiation, on treatment visits will be schedule at week-1, week-4, week-8 and week-12 for non-cirrhotic subjects. Cirrhotic subjects will have additional on treatment visits at week 16, week 20 and week 24.

Visit at week 1 will have a window of ± 3 days. Visits at Weeks 4, 8, 12, 16, 20 and 24 have a window of ± 7 days.

During study visits without PK sampling subjects can take the study treatment at home. During study visits with PK sampling (Intensive or sparse), subjects will be instructed to take the study treatment at the hospital. For PK visits, subjects will be instructed to fast at least 6 hours before the visit and until 2 hours after dosing at site.

On treatment visits will focus on recording vital signs, inquiring about new signs and symptoms, adherence to therapy, concomitant medications and symptom targeted clinical examination. Study drugs will be dispensed every 4 weeks until end of therapy (12 weeks for subjects without cirrhosis, or 24 weeks for cirrhotic subjects).

The PROQOL-HCV quality of life questionnaire will be administered at the W8 treatment visit.

New or discontinued concomitant prescription and nonprescription medications taken since the last on treatment study visit will be recorded, the dose, frequency, route of administrations as well as start and stop dates will need to be documented. All study drug modifications, including initial doses, subject-initiated and/or protocol-mandated modifications, inadvertent and deliberate interruptions will be recorded on CRFs at each visit. If one of the study medication has to be stopped, the subject cannot continue with the remaining study medication. The subject will need to be advised to stop ALL study medications and return for end of treatment assessment and then post treatment follow-up assessment.

13.5. Follow-up visits

13.5.1. SVR4, SVR 12, SVR 24 and end of study visit

The week 4 post-treatment visit will have a window of -1 day and +7 days

The week 12 post-treatment visit (SVR 12, key endpoint) will have a window of -1 day and +28 days.

The week 24 post-treatment visit (SVR 24) will have a window of -3 days and +28 days.

This final visit will focus on assessing SVR 24 weeks after treatment discontinuation. Post-treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data.

13.5.2. Long term follow-up visits

A series of long-term follow-up visits will be implemented retrospectively for stage 1 (only for newly consented patients with virological failure) and for stage 2.

A representative subset of the cured patients (i.e achieving SVR12) will be followed up for one year after end of treatment to assess durability of response. One additional follow-up visit will be scheduled 12 months (+/- 28 days) after the end of treatment visit

All patients with virological failure at SVR12 or SVR24 will be followed up for three years after end of treatment or until they receive another treatment for HCV, whichever comes first. Five additional follow-up visits will be scheduled at one year, 18 months, 2 years, 30 months and 3 years after the end of treatment visit. Each of these long term follow-up visits has a window of +/- 28 days.

The following assessments will be performed at each long term follow-up visit, depending on cirrhosis status and achievement of SVR12 and SVR24:

	Non-Cirrhotics	Cirrhotics
Cured patients (1 year FU post end of treatment) **Stage 2 only**	HCV viral load and genotyping Biochemistry and Haematology blood sample[1] Symptom directed assessment AE review[2]	HCV viral load and genotyping Biochemistry and Haematology blood sample[1] Symptom directed assessment AE review[2] INR[3] Fibroscan[4] Ultrasound[5]
Patients with virological failures (3 years FU post end of treatment) **Stage 1 and stage 2**	HCV viral load and genotyping and resistance assessment Biochemistry and Haematology blood sample[1] Symptom directed assessment AE review[2] INR[3] Fibroscan[4]	HCV viral load and genotyping and resistance assessment Biochemistry and Haematology blood sample[1] Symptom directed assessment AE review[2] INR[3] Fibroscan[4] Ultrasound[5]

[1] Biochemistry and haematology including ALT and AST and bilirubine (direct and free)
[2] AE monitoring as per safety section
[3] INR is performed to assess the evolution of the liver condition
[4] A Fibroscan is performed to assess the evolution of fibrosis
[5] An ultrasound is performed to assess the occurrence of HCC as part as the standard of care.

14. Samples management

14.1. Sample collection

Routine blood and urine test will be collected according to the protocol schedule and will be analyzed by the laboratory of each site. These laboratories are accredited by Competent Authorities and follow locally defined Good Laboratory practices. Sponsor monitors, during site monitoring visits will monitor laboratory results, check normal ranges, verify quality assurance processes and maintenance of the laboratory equipment. For pharmacokinetic samples and hair samples, please refer to the relevant protocol sections.

14.2. Sample Labelling

Each sample will be identified with the study number, the subject initials and their unique identification number. The date and time of sampling will be written on the label.

14.3. Samples storage

Plasma will be stored at all visits for confirmation tests (HCV genotyping, HCV sequencing, HCV resistance testing RAV, IL28B gene) as needed. The plasma samples will be centrally stored in laboratory of Institute for Medical Research, Kuala Lumpur, Malaysia for the Malaysian patients samples and in PHPT-AMS Laboratory for the Thailand patients samples up to 5 years, in order to allow regulators to inspect and control the data. Stored samples will not be used for future studies.

14.4. Shipment of samples

Full blood count, Liver function test, total bilirubin, ALT/ AST, serum Creatinine, fasting blood sugar, Coagulation, Urinalysis, anti-HCV, HBsAg, HIV, will be done in respective study sites' laboratories.

Urine pregnancy tests (dipstick) will be done on each site.

Samples for HCV RNA and HCV genotype will be sent to laboratories as described in the contact details section.

For Thailand, samples for HIV RNA and CD4 count will be performed at each site or will be shipped and analysed at the Associated Medical Science laboratory, Chiang Mai University.

For Malaysia, samples for HIV RNA and CD4 count will be shipped and analysed in Hospital Kuala Lumpur for stage 1 and to laboratories in Hospital Kuala Lumpur or in IMR for stage 2.

Pharmacokinetic samples will be stored at -80°C and shipped to the central laboratory on a regular basis on dry ice together with the sample log to PHPT-AMS Laboratory, Chiang Mai, Thailand.

Hair samples will be stored at room temperature, and not in a fridge and will be shipped on a regular basis to the central laboratory Service de Pharmacologie-Toxicologie, Faculté de Médecine PIFO, INSERM U-1173, Université Versailles Saint-Quentin, Garches at room temperature.

Stored plasma samples will be kept in laboratory of Institute for Medical Research, Kuala Lumpur, Malaysia for the Malaysian patients samples and in PHPT-AMS Laboratory for the Thailand patients samples

Stored plasma samples for HCV sequencing, HCV resistance testing RAV, IL28B gene will be shipped to and analysed by PHPT-AMS Laboratory, Chiang Mai, Thailand and/or at Laboratory of Virology in the Geneva University Hospital, Switzerland.

14.5. Laboratory analysis

All laboratory analysis will be performed in accordance to the laboratory manual derived from the individual institution.

15. Assessment of safety

- Incidence of premature discontinuation of treatment and premature discontinuation of study – for any reason, for non-compliance, and for safety-related reasons
- Incidence of adverse events, and laboratory abnormalities during the observation period, i.e. from signature of informed consent to 24 weeks after end of treatment;
- Incidence of serious adverse events from signature of informed consent to 24 weeks after end of treatment;
- Incidence of grade 3-4 clinical and laboratory Aes through 24 weeks after the end of treatment.

Subjects will be monitored for clinical and biological adverse events. These will be reported using DAIDS toxicity grading tables [xi].

15.1. Adverse Events definitions

15.1.1. Adverse event (AE)

An adverse event is defined as any untoward medical occurrence (any 53nfavourable and unintended sign, symptom or disease, including an abnormal laboratory finding) in temporal association with the use of the investigational treatment and may or may not be causally related to it.

Definition of an AE includes worsening (in severity and frequency) of pre-existing conditions (“Medical history”) before first administration of the investigational treatment and abnormalities of procedures (i.e. ECG, X-ray…) or laboratory results which are assessed as “clinically significant”.

Abnormal laboratory (hematology and biochemistry) results will be reported as adverse events if the abnormality occurs or worsens after institution of the study treatment, and if the subject requires clinical intervention or further investigation, unless associated with an already-reported clinical event.

15.1.2. Surgical Procedures

Surgical procedures themselves are not Aes; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE, if it occurs or is detected during the study period.

[xi] http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx

15.1.3. Serious adverse event (SAE)

Any untoward medical occurrence (i.e. an adverse event) that meets at least one of the following criteria

- Results in death: i.e. causes or contributes to the death.
- Is life threatening
  In this context refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE that hypothetically might have caused death if more severe
- Requires inpatient hospitalization or prolongation of an existing hospitalization
  i.e. the AE requires at least an overnight admission or prolongs a hospitalisation beyond the expected length of stay. Hospital admissions for a surgery planned before study entry, for social reasons for any elective surgery (i.e. plastic surgery) or for normal disease management (including treatment adjustment) are NOT to be considered as a SAE
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
  i.e. the AE resulted in a substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly/birth defect, or
  i.e. an AE outcome in a child or foetus of a subject exposed to the investigational Product before conception or during pregnancy.
- is an important medical events, i.e. is medically significant that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse event.

15.2. Adverse events reporting

15.2.1. Detecting and documenting AE

The investigator is required to report all directly observed Aes and all Aes reported by the trial subject using concise medical terminology. In addition, at each visit the subjects will be questioned about the occurrence of Aes, with a generic question such as “Since your last visit have you experienced any health problems?”

Stage 1 (for patients who did not consent for long-term follow-up visits): The AE reporting period for this stage of the trial begins upon subject enrolment in the trial (after signature of informed consent for treatment initiation) until 24 weeks’ post-treatment completion.

Stage 1 (for patients who consented for long-term follow-up visits) and stage 2: The AE reporting period for this stage of the trial begins upon subject enrolment in the trial (after signature of informed consent for treatment initiation) until:

- End of long-term follow-up visits (SVR 24 + one additional visit for cured patients and 5 additional visits for virological failures): for all serious adverse events.
- End of long-term follow-up visits (SVR 24 + one additional visit for cured patients and 5 additional visits for virological failures): for all liver-related serious and non-serious adverse events.
- 24 weeks’ post-treatment completion (SVR 24 visit): for adverse events not associated with any liver-related and not serious.

For both stages of the study:

Serious adverse events will be followed and reported until resolution or stable state.

Information on Aes must be evaluated by a physician. Each adverse event is to be classified by the investigator as serious or non-serious. This classification will determine the reporting procedure for

the event to DNDi and Regulatory Authorities/Ethics Committees (as per local regulatory requirements).

All patients who have Aes, whether considered associated with the use of the investigational product or not, must be monitored to determine the outcome. The clinical course of the AE will be followed-up according to accepted standards of medical practice (i.e. until they are resolved or the investigator assesses them as chronic or stable or the subject participation in the trial ends (i.e., until a final report is completed for that subject), even after the end of the period of observation, until a satisfactory explanation is found or the Investigator considers it medically justifiable to terminate follow-up.

All Aes must be recorded in the AE log of the CRF, regardless of apparent causality from use of the study treatment. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. If a definitive diagnosis is not possible, the individual symptoms and signs should be recorded. The following information should be captured for all Aes: date, time of onset and end date or outcome (e.g., ongoing), severity of the event, seriousness of the event, Investigator's opinion of the relationship to each investigational product, action taken with regards to each study drug and treatment required for the AE, cause of the event (if known), and information regarding the AE resolution/outcome.

In the CRF, a given AE will be recorded only one time per patient, and the severity recorded will be the maximum level reached. If several distinct episodes of the same condition occur, each episode will be recorded in the CRF.

Serious adverse events should also be reported on the clinical trial AE CRF (in addition to SAE(EAE) form). It should be noted that the form for reporting of SAE (SAE form) is not the same as the AE section of the CRF. Where the same data are collected, the two forms must be completed in a consistent manner, and the same medical terminology should be used.

In addition all medications used to treat the SAE should be documented on the concomitant treatments CRF.

A copy of the submitted SAE form must be retained on file by the Investigator. The Investigator must submit the SAE to the Sponsor and IRB/ IEC and retain documentation of these submissions in the site study file. If the Investigator detects an SAE in a study subject after the end of the period of observation, and considers the event possibly related to prior study treatment, he/she should contact the Sponsor to determine how the event should be documented and reported, and complete a SAE form.

15.2.2. Adverse Event reporting processes

Initial SAE reports will be reported to EAE Group if they meet the following minimal criteria:

a. An identifiable patient
b. A suspect medicinal product (at least one)
c. An identifiable reporting source
d. An event or outcome that can be identified as serious and unexpected

   Causality assessment will be reported asap.

All serious adverse events must be reported in an expedited manner to DNDi through S*AEHCVstudy@dndi.org*, whether or not the event is considered medication-related (within **24 hours of awareness of SAE** by the investigator), using the SAE (EAE) report form. This includes a description of the event, onset date and type, duration, severity, relationship to each study drug, outcome, actions taken, and all other relevant clinical and laboratory data.

Event	Time Frame	How to report	Report to
AE	NA (same time frame as other CRF forms)	AE CRF	Data Management Center
SAE	24 hours	AE CRF + EAE (at least email notification shortly followed by EAE form)	DNDi EAE Group; Data Management Center
Pregnancy*	72 hours	Pregnancy surveillance form	DNDi EAE Group; Data Management Center
Spontaneous Abortion	24 hours	EAE (EAE form) + Pregnancy surveillance form	DNDi EAE Group; Data Management Center
Other Pregnancy Outcome incl. birth	72 hours	Pregnancy surveillance form and Child surveillance form	DNDi EAE Group; Data Management Center

*if pregnancy leads in a reportable SAE, EAE form is to also be used and reported within 24 hours

The initial SAE report is to be followed by submission of additional information (follow-up SAE form and any other relevant source documents) as they become available.

Any follow-up report should be submitted as soon as possible, preferably within 5 working days.

Timelines for regulatory reporting in Malaysia (NPRA) and Thailand (Thai FDA):

Fatal and life-threatening Suspected Unexpected Serious Adverse Reaction (**SUSAR**) will be notified to National Pharmaceutical Regulatory Agency (NPRA)/Thailand FDA as soon as possible but **no later than** 7 calendar days after first knowledge by the sponsor that a case qualifies, followed by a report as complete as possible within 8 additional calendar days. The report will include an assessment of the importance and implications of the findings, including relevant previous experience with the same or similar medicinal product. Follow-up information will be actively sought and follow-up reports will be submitted to the NPRA/TFDA when it becomes available.

SUSARs that are not fatal or life-threatening will be notified to the NPRA/TFDA/site ECs as soon as possible but **not later than 15 calendar days after first knowledge by the sponsor** that the case meets the minimum criteria for expedited reporting. Follow-up information will be actively sought and follow-up reports will be submitted to the NPRA/TFDA when it becomes available.

15.3. Grading of Adverse Event severity

All toxicities and intensity of AEs will be evaluated by the investigator ad graded according to the DAIDS AE grading table version 2.0 / November 2014 (see Appendix II).

The decision to continue, put the study on hold or discontinue therapy is applicable to both drugs, sofosbuvir and ravidasvir, whatever the assumed relationship between one or both drugs and an adverse event. Using either drug alone may not only result in virological failure, but also may select resistance mutations which may jeopardize future therapy.

- **Grade 1 and 2 Adverse Event**
  - Continue study treatment
- **Grade 3 Adverse Event**
  - For clinical events, or while awaiting a repeat assessment / confirmation as soon as possible (at most within 1 week) of an abnormal laboratory test the study treatment can be continued upon the judgment of the site investigator.
  - If repeat assessment of an abnormal laboratory test confirms Grade 3 toxicity and if the site investigator considers that the toxicity is possibly, probably, or definitely related to one or both study drugs, the treatment should be put on hold and laboratory values will be followed weekly and notified to the research team within 72 hours. Management of adverse events probably not related to study drugs will be determined on a case-by-case basis at the discretion of the site investigator.

- If toxicity resolves to ≤ Grade 2 within 7 days, study treatment can be restarted for the remaining planned treatment duration.
- If Grade 3 toxicity persists for >7 days, restart of the treatment will be under judgement of investigator in consultation with the sponsor.

  If Grade 3 recurs to > Grade 3 after reintroduction of study drugs, treatment must be permanently discontinued. The site investigator and the study team will consult each other on treatment options on a case-by-case basis.

- **Grade 4 Potentially-Life-Threatening Adverse Event**
  - If the site investigator and the study team consider that the adverse event is possibly, probably, or definitely related to one of the study drugs, the dual study treatment should be withheld and the study team be notified within 24 hours. For abnormal laboratory tests, repeat assessment/confirmation should be done as soon as possible (at most within 1 week).
  - If repeat assessment confirms Grade 4 toxicity and site investigator and the study team consider that the adverse event may be related to the study drug, the study drug should be permanently discontinued.
  - If repeat assessment shows Grade 3 toxicity, clinicians should continue to withhold the study drug and follow abnormal laboratory values weekly and notify the team within 72 hours.
  - If toxicity resolves to < Grade 2 within 7 days, the study drug can be restarted from when it stopped for the remaining treatment duration. Restart of the treatment will be under the judgement of investigator in consultation with the sponsor.
  - If >Grade 3 toxicity recurs after reintroduction of the study drug, the study drug must be permanently discontinued.
  - Subjects who prematurely discontinue study treatment will continue to be followed at scheduled study visits as indicated in the schedule of evaluations.

In case of AEs that are not described in the DAIDS AE grading table version 2.0 / November 2014, the Investigator will use the terminology “mild”, “moderate”, “Severe” or “life-threatening” to describe the maximum severity of the adverse event.

- Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated (e.g. no reduction in daily activities is required).
- Moderate: The subject experiences sufficient discomfort to interfere with or reduces his or her usual level of activity.
- Severe: Significant impairment of functioning: the subject is unable to carry out usual activities and/or the subject’s life is at risk from the event.
- Life threatening: refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe.

When the intensity of an AE changes over time, each change in intensity will be recorded in the source documents until the event resolves. However, only one AE and the maximum intensity will be recorded in the CRF for each separate event. If the AE resolves but then recurs, each will be recorded as a separate AE, with the appropriate start and stop times.

Note: *It is to be noted the distinction between severity and seriousness of adverse events. A severe adverse event is not necessarily a serious event.*

15.4. Adverse event causality assessment

For <u>each</u> serious and non-serious adverse event, the investigator is required to assess the possible relationship between the adverse event and each study drug(s)/IMP(s) (i.e**. to determine whether**

there exists a reasonable possibility that the study drug caused or contributed to the adverse event). This means that there are facts (evidence) or arguments to suggest a causal relationship.

To help investigators with the decision binary tree yes/no (i.e. Related/Not related) in the evaluation of causality, the Council for International Organizations of Medical Sciences (CIOMS VI) group recommends that investigators be asked to consider the following before reaching a decision:

- Medical history (including presence of risk factors)
- Lack of efficacy/worsening of existing condition
- Study medications
- Other medications (concomitant or previous)
- Withdrawal of study medication, especially following trial discontinuation / end of study medication
- Erroneous treatment with study medication (or concomitant)
- Protocol-related procedure

The terms for reporting are:

- **Definitely Related**. The adverse event and administration of study agent are related in time, and a direct association can be demonstrated.
- **Probably Related**. The adverse event and administration of study agent are reasonably related in time, and the adverse event is more likely explained by study agent than other causes.
- **Possibly Related**. The adverse event and administration of study agent are reasonably related in time, and the adverse event can be explained equally well by causes other than study agent.
- **Probably not related** A potential relationship between study agent and the adverse event could exist (i.e., the possibility cannot be excluded), but the adverse event is most likely explained by causes other than the study agent.

  Not Related. The adverse event is clearly explained by another cause not related to the study agent.

15.5. Exposure during pregnancy

All female participants of child-bearing capacity should be counseled about not becoming pregnant while on study.

Pregnancy tests are required for subjects who are classified as women of child bearing potential during the study: prior to treatment initiation, and at each visit during the treatment period (12 weeks for non-cirrhotic and 24weeks for cirrhotic patients) and 4 weeks post treatment.

If a participant has a positive pregnancy test during study participation, the site should perform the following procedures:

- The participant should immediately discontinue the study drug.
- The pregnancy should be reported to the DNDi EAE team within 72 hours of awareness of the pregnancy. Record pregnancy using the pregnancy surveillance form and submit to DNDi/EAE group and Data Management Center within 72 hours of awareness of pregnancy.
- Participant should remain on the study and should be followed up for safety concerns as per the regular visit schedule until the outcome is determined (e.g. birth, premature termination etc).
- Once the outcome has been determined, the status of the mother and infant should be recorded using the pregnancy surveillance form.
- It is requested that the investigator ask the parents to return to clinic for a follow-up on infant exposed to the study treatment in utero until they reach 24 months of age. (Child surveillance form to be used).

- Pregnancy complications and elective terminations for medical reasons/SAEs of new born should be reported as an AE or SAE, as appropriate. Elective terminations should also be reported on the pregnancy surveillance form.
- Spontaneous abortions MUST be reported as an SAE and reported on the EAE form and pregnancy surveillance form.

15.6. Emergency Procedures

In emergency situations, the Investigator should contact as soon as possible the Sponsor's Medical expert for the trial, indicated below:

[redacted]
[redacted]
Drugs for Neglected diseases *initiative*
15 Chemin Louis Dunant,
1202 Geneva, Switzerland
[redacted]
[redacted]

16. Data Analysis and Statistical Methods

16.1. Sample size determination

A WHO publication[71] describes the ideal HCV treatment as having efficacy ≥85% in all populations in a public health setting, while DNDi's target product profile sets an acceptable real world effectiveness target of ≥80% with 12 weeks' treatment for non-cirrhotics and 24 weeks for those with compensated cirrhosis.

16.1.1. Sample size determination for stage 1

Stage 1 of this study will be intended to give a clear indication of likely real world effectiveness. It is recognised that some sub-groups of HCV patients are more difficult to cure than others. This includes those with cirrhosis (particularly when infected with genotype 3 virus), those co-infected with HIV and those who have failed previous treatment. Within these categories, only subjects with decompensated cirrhosis and those with prior treatment with an NS5A inhibitor will be excluded. No restrictions will be imposed on the number of subjects in each sub-group and subjects with more than one of the difficult to treat characteristics (for example treatment experienced, GT3, and with compensated cirrhosis) can be enrolled. As a consequence, it is not expected that the efficacy in this study to reach the levels that could be achieved in studies with much tighter inclusion criteria. Based on published results for other treatments, we considered that the overall SVR12 rate should be superior to 85%. A sample size of 300 subjects in Stage 1 will ensure that the width of the exact Clopper-Pearson 95% confidence interval (CI) around the overall SVR12 rate expected to be observed is as small as 6-7% (see table below). It would provide over 86% power to detect at least 6% improvement in the overall SVR12 rate from this pre-specified performance goal of 85%, using a two-sided exact one-sample binomial test at a significant level of 0.05. With this sample size, the lower bound of the 95% CI will be greater than 85% if the observed overall SVR12 rate is 90% or higher.

16.1.2. Sample size determination for stage 2

As there are no changes to the design for Stage 2, a further 300 subjects will be recruited in Stage 2. The objective of Stage 2 is to provide further data on the efficacy and safety of SOF-RDV in all key subgroups. Additional subjects will be enrolled in order to reach ideally 50 subjects per subgroup (30 for GT2) when combining both stages.

If recruitment of some sub-groups proves very slow, we will adjust recruitment of other sub-groups to achieve the target of 300 subjects for stage 2 within a reasonable timeframe. This is most likely to apply to GT2.

16.1.3. Sample size determination for the global study

A total sample size of 600 patients will ensure that the width of the 95% CI around the overall SVR12 rate expected to be observed will be as small as 4-5% (see Figure 3). With this sample size, the lower bound of the 95% CI will be greater than 85% if the observed overall SVR12 rate is 88% or higher.

Figure 3: Confidence intervals for expected observed SVR12 rates in 300 and 600 subjects

Observed overall SVR12 rate	N=300		N=600	
	95% CI	Width of 95% CI	95% CI	Width of 95% CI
87%	82.7% to 90.6%	7.9%	84.0% to 89.6%	5.6%
88%	83.8% to 91.4%	7.6%	85.1% to 90.5%	5.4%
89%	84.9% to 92.3%	7.4%	86.2% to 91.4%	5.2%
90%	86.0% to 93.2%	7.2%	87.3% to 92.3%	5.0%
91%	87.2% to 94.0%	6.8%	88.4% to 93.2%	4.8%
92%	88.3% to 94.8%	6.5%	89.5% to 94.0%	4.5%
93%	89.5% to 95.6%	6.1%	90.7% to 94.9%	4.2%
94%	90.7% to 96.4%	5.7%	91.8% to 95.8%	4.0%
95%	91.9% to 97.2%	5.3%	92.9% to 96.6%	3.7%

The study population will comprise up to 50% subjects with compensated cirrhosis. Based on preliminary site assessment, HIV/HCV co-infected subjects will represent approximately 30% of the study population. It is expected that 35-40% of the subjects will be infected by HCV genotype 3, 35-40% genotype 1, 15-20% genotype 6 and 5-10% genotype 2. In addition, a substantial fraction of the subjects may not be treatment naïve, and may have been previously exposed to interferon/ribavirin.

16.1.4. Sample size for the intensive PK substudy (Stage 1)

The sample size necessary to assess drug-drug interactions in HCV/HIV co-infected subjects will be also met. It is estimated that approximately one third of the subjects will be co-infected (see section 16.1.4).

In the intensive PK substudy (Stage 1), a total of 25 subjects will be enrolled in order to ensure adequate precision of PK parameter estimates. The precision required is a mean plasma ravidasvir AUC0-24h within ±20% of the true population mean (i.e. margin of error). The reported coefficient of variation (CV) of the AUC in HCV-infected adults for ravidasvir is 45.8% following multiple doses once daily. This is estimated to correspond to ±2,800 ng.hr/mL for a 200 mg daily dosing. Assuming the true mean and CV for the ravidasvir AUC0-24h are the same for Thai and Malaysian subjects as in the reported studies, the sample size calculation ensured that the 95% confidence interval of the sample mean for the AUC0-24h of ravidasvir is within ±20% of the true mean i.e. within ±2,800 ng.hr/mL.

Based on the reported variability at the standard dose and assuming mean AUC results are normally distributed, a sample size of 25 participants (taking into account 5-10% non-evaluable) is required. This sample size would also be sufficient to ensure the same precision for sofosbuvir and the sofosbuvir metabolite (GS31007) exposure based on the reported CV% for each drug (if also measured).

16.2. Statistical Analysis

A comprehensive analysis of the study results will be performed at the end of stage 1 and an interim Clinical Study Report will be released. An analogous analysis will be performed at the end of stage 2 with data from stage 1 + stage 2 and a final Clinical Study Report will be released.

The final Statistical Analysis Plan (SAP) will be submitted and approved by the DSMB prior to the database lock for the final study analysis (stage 1 + stage 2).

16.2.1. Analysis Sets

Five analysis sets will be used in this study:

- *All enrolled subjects:* composed of all subjects who signed an informed consent form and were enrolled in the study.
- *Safety Analysis Set (SAF):* composed of all enrolled subjects who received at least one dose of a study drug. This set will be used for safety analyses.
- *Full Analysis Set (FAS):* composed of all enrolled subjects with no current injection drug use at screening who received at least one dose of a study drug. This set will be used for the primary analysis of SVR endpoints.
- *Per Protocol Set (PPS):* composed of all subjects in the FAS who did not prematurely discontinue the study, had an adherence to SOF+RDV ≥ 90%, had no missing SVR12 results and had no major protocol deviation during the study. The PPS will only be used for the secondary analysis of SVR endpoints.
- *Pharmacokinetic Analysis Set (PKAS):* composed of all enrolled subjects who participated in the intensive PK analysis or for whom sparse PK data are available.

The reasons for excluding a subject from any of the analysis sets will be described in the clinical study report.

16.2.2. Subject Flow Diagram

A subject flow diagram will describe eligibility, enrolment, receipt of intended treatment, completion of study visits, and retention in the study and availability of primary endpoint (www.consort-statement.org).

16.2.3. Descriptive Statistics

Participant's characteristics at base line and over time will be tabulated. Categorical variables will be described using frequencies and proportions, and discrete and continuous variables using means (standard deviations), medians (25th; 75th percentiles) and ranges (minimum-maximum).

Most important subjects' characteristics at enrolment include liver disease classification (F0 to F4), HCV viral load (median, IQR), haemoglobin level, anthropometry and demographic characteristics.

16.2.4. Efficacy Analysis

The efficacy of SOF-RDV will be evaluated overall and for each of the pre-specified subgroups: presence/absence of cirrhosis, genotype, prior/no prior therapy, and HIV/no HIV co-infection.

Non-virological failures (including deaths and lost to follow-ups), on-treatment virological failures and virological relapses, will be considered as failures. Reinfections are not considered as failures.

Time-to-event endpoints will be estimated using the Kaplan-Meier method. Changes in continuous variables from baseline will be assessed using Wilcoxon signed-rank test.

In exploratory analyses, multivariable logistic regression models and Cox proportional hazards regression models may be used to evaluate risk factors associated with binary and time-to-event endpoints, respectively.

16.2.5. Safety Analysis

Adverse events will be described during the study period, until 24 weeks after treatment discontinuation. AEs and Medical History will be coded using MedDRA and tabulated by severity / DAIDS AE grading table version 2/ November 2014. Causality of AEs for each sudy drug will also be tabulated.

The number and percentage of subjects who experienced each of the safety events listed as secondary endpoints will be presented overall, by assigned treatment duration and by key subgroup. In addition, the number and percentage of subjects who experienced these events will be

summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT) and presented overall and by assigned treatment duration.

Safety and tolerance of the study agents will be evaluated by summarizing the number and percentage of subjects with documented Grade 3 or higher adverse events; each summary will be conducted overall and by assigned treatment duration. The proportion of subjects experiencing Grade 3+ adverse events will be presented overall and by assigned treatment duration , with these proportions bounded by exact 95% confidence intervals; this will also be done for the proportions of subjects with Grade 3+ intensity adverse events which have been judged to be at least possibly related (possibly/probably/definitely related) to treatment.

Serious Adverse Events will be described by individual narratives based on the SAE reports provided by the site investigators.

16.2.6. Pharmacokinetics

In stage 1, the pharmacokinetics of RDV will be evaluated using an intensive PK schedule for a small proportion of the subjects enrolled in healthcare institutions to establish the PK model and by population approach (sparse sampling) for the others. Twenty-five evaluable intensive PK evaluations will provide sufficient precision in the estimates of the PK parameters to use as initial estimates in the population model.

The population PK model (stage 1 and stage 2) built using these parameters allows, with a small number of samples per subject, collected at variable times between drug intake and sampling, to re-estimate the pharmacokinetic parameters of the drugs as well as their variability in the population. This approach enables to explain the observed variability with various pertinent covariates such as possible antiretroviral co-treatment and patient's characteristics (e.g., BMI, sex, etc.).

Individual pharmacokinetic parameters are derived using Bayesian estimation from the population model. Association between individual exposures (i.e. trough concentration, area under the curve) and efficacy/tolerance endpoints are then investigated. The pharmaco-statistical analysis is performed using non-linear mixed effects modelling software (e.g. Monolix v4.2 or NONMEM v7.3) to calculate the pharmacokinetic parameters of all drugs as well as the covariates associated with inter-subject variability.

Given the reported drug-drug interactions between antiretrovirals and DAAs, RDV, NNRTI or PI morning troughs or mid dose concentrations are systematically measured in HIV/HCV co-infected subjects to verify that RDV as well as antiretrovirals are within exposure targets. Given the metabolic route of elimination of RDV, it is anticipated that drug-drug interactions, if any would be minimal.

Hair analysis has proved to be a suitable method to detect chronic or acute abuse of many drugs of abuse such as opiates, cocaine, amphetamines and many others. Hair samples are collected at baseline and at end of treatment for all subjects where possible. These samples will be used to assess drug use in subjects who fail to meet the primary study endpoint (SVR12).

Data management programs and all statistical analyses except pharmacokinetic modelling will be performed using Stata version 13 or higher.

17. Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB), composed of diverse members independent of the investigator and sponsors, will be set up prior to study initiation. The DSMB monitors the study in order to ensure that harm is minimized and benefits maximized for the study subjects. They will review the study data at pre-determined intervals and issue recommendations about the study. In particular, they will review the analysis results after each stage of the study. The analysis strategy

will be agreed prior to analysis of the study results and documented in the DSMB Charter. A Charter will define the membership and responsibilities of the DSMB.

18. Adjudications Committees

18.1. Clinical Adjudication Committee

The primary purpose of the Clinical Adjudication Committee is to adjudicate key data to be used for the analysis of the study. A Charter will define the membership and responsibilities of the Adjudication Committee.

18.2. Virology Adjudication Committee

The primary purpose of the Virology Adjudication Committee is to adjudicate key data to be used for the analysis of the study. A Charter will define the membership and responsibilities of the Adjudication Committee.

19. Quality assurance and quality control procedures

19.1. Essential documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents include Investigator's Site File, subject clinical source documents and screening / enrolment logs. The Investigator's Site File will contain the protocol/protocol amendments, CRF and query forms, any forms or documents sent to DNDi Pharmacovigilance (PV), IEC and regulatory approval with correspondence, sample informed consent, drug accountability records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence etc.

19.1.1. Subject identification list/Enrolment log

A subject identification list will be maintained by the sites and will allow reconciliation of subject number and real subject identification in case a follow-up is required. The site keeps this confidential list in the study documents locked cabinet. The subject enrolment log is maintained by the site to document chronological enrolment of subject by study number.

19.1.2. Site signature/authorization log

A site signature list and authorization log will be maintained by the site and completed by each member of the study site to allow identification of the team. On this form, the site principal investigator delegates study activity to the team under his responsibility and updates the form every time a team member is leaving or a new team member is joining.

19.1.3. Curriculum Vitae

Curriculum vitae of each site member will be filed in the investigator file to document qualifications and eligibility to conduct study and /or provide medical supervision of subjects. The curriculum vitae must contain qualifications and training and will be updated when a new information is available. It must be dated and signed.

19.2. Case report forms (CRFs)

Data will be collected by the study personnel authorized by the investigator. It will be supervised by the investigator and signed by the investigator or by an authorized staff member. Study-specific information will be entered into the Case Report Form (CRF). All data will be supported by source data and no data will be entered directly into the CRF. All CRF data will be identified by study subject number only.

The investigator at each trial site should ensure the accuracy, completeness, legibility, and timelines of all data reported to the sponsor in the CRFs and any other additional information that is required.

The investigator is responsible for keeping all consent forms, screening forms, CRF and the completed subject identification code list in a secure location.

After the CRF has been completed, CRFs will be uploaded and data will be entered onto a database using double independent data entry. The trial data will be stored in a computer database maintaining confidentiality in accordance with national data legislation. Source documentation will be monitored by CRAs on a regular basis.

19.3. Record Retention

The investigator must keep all records pertaining to the conduct of the clinical study, ICFs, drug accountability records, source documents, and other study documentation on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed with prior permission from DNDi, subject to local regulations.

Should the investigator wish to assign the study records to another party or move them to another location, DNDi must be notified in advance.

The Investigator must notify the Sponsor in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, the Sponsor must be contacted to arrange alternative record storage options. Whenever possible, an original recording of an observation must be retained as the source document. However, a photocopy of a record is acceptable provided it is legible and is a verified copy of the original document. All CRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The Sponsor will retain the original CRF data and audit trail.

19.4. Audits and Inspections

The trial site may also be subject to quality assurance audits by DNDi or designated representatives and/or to inspection by regulatory authorities or Independent Ethics Committees (IEC) to ensure that Good Clinical Practices (GCP) and all aspects of the protocol are followed.
It is important that the investigators and their relevant personnel are available for possible audits or inspections.
The investigators will permit representatives of DNDi and/or of regulatory authorities/IECs direct access to source and trial documents and will allow the review of all CRFs, medical records, laboratory work sheets and assessment of the status of drug storage, dispensing and retrieval at anytime during the study. The corresponding source documents for each subject will be made available provided that subject confidentiality is maintained in accord with local regulations.

19.5. Study Administration

19.5.1. Study initiation

The study will be conducted in accordance to local regulatory requirement. A study may not be initiated until all regulatory requirements are met

The following documents must be obtained or in place prior to the initiation of the study at each site:

- Documentation of IEC approval of the study protocol, informed consent form, case report form, questionnaire and other relevant study related documents.
- Current IEC membership list
- A copy of the protocol signature page signed by the PI
- CTIL approval from the regulatory
- Clinical trial insurance policy
- Clinical Trial Agreement

19.5.2. Notification of primary care physician

The investigator should inform the subject's primary care physician about the subject's participation in the study if the subject has a primary care physician and the subjects agrees to the primary care physician being informed.

19.5.3. Source documents

Qualified representatives of the Sponsor or Sponsor designee will monitor the study. Monitoring visits provide the Sponsor with the opportunity to:

1. Evaluate the progress of the study.
2. Verify the accuracy and completeness of CRFs and forms/documents sent to DNDi PV.
3. Assure that all protocol requirements, applicable laws and/or regulations, and Investigator's obligations are being fulfilled.
4. Resolve any inconsistencies in the study records.

Four visit types are planned: pre-study, study start, during the study, and study end. Visits may also be performed by regulatory authorities.

The Investigator must allow the Study Monitor to periodically review, at mutually convenient times during the study and after the study has been completed, all CRFs and office, hospital, and laboratory records supporting the participation of each subject in the study.

The CRFs forms as well as the documents sent to DNDi PV and other documentation supporting the study must be kept up-to-date by the Investigator and the research staff at the investigative site. These study materials must be available for review by the Study Monitor, and/or other qualified representatives of the Sponsor, at each monitoring visit. The study monitor will review the various records of the study (CRFs, subject medical and laboratory records, and other pertinent data including forms/documents sent to DNDi PV). The Study Monitor will verify the CRF data against original source documentation for accuracy and completeness.

The study monitor will identify data discrepancies and collaborate with the Investigator and research staff to resolve the discrepancies in a timely manner. Protocol deviations will also be identified and recorded on a "Protocol Deviation Log" (see section 19.5.6). The study monitor will follow an "Issue Escalation" plan in order to ensure that each issue identified during a monitoring visit is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

Monitoring visits to the trial site will be made periodically by DNDi representatives or designated clinical monitors to ensure that GCPs and all aspects of the protocol are followed. Source documents will be reviewed for verification of consistency with data on CRFs. The investigator will ensure direct access to source documents by DNDi or designated representatives.

The investigators will permit representatives of DNDi and/or designated clinical monitors to inspect all CRFs, medical records, and laboratory work sheets, and to assess the status of drug storage, dispensing, and retrieval at any time during the study. The corresponding source documents for each subject will be made available provided that subject confidentiality is maintained in accord with local regulations. The inspections are for the purpose of verifying the adherence to the protocol and to ensure the study is conducted according to GCP. It is important that the investigators and other trial site staff are available at these visits.

It will be the clinical monitor's responsibility to inspect the CRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

19.5.4. Statement of Good Clinical Practices

This trial will be conducted in adherence to the study protocol, Malaysian Guideline for Good Clinical Practice, Good Clinical Practices (GCP) as defined the ICH E6: Guideline for Good Clinical Practice

(ICH E6 GCP) consolidated guidelines and other applicable regulatory requirements (http://www.fda.gov/cder/guidance/index.htm).

19.5.5. Protocol Adherence

The Investigator must adhere to the protocol as described in this document and agree that deviations to the protocol, with the exception of medical emergencies, must be discussed and approved by the Sponsor prior to seeking approval from the IRB/IEC. The Investigator is responsible for enrolling patients who have met the protocol inclusion and exclusion criteria or must have obtained prior documented approval from the Sponsor prior to enrolment in the study. The IRB/IEC that granted original approval, or the IRB/IEC currently responsible for overseeing the conduct of the study, must be notified of all changes in and deviations from the protocol that may increase risk to the subject, and/or that may adversely affect the rights of the subject or validity of the investigation. The Investigator must send a copy of the approval letter from the IRB/IEC to the Sponsor and retain the original in the site study regulatory file.

19.5.6. Protocol deviation

Protocol deviations will be documented in a protocol deviation log and kept at site. If protocol violations are detected, they will be reported promptly to the IEC according to the local regulation. Findings from monitoring visits and deviations reported by study sites will be documented in a central database and reported in the clinical study report.

19.5.7. Protocol Amendments

The Principal investigator will ensure that the study protocol is strictly adhered to throughout, and that all data are collected and recorded correctly on the CRF. The Principal investigator may contact the sponsor for a protocol waiver for minor deviations from the protocol (e.g. subject unable to attend during visit window).

All protocol modifications must be documented in writing. Any protocol amendment must be approved and signed by the sponsor and the Principal investigator and is to be submitted to the appropriate IEC for information and approval in accordance with local requirements, and to regulatory agencies if required.

Approval by IEC (and Regulatory Authority, if applicable) must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the change involves only logistical or administrative aspects of the trial (e.g. change in clinical monitor[s], change of telephone number[s]).

The protocol amendment can be initiated by either sponsor or by any Principal investigator.

The investigator will provide in writing the reasons for the proposed amendment and will discuss with the medical coordinator and sponsor.

19.5.8. Conflict of Interest

Any investigators who have a conflict of interest with the study must sign a declaration form and have the conflict reviewed by the independent ethics committee.

20. Early Termination of the study

Both the sponsor and the investigator reserve the right to terminate the study at any time prior to inclusion of the intended number of subjects, and according to the terms specified in the study contract. They intend to exercise this right only for valid scientific or administrative reasons. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the subject’s interest.

The Investigator is to notify the IRB/IEC in writing of the study's completion or Early Termination, and send a copy of the notification to the Sponsor or CRO and retain one copy for the site study regulatory file.

Reasons for termination by the sponsor(s) may include but not be limited to:

- Too low enrolment rate.
- Protocol violations.
- Inaccurate or incomplete data.
- Unsafe or unethical practices.
- Questionable safety of the test products.
- Suspected lack of efficacy of the test products.
- Following the recommendation of the DSMB or IEC.
- Administrative decision.

Reasons for termination by the investigator may be:

- Insufficient time or resource to conduct the study.
- Lack of eligible patients.

In the event that a study is terminated either by the sponsor or by the investigator, the investigator has to:

- Complete all CRFs to the greater extent possible.
- Return all test products, CRF, and related study materials to the sponsor who provided them.
- Answer all questions of the sponsors or their representatives related to data of subjects enrolled at the site prior to study termination.
- Ensure that subjects are followed up with the necessary medical care.
- Provide in writing the reasons for the decision to the national health authority and the sponsor.

21. Ethics

21.1. Institutional Review Board or Independent Ethics Committee

For Malaysia and Thailand,

It is the responsibility of the Investigator to apply for review to the IEC of the country where the study takes place regarding local rules and regulations. Written approval from all involved IECs must be obtained before implementation of any protocol-specified intervention/investigation provided to the subject (such as subject information sheets or descriptions of the study).

Ethical approval will be obtained by the coordinating PI from the required independent ethics committee.

Regulatory approval will be obtained from the Regulatory Authorities.

Any modifications made to the protocol after receipt of the IEC approval must also be submitted by the investigator in writing to the IEC in accordance with local procedures and regulatory requirements.

21.2. Notification of Regulatory Authority (ies)

For Malaysia:

Drug accountability report for importation will need to be submitted to the Drug Control Authority (DCA). Evidence of delivery to the approved investigator sites shall be supplied to the DCA at the end of study.

DCA should be notified should there be any amendment/update to the clinical trial protocol, pharmaceutical data, IB and other related documents. For protocol amendment, the DCA will be notified after EC approval for each site involved.

The sponsor will inform NPRA within 48 hours of the occurrence of any new, significant safety events that may jeopardize the safety of the subjects, which have arisen from an analysis of overseas reports or action with respect to safety which has been taken by another country's regulatory agency. Sponsor will inform all Malaysian investigator(s) and through the investigator, the EC of this information.

The sponsor will also provide promptly clinical details of any individual overseas adverse drug reaction if requested by DCA.

A periodic report will be submitted for each trial site every 6 month from the time the previous report was submitted to DCA. In addition, all protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment and the corrective action / preventive action taken shall be reported to DCA periodically.

DCA shall be informed within 3 months from the last site closure in Malaysia. The CTIL holder shall also notify DCA when the whole trial is completed / data is frozen / locked for international multi-centre studies.

The CTIL holder shall inform the DCA immediately or within 15 working days of early termination of the clinical trial in its entirety or at a clinical trial site.

The CTIL holder shall submit End of Study Summary Report and Drug Accountability and Disposal Report pertaining to the site conducting the trial to the DCA within 3 months from the site closure. The report shall be submitted for each trial site.

Clinical study report shall be submitted to DCA within 1 year after completion of the whole trial. The report shall comply with ICH E3 Structure and Content of Clinical Study Report in CD-ROM format.

<u>For Thailand:</u>

After the Thai-FDA have approved for clinical trial drug importation, the Clinical trial drug import permit holder need to submit the following reports to the Thai-FDA;

1. Annual progress report of the study, using the report template of Thai-FDA. Must be submitted on 1-31 October every year until the end of the study.
2. Annual Safety Report and End of Study Safety Report
    - Annual Safety report: must be reported within 3 months of the Annual Safety Data Cut-off Date.
    - End of Study Safety Report: must be reported within 6 months after study completion

Report by using the Thai-FDA report template:

- Line Listing of All Suspected Serious Adverse Drug Reactions, which include following information:
    - Reporting Period: Annual or End of Study, duration date, and numbers of reports
    - Protocol name, protocol code number
    - Subject identification, reference number, country, Age, Sex, Daily dose, Date of Onset, Dates of treatment, Adverse Reaction, patient's outcome
- Aggregate Summary Tabulation of All Serious Adverse Drug Reactions, which include following information:
    - Reporting Period: Annual or End of Study, duration date, and numbers of reports

- Protocol name, protocol code number
- Number of reports by terms (signs, symptoms and diagnoses) for the trial

21.3. Informed consent process

Preparation of the consent form is the responsibility of the Investigator and the Sponsor or designee and must include all elements required by the ICH, GCP, and applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki (see Appendix III).

A template will be prepared by the Sponsor. The Sponsor or designee must review and approve all changes to site-specific ICFs. The consent form must include a statement that the Sponsor or designee and regulatory authorities have direct access to subject records.

Prior to the beginning of the study, the Investigator must have the IRB/IECs written approval/favourable opinion of the written ICF and any other information to be provided to the patients. Before being enrolled in the clinical study, patients must consent to participate after the nature, scope, and possible consequences of the study have been explained in a form understandable to them. An informed consent document that includes both information about the study and the consent form will be prepared and given to the subject. This document will contain all the elements required by the GCP guideline ICH E6 and any additional elements required by local regulations. The document must be in a language understandable to the subject.

Patients are free to withdraw from the study at any time during the study period without stating any reason. In the event if the Principal Investigator received any new information from the Sponsor which may significantly affect the subject's risk to continue the study, the same information shall be shared with patients and re-consent shall be taken from the patients.

Two copies of the ICF are signed: one copy of the signed consent document must be given to the patient. The original signed consent document will be retained by the Investigator.

The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

Inclusion in the study will occur only if the subject gives written informed consent. It is the responsibility of the investigator / designee to obtain written informed consent after adequate presentation of aims, methods, anticipated benefits, and potential hazards of the study. The written informed consent document will be translated into the local language or a language understood by the subjects. If needed, the person will be given time to discuss the information received with members of the community or family before deciding to consent.

If the subject is illiterate, a literate impartial witness must sign (this person should have no connection to the research team, and, if possible, should be selected by the participant).

If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All subjects should be informed of the new information, given a copy of the revised form, and will need to give their consent in order to continue in the study.

21.4. Subject protection procedures

21.4.1. Procedures in the event of Emergency

Each subject will be given an emergency card with the details of his participation in the study and the contact details of the investigator. Subjects will be instructed to contact immediately the investigator in case of emergency.

21.4.2. Subject data protection

Subject names will not be supplied to the Sponsor nor to unauthorized parties. Only the subject number will be recorded in the CRF, and if the subject name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to the Sponsor.

All laboratory specimens, evaluation forms and reports will only be identified by a coded number. All records will be kept in a locked file cabinet in the clinical research unit. All computer entry and networking programs will only be processed with coded numbers. Clinical information will not be released without the written permission of the patient.

Study subjects may have the right to access, and make a copy of their medical and/or clinical study records as allowed by applicable privacy laws. Subjects may ask to see their records by requesting such records from the study doctor or the facility(ies) where the study is being conducted. However, to ensure the valid results of the study, subjects may not be able to review or make a copy of some of the records related to the study until after the study has been completed.

The investigator should keep a subject enrolment list showing codes, names, and addresses. The investigator should maintain documents for submission to sponsor authorized representative, and subjects' signed written consent forms, in strict confidence.

21.5. Other Ethical aspects of the study

The experimental protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki (see Appendix III) and ICH (International Committee for Harmonization) guidelines for Good Clinical Practice. DNDi assures that it will comply with all applicable state, local and foreign laws for protecting the rights and welfare of human subjects. This protocol and any protocol amendments will be reviewed / approved by an IEC before its implementation.

21.5.1. Ethical aspects of subject inclusion and study procedures

Subjects participating in this study may experience discomfort during examination and blood sampling, in particular for intensive PK analyses. To minimize discomfort, phlebotomy personnel should be trained or experienced in drawing blood.

The total volume of blood drawn is mentioned in the participant information sheet and informed consent form.

21.5.2. Subject Reimbursement Fee

Patients will be reimbursed for travel to and from the study site but will not receive any payment for trial participation. Any medication that is required during the trial period will be provided according to the national programs and patients referred accordingly for care.

22. Insurance and Liability

DNDi is insured to indemnify the investigator against any claim for damages brought by a research subject who suffers from a research related injury during the performance of the trial according to the protocol.

23. Publication policy

The clinical trial will be registered in the clinicaltrial.gov database by DNDi.

Before publication, all study results are considered confidential and shall not be made available to any third party by any member of the investigating team without an appropriate confidentiality agreement and/or written authorization of the sponsor. It is anticipated that the results of this trial will be of sufficient medical importance to warrant publication(s) in an international peer-reviewed journal, and/or presentations at scientific meetings.

In accord with standard editorial and ethical practice, the sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. DNDi as sponsor will render all necessary assistance to the investigators to ensure this occurs in a timely manner.

No publication of any data, results, other deliverables or records is permitted by any Service Provider providing services related to the study protocol or by the Investigators or research staff involved in

performing this study without a written approval from the Sponsor. Authorship will be determined by mutual agreement between the sponsor and the principal investigators according to DNDi policy WT07.

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25. Appendices

Appendix I: Name and title of the Investigators who are responsible for conducting the trial, and the address and telephone number(s) of the trial site(s)

For Malaysia

National Coordinating Investigator

[redacted]
Selayang Hospital
Lebuhraya Selayang-Kepong
68100 Batu Caves
Selangor, Malaysia
[redacted]

Site Principal Investigators

Site Number	Study Site	Site Principal Investigator
01	Hospital Selayang Departement of Hepatology Lebuhraya Selayang-Kepong 68100 Batu Caves, Selangor Darul Ehsan	[redacted]
02	Hospital Sungai Buloh Department of Medicine/Infectious Disease Jalan Hospital 47000 Sungai Buloh, Selangor Darul Ehsan	[redacted]
03	Hospital Ampang Department of Medicine / Gastroenterology Jalan Mewah Utara, Taman Pandan Mewah, 68000 Ampang Jaya, Selangor Darul Ehsan	[redacted]
04	Hospital Sultanah Bahiyah Department of Medicine/Gastroenterology KM 6, Jalan Langgar 05460, Alor Setar, Kedah	[redacted]
05 *(stage 1 only)*	Hospital Tengku Ampuan Afzan Hospital Department of Medicine / Gastroenterology Jalan Tanah Putih 25100, Kuantan, Pahang	[redacted]
06 *(stage 1 only)*	University Malaya Medical Centre Department of Medicine / Gastroenterology Lembah Pantai 59100 Kuala Lumpur	[redacted]
12 *(stage 2 only)*	Hospital Raja Perempuan Zainab II 15586, Jalan Hospital, Bandar Kota Bharu 15200 Kota Bharu, Kelantan	[redacted]
13 *(stage 2 only)*	Hospital Sultanah Aminah Department of Medicine Jalan Abu Bakar 80000, Johor Bahru, Johor	[redacted]

14 *(stage 2 only)*	Hospital Sultanah Nur Zahirah Department of Hepatology/Gastroenterology Jalan Sultan Mahmud, 20400 Kuala Terengganu, Terengganu	[redacted]

For Thailand

National Coordinating Investigators

Stage 1: [redacted]
Department of Disease Control
Ministry of Public Health
Tivanont Road, Muang
Nonthaburi 11000, Thailand

Stage 2: [redacted]
Department of Internal Medicine
Chiang Mai Hospital, Faculty of Medicine
Chiang Mai University
Muang, Chiang Mai 50200, Thailand

National Regulatory Advisors

[redacted]
Director Office of Diseases Prevention and Control, 1 Chiang Mai.
447 Lamphun Rd. Watgeth sub-district, Muang, Chiangmai 50000, Thailand

[redacted]
Department of Disease Control
Ministry of Public Health
Tivanont Road, Muang
Nonthaburi 11000, Thailand

[redacted]
Director of Bureau of AIDS, TB and STIs.
Bureau of AIDS, TB and STIs, Department of Disease Control Ministry of Public Health
Tivanont Road, Muang
Nonthaburi 11000 Thailand

[redacted]
Department of Disease Control
Ministry of Public Health
Tivanont Road, Muang
Nonthaburi 11000 Thailand

[redacted]
Bureau of AIDS, TB and STIs, Department of Disease Control Ministry of Public Health
Tivanont Road, Muang
Nonthaburi 11000 Thailand

Site Principal Investigators

Site Number	Study Site	Site Principal Investigator
07	Gastroenterology unit, Department of Internal Medicine, Maharaj Nakorn Chiang Mai Hospital, Faculty of Medicine, Chiang Mai University Muang, Chiang Mai 50200, Thailand	[redacted]
08	Internal Medicine unit, Medical Department, Nakornping Hospital, 159 M.10 Chotana Rd., T. Don Keaw, Mae Rim, Chiang Mai 50180, Thailand	[redacted]
09	Internal Medicine, Bamrasnaradura Infectious Diseases Institute, 38, Tiwanon 14, Talat Khwan, Muang, Nonthaburi, 11000, Thailand	[redacted]
10	King Chulalongkorn Memorial Hospital/HIV-NAT, Faculty of Medicine, Chulalongkorn University 1873 Rama IV Road, Pathum Wan, Bangkok, 10330, Thailand	[redacted]

Appendix II: DAIDS Grading Tables for Adverse Events version 2.0 / November 2014

DAIDS_AE_Grading_
Table_v2_NOV2014.p

Appendix III: Declaration of Helsinki

World Medical Association - Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of

research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable

group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix IV: Changes introduced in protocol version

From the initial approved protocol to the 4th amendment, there were two different versions of Protocol: one for Malaysia sites and one for Thailand sites but with the same content. The only changes were administrative (site details).

Amendment number	Release date	Purpose of amendment (key changes)
Initial approved protocol Malaysia: version 3.1 Thailand: version 3.2	 28 Jul 2016 31 Oct 2016	Not applicable (initial approved protocol)
1st Amendment to the protocol Malaysia: version 4.1 amendment 1 Thailand: version 4.1	 10 Apr 2017 10 Apr 2017	Synopsis; secondary objective added: To evaluate the presence of RAVs to RDV-SOF in subjects with failure to achieve SVR12 and their persistence until 1 year after treatment cessation or the initiation of an alternative HCV therapy. Section 4.4.2; exclusion criteria added: Corticosteroid used to treat any medical condition are allowed if systemic for not more than 2 weeks or if topical. QTcF value (Fridericia method to be used) Use of medications associated with QT prolongation must be excluded except - commonly used and essential medications for this study population like methadone and/or efavirenz is allowed as long as QTcF value <450 milliseconds. Section 4.4.4; subject withdrawal & drop-out, procedures for handling withdrawal added, and study duration changed Section 5.6; assessment of efficacy updated: For HCV viral load assessment, Hospital Kuala Lumpur microbiology department, the central reference study laboratory, uses COBAS® AmpliPrep/COBAS® Taqman Hepatitis C Virus Quantitative test version 2.0 is a nucleic acid amplification test for the quantitation of HCV RNA in human serum or Ethylenediaminetetraacetic acid plasma. Specimen preparation is automated using the COBAS® Ampliprep Instrument with amplification and detection automated using the COBAS® Taqman Analyzer or the COBAS® Taqman Analyzer. Section 5.7; assessment of safety changed: Incidence of AEs, and laboratory abnormalities during the observation period, i.e. from signature of informed consent to 24 weeks after end of treatment;

Amendment number	Release date	Purpose of amendment (key changes)
		Incidence of SAEs from signature of informed consent to 24 weeks after end of treatment; Incidence of Grade 3-4 clinical and laboratory AEs through 24 weeks after the end of treatment. Section 7.1; schedule of visits and study assessments for non-cirrhotic subjects changed: Treatment Visit Week 12 (End of Treatment or premature discontinuation) ± 7 days (added in study procedure: 12 leads ECG) Follow up Week 12 (-1 day and +28 days) (added in study procedure: CD4 Count) Follow up Week 24 (-3 days and +28 days) (added in study procedures: Symptom directed assessment, HCV RNA, Stored Plasma and dried blood spots (DBS), Chemistries (liver function test [LFT], Bili-D/ID, ALT/ AST, Serum Creatinine (not required for SVR24 only), Coagulation Markers (INR). Section 7.2; schedule of visits and study assessments schedule of events for cirrhotic subjects changed: Treatment Visit Week 24 (end of Treatment Premature discontinuation) ± 7 days (added in study procedure: 12 leads ECG) Follow up Week 12 (-1 days and +28 days) (added in study procedure: CD4 Count) Follow up Week 24 (-3 day and +28 days) (added in study procedures: Symptom directed assessment and Child Pugh Scores, HCV RNA, CD4 Count, Stored Plasma and DBS, Chemistries (LFT, Bili-D/ID, ALT/ AST, Serum Creatinine (not required for SVR24 only), Coagulation Markers (INR). Section 9.2.7. planned interim analysis changed: The interim analysis will proceed in two steps: Step 1: Assessing if the response rate in the most difficult to treat population of subjects infected by Genotype 3 with cirrhosis (Genotype 3-F4; approximately 50 subjects), is similar to the response rate in the rest of the population (non-Genotype 3-F4; approximately 250 subjects). Step 2: Deciding if the study should proceed as planned with the enrolment of 300 more subjects to receive RDV-SOF, or should be amended to allow comparison with a potent pan-genotypic reference regimen, like SOF + daclatasvir or SOF/velpatasvir.
2nd Amendment to the protocol		Synopsis; study period updated: Planned date of last visit completed for interim analysis: SVR4: July 2017, SVR12: November 2017

Amendment number	Release date	Purpose of amendment (key changes)
Malaysia: version 4.1 amendment 2 Thailand: version 4.2	29 May 2017 29 May 2017	Planned enrolment restart after interim analysis: December 2017 Planned enrolment duration for the second stage of the study: Up to 6 months Planned date of last visit completed: March 2019 Final report: June 2019 Sections 7.1 and 7.2; schedule of events for cirrhotic and non-cirrhotic subjects updated: Added 'X' in Follow up Week 24 in Conc. Medication Review and AE review 4 FibroScan will be conducted only at screening visit or baseline FibroScan within 12 months to screening maybe use to assign treatment duration. 6 Will be performed on stored samples if SVR12 is not achieved or on any subject at any time if needed sequencing will be performed on all positive RNA results 6a Will be performed on stored samples for all subjects Section 7.2.6, text added: During the Week 4 post-treatment visit (SVR4), HCV viral load will be performed for all the subjects on stored plasma. During the Week 12 post-treatment visit (SVR12), HCV viral load will be performed for all the subject on plasma taken during the visit.
3rd Amendment to the protocol Malaysia: version 4.2 amendment 3 Thailand: version 4.3	05 Oct 2017 05 Oct 2017	Synopsis, and Section 3.1; primary and secondary objectives updated: o Primary Objective To assess the efficacy of 12 weeks RDV-SOF in subjects with chronic HCV infection and no cirrhosis (Metavir F0 to F3), and of 24 weeks RDV-SOF in subjects with compensated cirrhosis (Metavir F4 and CTP Class A) at 12 weeks after the end of study treatment. o Secondary Objective To assess the efficacy of 12 weeks RDV-SOF in subjects with chronic HCV infection and no cirrhosis and 24 weeks RDV-SOF in subjects with compensated cirrhosis at 4 and 24 weeks after the end of study treatment. Synopsis, Section 9.1, and Section 9.2.3 Strategic transformation of the market of HCV treatments (STORM-C)-1 Stage 1 was intended to give a clear indication of likely real world effectiveness, where some sub-groups of HCV patients are more difficult to cure than others, i.e. subjects with cirrhosis (particularly when infected with Genotype 3 virus), HIV co-infection or those who have failed previous treatment. Within these categories, only subjects with decompensated cirrhosis and those with prior treatment

Amendment number	Release date	Purpose of amendment (key changes)
		with an NS5A inhibitor were excluded. No restrictions were imposed on the number of subjects in each sub-group and subjects belonging to more than one of the difficult to treat categories were enrolled. Therefore, the efficacy in this study was not expected to reach the levels that could be achieved in studies with much tighter inclusion criteria. Based on published results for other treatments, it was considered that the overall SVR12 rate should be superior to 85% instead of the original 90% and an amendment was submitted accordingly (protocol v4.2, 05-October-2017 amendment 3). This 85% cut off point is also in line with a WHO publication that describes the ideal HCV treatment as having efficacy ≥85% in all populations in a public health setting. Throughout the protocol; The addition of and explanation of Stage 2, including an additional explanation of Stage 2 statistical analysis Section 5.6; Assessment of efficacy updated: o Sustained Virologic Response 4 weeks and 24 weeks after end of Study Drug Treatment (SVR4 and SVR24) will be evaluated in order to provide a comprehensive view of the time course of reduction in viral load
4th amendment to protocol Malaysia: version 5.1* version 6.0* Thailand: version 5.0	 04 Sep 2018 16 Nov 2018 20 Dec 2018	Sponsor: Ministry of Public Health Thailand was added on page 1. Protocol synopsis and study timelines section 4.4: The study timelines are revised Protocol synopsis and 3.2 secondary objectives: o Secondary Objective To evaluate the presence of viral resistance-associated variants (RAVs) to SOFRDV at the time of failure or at first point after failure when viral load is sufficient to get a positive result in patients with virological failure and their persistence until 1 year after treatment cessation or the initiation of an alternative HCV therapy. Protocol synopsis and 3.3 exploratory objectives: o Exploratory objective To evaluate the effect of drug use, as determined by hair analysis on safety and efficacy (Stage 1 only) To assess the occurrence of drug use in virological failures (both stages) Protocol synopsis: Planned number of patients: % of cirrhotic patients: Previous wording: the study population will comprise up to 30% subjects with compensated cirrhosis.

Amendment number	Release date	Purpose of amendment (key changes)
		New wording: In Stage 1, the study population included 27% subjects with compensated cirrhosis. In Stage 2, the study population will include a minimum of 50% of subjects with compensated cirrhosis. Eligibility: "with mild to compensated cirrhosis" was replaced by "with no or compensated cirrhosis". The patients with Metavir F0 have always been eligible to the study Inclusion criteria: Inclusion criteria for drug users was reworded to better reflect the ones under methadone. Separate stratum for active drug users was reworded to say their data will not contribute in the primary intent to treat analysis. A specific set of bullet points for PWID, and another set for HCV-HIV co-infected patients were added. The content remains the change, only rewording occurred Exclusion criteria: The exclusion of Drug users was decided by Presidio. In Stage 1, DNDi found a compromise and created a separate exploratory stratum of the study to have access to their data if needed. In Stage 1, we have a discrepancy between CRF (which excludes IV drug users) and protocol (which excludes ALL active drug users). Decision was made to align protocol with CRF and exclude only IV drug users (which reflects the reality of what was done in Stage 1) Exclusion criteria for cardiovascular conditions was modified and 2 new criteria were added for patients' safety rewording for Where did you find the key changes QTcF value at baseline vs during study: Limit for QTcF value at baseline is <450 milliseconds. New addition: A QTcF value increase up to 500 milliseconds during study conduct is accepted (see pages 40 and 45). Synopsis: Primary Efficacy Endpoint: Wording was changed "In case of positive HCV RNA, HCV sequences at baseline and 12 weeks post treatment completion will be compared to rule out reinfection" was replaced by "For patients with quantifiable HCV RNA during the post-treatment period, HCV sequences at baseline and at time of first quantifiable HCV RNA or as soon thereafter as possible will be compared to distinguish between relapses and reinfections." Synopsis: efficacy analysis: Rewording on categorisation of failures and not failures. Clarification added for Stage 2 analysis

Amendment number	Release date	Purpose of amendment (key changes)
*The difference between protocol version 5.1 and version 6.0 for Malaysia is the clarification of the inclusion criteria regarding the evidence of chronic HCV infection (section 5.1.1). Schedules of events (section 7.1, footnote #6 and section 7.2 – footnote #7) have been updated accordingly. Both protocol version 5.1 and version 6.0 for Malaysia have been approved. No patient has been recruited under protocol 5.1.		
5th amendment to the protocol version 7.0 (applicable for Malaysia and Thailand)	30 Aug 2019	Main reason of this amendment is to unify the protocols for Malaysia and for Thailand in order to have one common protocol applicable for both Malaysia and Thailand. Cover page and Appendix I: Clarification about National Coordinating Investigator in Thailand. Contact details: Addition of HCV genotying laboratory for Thailand. Section 4.4; study timelines: The study timelines are revised. Sections 5.2-5.3; Inclusion/Exclusion criteria: Harmonization between information Malaysia and Thailand. Protocol synopsis: Descriptive statistics as per section 16.2.3, DAIDS AE grading table as per Appendix II. Section 15; Assessment of safety: DAIDS AE grading table as per Appendix II. Appendix I: Harmonization between information for Malaysia and Thailand.
6th amendment to the protocol version 8.0 (applicable for Malaysia and Thailand)	18 Mar 2020	Cover page Modification of short title with the study acronym. Addition of National Science and Technology Development Agency (NSTDA) Thailand as co-sponsor (responsible for financing in Thailand only). Clarification of National Coordinating Investigator for Thailand during stage 1 and stage 2. Contact details Addition of co-sponsors (with responsibilities for each co-sponsor). Addition of structures responsible for local monitoring in both countries. Addition of structure responsible for statistics. Addition of structures responsible for HCV RNA analysis. Protocol synopsis

Amendment number	Release date	Purpose of amendment (key changes)
		Amended to be aligned with changes done in the protocol. Simplification of the wording and removal of duplicate information. Section 3: Study Objectives and Endpoints Addition of exploratory objective "To evaluate the change in HCV RNA values over time during the treatment period." Addition of study endpoints as per Statistical Analysis Plan used for interim analysis on stage 1 data. Section 4.3: Study duration and duration of subject participation Addition of Study duration for the subject. Update of Study duration stage 2 and long-term follow-up. Section 5: Selection of subjects Update of inclusion criteria for women of child bearing potential as per "Recommendations related to contraception and pregnancy testing in clinical trials" from Clinical Trial Facilitation Group (CTFG) dated 15-Sep-2014 for IMPs with possible human teratogenicity/fetotoxicity in early pregnancy. Rewriting of exclusion criteria for active injection drug user for stage 2 ("Self-reporting active injection drug use at screening (only for stage 2).") Section 8: Enrolment procedures Clarification on enrolment per subgroup during stage 1 and 2. Section 9.1: Description of study drug Addition of instructions in case patient vomits. Section 9.5: Contraception methods Update of contraception methods for women of child bearing potential as per "Recommendations related to contraception and pregnancy testing in clinical trials" from Clinical Trial Facilitation Group (CTFG) dated 15-Sep-2014 for IMPs with possible human teratogenicity/fetotoxicity in early pregnancy. Section 9.7: Discontinuation and interruption of treatment Clarification on rechallenge of subjects with significant ALT/AST elevations as per FDA guidelines. Section 10.9: Hair sampling Clarification on use of hair sampling and measures to maintain confidentiality of information. Section 11: Assessment of efficacy Addition of table with Assay (Machine) used for HCV RNA and lower limit of quantification.

Amendment number	Release date	Purpose of amendment (key changes)
		Section 15.2.2: Adverse Event reporting processes Clarifications on events to be reported. Section 16.2: Statistical Analysis Clarifications on interim and final analysis. Section 18: Adjudications Committees Addition of clinical adjudication committee and virology adjudication committee. Appendices Addition of 2 new sites in Malaysia in Appendix I (Name and title of the Investigators who are responsible for conducting the trial). Addition of appendix III (Declaration of Helsinki). Addition of appendix IV (Changes introduced in protocol version).