Clinical Trial Protocol

A Drug Interaction Study to Assess the Pharmacokinetics of Narlaprevir and Antiretroviral Drugs

Product / formulation:	Narlaprevir (J05013, Arlansa®), 100 mg tablets
Indication:	Treatment of HCV
Sponsor:	R-Pharm JSC, Russia
	Legal address:
	19 build. 1, Berzarina str., 123154, Moscow, Russia
	Mailing address:
	111Б, Leninsky prosp. 119421, Moscow, Russia
Protocol Number:	CJ05013019
Phase:	Phase I
Version of protocol:	Version 8.0 (Incorporated Amendment #5)
Date:	20 February 2017

Confidentiality Statement

This document is a confidential communication of R-Pharm JSC. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained within will be published or disclosed without prior written approval, except that this document may be disclosed to the appropriate ethics committee and regulatory authority under the condition that they are requested to keep it confidential.

1 ADMINISTRATIVE INFORMATION

1.1 Protocol approval and signatures

Hereby I confirm that the Protocol CJ05013019: "A Drug Interaction Study to Assess the Pharmacokinetics of Narlaprevir and Antiretroviral Drugs" is created in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

Mikhail Samsonov, MD, PhD

Chief Medical Officer,

"R-Pharm" JSC

_____

Date / Signature

Emilia Krasavina, MD

Scientific Advisor

"R-Pharm" JSC

_____

Date / Signature

1.2 Investigator Agreement

This protocol CJ05013019 “A Drug Interaction Study to Assess the Pharmacokinetics of Narlaprevir and Antiretroviral Drugs” is a confidential communication of R Pharm.

I confirm that I have read this protocol, I understand it, and I will work according to this protocol.

I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCPs and the applicable laws and regulations.

Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from R Pharm.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Investigator name: _____

Date / Signature

Center name and address

1.3 Trial contact list

1) Sponsor: R-Pharm JSC

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4) Central PK laboratory (ChromSystemsLab)

Name:	LLC Chromatography Systems Laboratory
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Email:	www.chromsystemslab.com, info@chromsystemslab.com

In case of emergency

For urgent medical advice Emilia Krasavina, Scientific Advisor on duty is available 24 h per day under the following:

Emergency number
Phone: [redacted]

For reporting of serious adverse events, please follow the procedures described in Section 7.7.2.2. The occurrence of SAEs will be notified by the Investigator to “Almedis” by fax or e-mail within 24 hours after becoming aware of their occurrence. The completed SAE form must be sent to the following number or address:

24 h SAE reporting
Fax: Number: +7 495 937 43 19
safety@almedis.ru

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

(S)AE	All Adverse Events, including Serious Adverse Events
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
AUC	Area Under the Concentration-time curve
AUC(tau)	Area under the concentration-time curve during a dosing interval τ at steady state
BID	Twice Daily
BMI	Body Mass Index
BP	Arterial blood pressure
BSA	Body Surface Area
CBC	Complete Blood Count
CCDS	Company Core Data Sheet
CD	Compact Disk
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F or CL	Apparent total body clearance or clearance
Cmax	Maximum observed plasma Concentration
Cmin	Minimum observed plasma Concentration
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTC	Clinical Trial Coordinator
CTD	Clinical Trial Directive
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
DRSP	Drosperinone
DSS	Drug Safety Surveillance; the Schering-Plough department responsible for the receipt, regulatory assessment, and, in the USA, reporting to FDA of all post marketing adverse events and all serious adverse events from clinical trials

ECG	Electrocardiogram
EDC	Electronic Data Capture
EU	European Union
FDA	Food and Drug Administration, USA
GCP	Good Clinical Practice
GCSP	Global Clinical Supply Planning
IATA	International Air Transport Association
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IMPQC	Investigational Medicinal Product Quality Complaint
IND	Investigational New Drug Application; legal instrument in the USA that allows study of unapproved, investigational new drugs in human subjects
Investigational Product	The drug, biologic, and/or device being investigated in the current trial
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit Of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
NA, N/A	Not applicable
PD	Pharmacodynamics
PDF	Portable Document Format
PK	Pharmacokinetics
PQC	Product Quality Complaint
QD	Once Daily
RBC	Red Blood Cell
RNA	Ribonucleic Acid
RSI	Reference Safety Information

SAE	Serious Adverse Event
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
t1/2	Terminal phase half-life
TEAE	Treatment-emergent adverse event
Tmax	Time to Maximum observed plasma concentration
User ID	User Identification
ULN	Upper limit of normal
V/F or V	Apparent volume of distribution
WBC	White Blood Cell

4 SYNOPSIS

Title of Study: A Drug Interaction Study to Assess the Pharmacokinetics of Narlaprevir and Antiretroviral Drugs (Protocol No. CJ05013019)	
Abbreviated Title: Drug interaction study for narlaprevir	
Study Centers: 1-2	
Protocol Type: Clinical Pharmacology	**Clinical Project Phase:** 1
Overview This will be a two-part study conducted in healthy adult subjects in compliance with Good Clinical Practices.	
Study Duration: 8 -12 months	
Purpose: The study purpose is to evaluate the potential for a pharmacokinetic drug-drug interaction, safety and tolerability when narlaprevir, ritonavir (used as a metabolic inhibitor) and tenofovir dizoproxil fumarate (part 1) and narlaprevir, ritonavir and raltegravir (part 2) are administered in combination to healthy volunteers **Objectives:** **Part 1** **Primary Objective** To evaluate the pharmacokinetic (PK) drug-drug interaction between narlaprevir/ritonavir and tenofovir (disoproxil fumarate) in healthy subjects. **Secondary Objective(s)** To evaluate the safety and tolerability of narlaprevir/ritonavir when coadministered with tenofovir in healthy subjects. **Part 2** **Primary Objective** To evaluate the PK drug-drug interaction between narlaprevir/ritonavir and raltegravir in healthy subjects. **Secondary Objective(s)** To evaluate the safety and tolerability of narlaprevir/ritonavir when coadministered with raltegravir in healthy subjects.	
Rationale: **a) Therapeutic Rationale:** Approximately 50% of patients infected with the hepatitis C virus	

(HCV) fail to respond to pegylated interferon/ribavirin combination therapy. Most of these nonresponders are infected with the more difficult to treat HCV genotype 1. Thus, there an urgent unmet medical need remains to offer new therapies that may eradicate HCV infection and prevent the serious sequelae (cirrhosis, hepatocellular carcinoma, liver failure and transplant) associated with persistent infection. Narlaprevir is a potent, orally administered, serine protease inhibitor specifically designed to inhibit the HCV NS3 (non structural protein 3) protease, preventing cleavage of the HCV polyprotein into functional viral proteins, thereby inhibiting viral replication in infected host cells. HCV NS3 protease inhibitors, combined with peginterferon/ribavirin have been shown to be an effective method for treating HCV.

b) Study Conduct Rationale: In vitro data show that narlaprevir is metabolized by CYP3A4, and there is some evidence of CYP enzyme induction preclinically and CYP3A4 inhibition in human liver microsomes. However, a clinical study of high dose narlaprevir with midazolam showed no clinically relevant effect of narlaprevir on midazolam PK, indicating no relevant induction/inhibition of CYP3A4 by narlaprevir. In vivo, narlaprevir is a sensitive CYP3A4 substrate and co-administration with ritonavir markedly increases narlaprevir exposure. In addition, in vitro data suggest narlaprevir is a P-gp substrate. Narlaprevir is being developed to be part of a therapeutic regimen that includes ritonavir, a metabolic inhibitor of CYP3A4, to boost the concentration of narlaprevir. This drug interaction study is designed to investigate pharmacokinetic drug-drug interactions between narlaprevir coadministered with ritonavir and antiretroviral drugs (tenofovir disoproxil fumarate and raltegravir) for labeling and clinical dosing guidance purposes.

c) Study Design Rationale: The current protocol includes 2 parts and additional parts may be added on an ongoing basis.

Part 1

Part 1 of the study is being conducted to evaluate the pharmacokinetic effect of coadministration of narlaprevir with ritonavir and tenofovir, as the drugs may be used concomitantly to treat HCV/HIV coinfection. Tenofovir disoproxil fumarate is the oral prodrug of tenofovir, a nucleotide reverse transcriptase inhibitor used in the treatment of HIV and hepatitis B. Tenofovir disoproxil fumarate is rapidly absorbed and converted in the plasma to tenofovir; tenofovir is largely eliminated unchanged through renal excretion.

P-glycoprotein (P-gp) is thought to mediate tenofovir disoproxil fumarate absorption from the intestine, as tenofovir disoproxil fumarate efflux has been decreased by several inhibitors including cyclosporin A [1]. As a clinical correlate, HIV protease inhibitors, often coadministered with tenofovir disoproxil fumarate, have variably increased tenofovir plasma concentrations based on their ability to inhibit P-gp mediated efflux, induce P-gp expression and inhibit tenofovir disoproxil fumarate hydrolysis at the level of the intestine [1]. In addition, other transporters are thought to participate in the renal elimination of tenofovir; tenofovir is a substrate for both human organic anion transporters 1 and 3 (hOAT1 and hOAT3) and inhibition of either transporter may alter plasma concentrations of tenofovir and decrease elimination.

Narlaprevir has been shown to be a P-gp substrate; it is unknown whether it is a P-gp inhibitor/inducer or alters hOAT1 and hOAT3 activity. Thus it is unknown whether narlaprevir could affect tenofovir exposure. As tenofovir disoproxil fumarate has affected HIV protease inhibitor (PI) drug absorption [1] and these PIs are peptidomimetics similar to narlaprevir, there is also the

potential for tenofovir disoproxil fumarate to affect narlaprevir absorption and plasma concentrations. From the other side tenofovir disoproxil fumarate was widely studied with first generation HCV PIs boceprevir, telaprevir, simeprevir, and ritonavir-boosted paritaprevir. Non-significant changes in pharmacokinetic parameters were shown when tenofovir was co-administered with all of them. The most prominent tenofovir exposure changes were reported in combination with telaprevir (30% increase in AUC and Cmax), but these changes didn't lead to safety profile worsening. That is why no dose correction is recommended during concomitant use of tenofovir with telaprevir. Exposure of HCV PIs was not significantly affected by tenofovir in conducted drug-drug interaction studies.

This study is designed as a randomized 3-period crossover study and will assess if there is any effect of tenofovir disoproxil fumarate/tenofovir on the pharmacokinetics of narlaprevir and vice versa.

Part 2

Part 2 of the study is being conducted to evaluate the pharmacokinetic effect of coadministration of narlaprevir/ritonavir and raltegravir. A considerable percentage of HIV infected patients are also infected with HCV. HIV/HCV co-infected patients commonly use HIV and HCV medications simultaneously. Therefore, it is important to know whether drug-drug interactions occur when combining those treatments or not.

Raltegravir is an HIV integrase inhibitor. In clinical trials in healthy volunteers in the presence of ritonavir, raltegravir pharmacokinetics were just weakly affected and did not require dose adjustment [2]. In the presence of protease inhibitors (atazanavir and tenofovir) boosted by ritonavir pharmacokinetics of raltegravir changed differently: PK parameters increased in the presence of atazanavir (direct inhibitor of UDP-GT1A1) and decreased in the presence of tenofovir. In both cases it was not considered as clinically significant [2]. When drug-drug interactions were investigated with HCV PIs boceprevir, telaprevir and simeprevir exposure parameters of raltegravir were slightly increased (up to 30% in combination with telaprevir), while exposure of PIs was changed up to 11% (in combination with simeprevir). That is why combinations of raltegravir with HCV PIs were considered safe and recommended for use in standard dosage regimens in patients with HCV/HIV-coinfection.

Combined use of narlaprevir/ritonavir and raltegravir is not expected to lead to a major drug-drug interaction as raltegravir is not a CYP3A substrate and thus will not be affected by the inhibition of CYP3A by narlaprevir/ritonavir. Raltegravir is metabolized by UGT but narlaprevir is not known to influence UGT. However, recent data indicate that raltegravir is a P-gp substrate and narlaprevir is a substrate and a moderate inhibitor of P-gp in vitro.

This study is designed as a randomized 3-period crossover study and will assess if there is any effect of raltegravir on the pharmacokinetics of narlaprevir and vice versa.

Study Design:

Both parts: Randomized, 3-period crossover study.

Study Plan

Subjects will be screened within up to 28 days before dosing in this two-part study. Subjects will be admitted to the study center the evening before the first dose for baseline assessments to confirm eligibility.

Part 1

Subjects will participate in a randomized 3-period crossover study.

In Part 1 subjects will receive the following:

- Treatment A: narlaprevir 200 mg once daily + ritonavir 100 mg once daily orally for 5 days
- Treatment B: tenofovir disoproxil fumarate 300 mg once daily, orally for 5 days
- Treatment C: narlaprevir 200 mg once daily + ritonavir 100 mg once daily + tenofovir disoproxil fumarate 300 mg once daily, orally for 5 days

On Day 1 of the first period, subjects will be randomized to one of 3 treatment sequences (A/B/C, or B/C/A, or C/A/B) and receive the first dose. Every subject will receive only one treatment (A or B or C) in one Period.

All treatments will be administered following a standard breakfast. Subjects will be confined to the study center throughout treatment in each period. Following completion of study procedures for each treatment period, subjects will be released from the clinic. Subjects will return to start hospitalization for the next treatment period after a 7-14 days interval.

Blood samples for determination of narlaprevir, ritonavir trough, and tenofovir concentrations will be collected as specified in the Study Flow Chart. Urine samples will be collected to evaluate the amount of tenofovir excreted (Treatment B and C).

Safety assessments including vital signs, ECGs, and clinical laboratory tests will be performed, and adverse events will be recorded, throughout the study. Subjects will be discharged from the study upon completion of all study related procedures in Period 3.

Part 2

Subjects will participate in a randomized 3-period crossover study.

Subjects in Part 2 will receive the following:

- Treatment A: narlaprevir 200 mg once daily + ritonavir 100 mg once daily orally for 5 days
- Treatment B: raltegravir 400 mg twice daily, orally for 5 days
- Treatment C: narlaprevir 200 mg once daily + ritonavir 100 mg once daily + raltegravir 400 mg twice daily, orally for 5 days

On Day 1 of the first period, subjects will be randomized to one of 3 treatment sequences (A/B/C, or B/C/A, or C/A/B) and receive the first dose. Every subject will receive only one treatment (A or B or C) in one Period.

All treatments will be administered following a standard breakfast, evening dose of raltegravir will be administered after standard dinner. Subjects will be confined to the study center throughout

treatment in each period. Following completion of study procedures for each treatment period, subjects will be released from the clinic. After a 7-14 (maximum) days interval between dosing, subjects will return to start hospitalization for the next treatment period.

Blood samples for determination of narlaprevir, ritonavir trough, and raltegravir concentrations will be collected as specified in the Study Flow Chart.

Safety assessments including vital signs, ECGs, and clinical laboratory tests will be performed, and adverse events will be recorded, throughout the study. Subjects will be discharged from the study upon completion of all study related procedures in Period 3.

Sample Size Calculation:

Based on study P04986, the inter-subject variability (CV%) for narlaprevir (tablet) Cmax and AUC is estimated to be about 33%; the inter- subject variability (CV%) for narlaprevir Cmax and AUC when coadministered with ritonavir is estimated to be about 20%. Assuming the intra-subject variability (CV%) is about 70% of the inter, the intra-subject variability (CV%) for narlaprevir and narlaprevir coadministered with ritonavir Cmax and AUC is estimated to be about 23% and 14%, respectively.

Part 1

The sample size for Part 1 will be 18.

The intra-subject variability (CV%) for tenofovir is assumed approximately 20% (10-15% for AUC24h and 15-20% for Cmax) as a maximum value estimated from the published CIs, the expected difference is set to 0 (Ratio = 1.00).

The study with 18 subjects will detect an increase in exposure of 22% or a decrease of 18% between tenofovir coadministered with narlaprevir and ritonavir vs. tenofovir alone with 80% power and alpha=0.1 two sided.

The study with 18 subjects will detect an increase of 15% or a decrease of 13% exposure between narlaprevir coadministered with ritonavir and tenofovir vs. narlaprevir coadministered with ritonavir with 80% power and alpha=0.1 two sided..

Part 2

The sample size for Part 2 is 18.

For raltegravir, sample size calculations were based on intrasubject CV% of 45% for AUC12h and 60% for Cmax. CVs estimated from the published CIs are 35-50% for AUC and 40-70% for Cmax.

The study with 18 subjects will detect an increase of 55% or a decrease of 35% exposure (AUC) as well as detect an increase of 76% or a decrease of 43% Cmax between raltegravir coadministered with narlaprevir and ritonavir vs. raltegravir alone with 80% power and alpha=0.1 two sided.

The study with 18 subjects will detect an increase of 15% or a decrease of 13% exposure between narlaprevir coadministered with ritonavir and raltegravir vs. narlaprevir coadministered with ritonavir with 80% power and alpha=0.1 two sided..

So, it is planned that 36 subjects complete the study overall. In case of premature withdrawal

subjects will be replaced by volunteers from among the subjects who signed the informed consent form. Considering 50% drop-out rate maximum 54 subjects will be enrolled in the study.

Subject Replacement Strategy

In case of premature withdrawal subjects will be replaced by volunteers from among the subjects who signed the informed consent form. Subjects may be replaced at the discretion of the sponsor.

Randomization:

Both parts: Subjects will be randomized to one of the treatment sequences on Day 1 of Period 1, according to the computer generated randomization schedule.

Stratification:

Not applicable.

Type of Blinding

Not applicable

Inclusion Criteria:

The subject must meet **ALL** the criteria listed below for entry at baseline and at Days -1 and 1 before each treatment Period:

1. Subjects must be willing to give written informed consent for the trial and able to adhere to dose and visit schedules.

2. Subjects of either sex and of any race between the ages of 21 and 55 years (both parts), inclusive, having a Body Mass Index (BMI) between 18,5 and 30, inclusive. BMI = weight (kg)/height^2(m).

3. Volunteers should diagnosed as "healthy": no pathology of the gastrointestinal tract, liver, kidneys, cardiovascular system, central nervous system (previously carried out by standard clinical and lab tests which did not reveal the presence of any diseases. AST and ALT must not exceed the normal range; QTcB for men should be ≤ 450 ms and ≤ 470 ms for women, the interval PR should be ≤ 200 ms).

4. Vital sign measurements (taken after ~3 minutes in a supine or sitting position) must be within the following ranges:

a. systolic blood pressure, 100 – 130 mm Hg

b. diastolic blood pressure, 60 -90 mm Hg

c. pulse rate, 60-80 bpm

5. Female subjects must be:

a. postmenopausal (defined as 12 months with no menses; age > 40 years and with a FSH level of >40 u/mL).

b. surgically sterilized at least 3 months prior to baseline (e.g., documented hysterectomy or

tubal ligation).

6. Men must agree to use a medically accepted method of contraception (condom and spermicide) during the trial and for 3 months after stopping the medication.

Exclusion Criteria:

The subject will be excluded from entry if **ANY** of the criteria listed below are met at baseline:

1. Females with childbearing potential
2. Subjects who, in the opinion of the investigator, will not be able to participate optimally in the study.
3. Positive results for hepatitis B surface antigen, hepatitis C antibodies or HIV, positive RW results.
4. Allergic reactions in history;
5. Intolerance to medication;
6. Chronic disease of cardiovascular, bronchopulmonary, and/or neuroendocrinal systems, gastrointestinal, liver, pancreas, kidney and/or blood disease;
7. History or presence of impaired renal function, lactase deficiency, lactose intolerance, glucose-galactose malabsorption;
8. History of urinary obstruction or difficulty in voiding;
9. Gastrointestinal surgery in history (except of appendectomy);
10. Acute infections less than 4 weeks before participation in the study
11. Subjects with a medical history of osteopenia and/or osteoporosis.
12. Regular administration of any medicines less than 4 weeks before participation in the study
13. Administration of medicines with marked influence on hemodynamics, liver function et al (barbiturates, omeprazole, cimetidine et al) less than 30 days before participation in the study;
14. Blood donation (450 ml or more of blood or plasma) less than 2 months before participation in the study;
15. Intake of more than 10 units of alcohol in a week (1 unit of alcohol is equal to 0.5 L of beer, 200 mL of wine or 50 mL of spirits) or history of drug abuse or alcoholism;
16. Smoking of more than 10 cigarettes or equivalent tobacco use per day;
17. Participation in phase 1 clinical trial less than 3 months before participation in the study;
18. Positive screen for drugs abuse and drugs use.
19. Subjects with a medical history of psychiatric or personality disorders that in the opinion of the investigator and sponsor, affects the subject's ability to participate in the trial.

20. Subjects who are part of the study staff personnel or family members of the study staff personnel.

Subject Key Inclusion/Exclusion Criteria

Healthy adult male and female subjects will be selected for all Parts of the study.

Test Product, Dose, Mode of Administration

Oral administration will be used for all studying drugs.

Part 1

Treatment C: narlaprevir 200 mg once daily coadministered with ritonavir 100 mg once daily and tenofovir disoproxil fumarate 300 mg once daily for 5 days.

Part 2

Treatment C: narlaprevir 200 mg once daily coadministered with ritonavir 100 mg once daily and 400 mg raltegravir twice daily for 5 days.

Reference Therapy, Dose, Mode of Administration

Part 1

Treatment A: narlaprevir 200 mg once daily with ritonavir 100 mg once daily for 5 days;

Treatment B: tenofovir disoproxil fumarate 300 mg once daily for 5 days.

Part 2

Treatment A: narlaprevir 200 mg once daily with ritonavir 100 mg once daily for 5 days;

Treatment B: raltegravir 400 mg twice daily for 5 days.

Duration of Treatment

Part 1

Subjects will be treated with each of narlaprevir, ritonavir, and tenofovir disoproxil fumarate for 5 days on 3 separate occasions for a total of 15 days. Total treatment duration excluding wash out intervals is 15 days (total duration maximum 43 days).

Part 2

Subjects will be treated with each of narlaprevir, ritonavir, and raltegravir for 5 days on 3 separate occasions for a total of 15 days. Total treatment duration excluding wash out intervals is 15 days (total duration maximum 43 days).

Number of Sites and Patients

36 healthy volunteers in approximately 1-2 sites in Russia.

Criteria for Evaluation

PK

Part 1

The following PK parameters will be evaluated for narlaprevir on Day 5 on treatments A and C: Cmax, Tmax, Cmin and AUC (tau). Additionally, if data permit, t1/2, CL/F and V/F will be calculated. Plasma concentrations of narlaprevir metabolites may be analyzed.

Ritonavir pre-dose concentrations on Day 4 and Day 5 will be analyzed on treatments A and C.

Pre-dose concentrations of drugs will be analysed on Days 4-5 to check for steady state.

The following PK parameters will be evaluated for tenofovir on Day 5 on treatments B and C: Cmax, Tmax, Cmin and AUC (tau). Additionally, if data permit, t1/2, CL/F and V/F will be calculated. Urine concentrations of tenofovir may be analyzed.

Part 2

The following PK parameters will be evaluated for narlaprevir on Day 5 on treatments A and C: Cmax, Tmax, Cmin and AUC (tau). Additionally, if data permit, t1/2, CL/F and V/F will be calculated. Plasma concentrations of narlaprevir metabolites may be analyzed.

Ritonavir pre-dose concentrations on Day 4 and Day 5 on treatments A and C will be analyzed.

Pre-dose concentrations of drugs will be analysed on Days 4-5 to check for steady state.

The following PK parameters will be evaluated for raltegravir on Day 5 on treatments B and C: Cmax, Tmax, Cmin and AUC (tau). Additionally, if data permit, t1/2, CL/F and V/F will be calculated.

Safety

Vital signs, ECGs, and clinical laboratory tests will be performed, and adverse events recorded.

Efficacy Assessments / Variables:

Not applicable.

Statistical Methods

Safety

Adverse events will be tabulated by treatment group, body system organ class, and severity. ECGs and clinical safety laboratory values will be listed by date and time, values and changes from baseline will be tabulated using summary statistics. Vital signs will be listed by day and time.

PK

Mean plasma concentrations of narlaprevir along with the derived PK parameters will be summarized by treatment separately for each part (cohort).

The primary PK parameters for Parts 1-2 are narlaprevir Cmax and AUC. All data will be log-transformed before analysis. An ANOVA model with treatment, period, sequence treated as fixed effects and subject nested within sequence treated as random effect will be performed separately for each part. Estimates of the adjusted mean differences (test-reference) and corresponding 90% confidence intervals will be constructed using the estimates of intrasubject variability obtained from

the model. The resulting estimates will then be exponentiated to provide the adjusted geometric mean ratios for the untransformed parameters (test/reference) with the corresponding 90% CIs for the ratios.

In addition for Parts 1 and 2 tenofovir and raltegravir Cmax and AUC will also be analyzed.

Part 1

Log transformed Cmax and AUC for narlaprevir and tenofovir will be analyzed separately. For narlaprevir, the primary comparison will be treatment C vs. A; and for tenofovir the primary comparison will be treatment C vs. B.

Part 2

Log transformed Cmax and AUC for narlaprevir and raltegravir will be analyzed separately. For narlaprevir, the primary comparison will be treatment C vs. A; and for raltegravir the primary comparison will be treatment C vs. B.

Day and Visit Structure

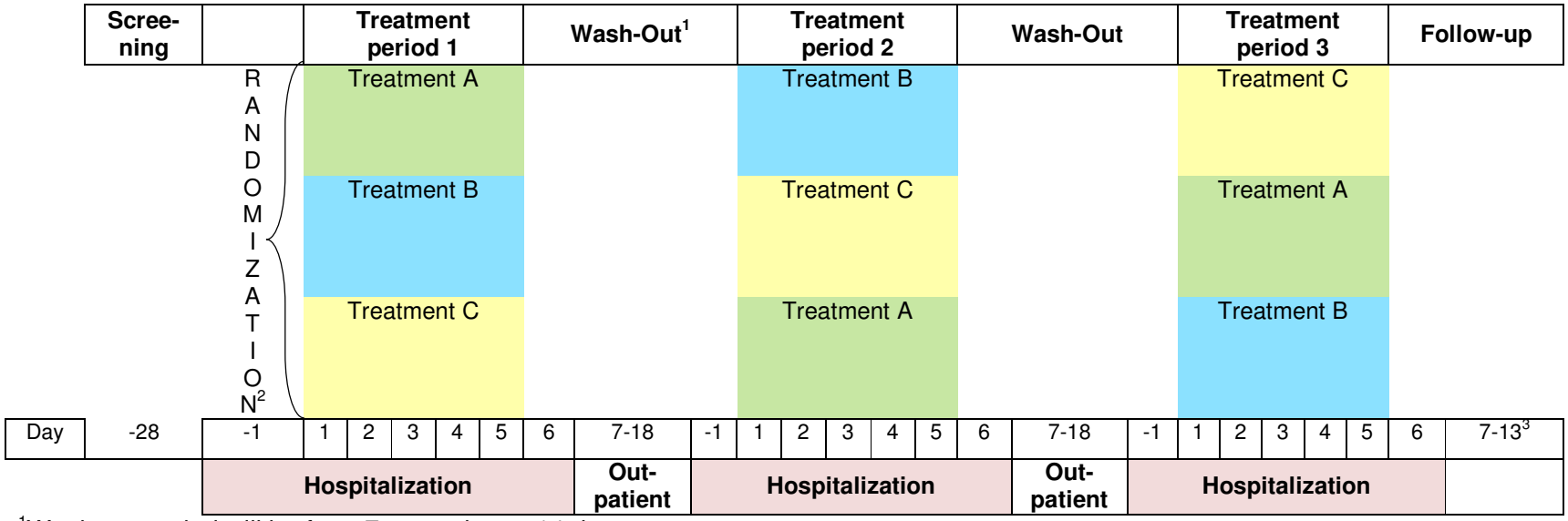
See **Section 4.2**, Study Flow Chart for further details.

Data Analysis:

Data analysis will be performed by the Central Laboratory and CRO designated by Sponsor in appropriate way described in the protocol.

4.1 Study Design Diagram

4.1.1 Part 1



[1]Wash-out period will be from 7 to maximum 14 days

[2]Randomization will be conducted at Day 1 before dispensing of study medication

[3]Phone call will be conducted at Day 11-13

Treatment Administration:

- Treatment A: narlaprevir 200 mg QD + ritonavir 100 mg QD, given orally for 5 days
- Treatment B: tenofovir disoproxil fumarate 300 mg QD, given orally for 5 days
- Treatment C: narlaprevir 200 mg QD + ritonavir 100 mg QD + tenofovir disoproxil fumarate 300 mg QD, given orally for 5 days

Every subject will receive one of 3 treatment sequences: (A/B/C, or B/C/A, or C/A/B). Only one treatment will be administered per period.

Dosing in each period must be separated by wash-out interval (from 7 to maximum 14 days).

4.1.2 Part 2

	Scree-ning		Treatment period 1						Wash-Out[1]		Treatment period 2						Wash-Out		Treatment period 3						Follow-up
		RANDOMIZATION[2]	Treatment A								Treatment B								Treatment C						
			Treatment B								Treatment C								Treatment A						
			Treatment C								Treatment A								Treatment B						
Day	-28	-1	1	2	3	4	5	6	7-18	-1	1	2	3	4	5	6	7-18	-1	1	2	3	4	5	6	7-13[3]
		Hospitalization							Out-patient	Hospitalization							Out-patient	Hospitalization							

[1]Wash-out period will be from 7 to maximum 14 days

[2]Randomization will be conducted at Day 1 before dispensing of study medication

[3]Phone call will be conducted at Day 11-13

Treatment Administration:

- Treatment A: narlaprevir 200 mg QD + ritonavir 100 mg QD, given orally for 5 days
- Treatment B: raltegravir 400 mg BID, given orally for 5 days
- Treatment C: narlaprevir 200 mg QD + ritonavir 100 mg QD + raltegravir 400 mg BID, given orally for 5 days

Every subject will receive one of 3 treatment sequences: (A/B/C, or B/C/A, or C/A/B). Only one treatment will be administered per period.

Dosing in each period must be separated by wash-out interval (from 7 to maximum 14 days).

4.2 Study Flow Chart

4.2.1 Part 1

Table 1 Study Flow Chart for Part 1 of the study

Day Relative to First Dose of Study Drug	**Screening**	**Period 1**							**Period 2**							**Period 3**							**FU visit (phone call)**
	Days -28 to -2	-1	1	2	3	4	5	6	-1	1	2	3	4	5	6	-1	1	2	3	4	5	6[g]	11-13
Informed consent form	x																						
Inclusion/ Exclusion Criteria	x	x	x						x[j]	x[j]						x[j]	x[j]						
Subject Identification card provided	x																						
Demographic Data	x																						
Medical History	x																						
Physical Exam	x	x						x	x						x	x						x	
Body height (cm) and Weight (kg)	x																						
BMI	x																						
HIV/ HBsAg/ HCV	x																						
Drug screen	x	x							x							x							
Laboratory tests[a]	x	x						x	x						x	x						x	
Screening number assignment	x																						
Randomization/ Treatment Number assignment			x																				
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG (12-lead)	x	x	x[h]					x	x	x[h]					x	x	x[h]					x	
Vital Signs (BP, Pulse rate, Body Temperature)	x	x	x[i]					x	x	x[i]					x	x	x[i]					x	
Treatment administration			x	x	x	x	x			x	x	x	x	x			x	x	x	x	x		
PK Blood Sampling																							
NVR PK blood sampling[b]						x	x	x					x	x	x					x	x	x	
Ritonavir PK blood sampling[c]						x	x						x	x						x	x		
Tenofovir PK blood sampling[d]						x	x	x					x	x	x					x	x	x	
PK Urine sampling																							
Tenofovir PK **Urine** sampling[e]							x	x						x	x						x	x	
Hospitalization[f]		x	x	x	x	x	x	x[f]	x	x	x	x	x	x	x[f]	x	x	x	x	x	x	x[f]	

BP – arterial blood pressure; ECG – electrocardiogram; HIV – human immunodeficiency virus; NVR – narlaprevir; PK – pharmacokinetic

a. Complete Blood Count (CBC), differential chemistry panel, and urinalysis collected in the fasted state (after an overnight fast for morning chemistry sample collections and at least 4 hours without food for other chemistry sample collections). Urinalysis will be performed at Screening only and results will not be captured in the CRF. On treatment days, blood samples should be drawn pre-dose.

b. Narlaprevir blood samples will be collected on Days 4 and 5: pre-dose (0 hr); and on Day 5 at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hrs post-dose (Treatments A and C).

c. A trough sample for ritonavir will be collected at 0 hr (predose) on Days 4 and 5 (Treatments A and C)

d. Tenofovir blood samples will be collected on Day 4 and Day 5: pre-dose (0 hr), and on Day 5 at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 18 and 24 hr post-dose (Treatments B and C).

e. Tenofovir urine samples will be collected on Day 5 in the following blocks: 0-6 hr, 6-12 hr, 12-18 hr, and 18-24 hr post-dose (Treatments B and C).

f. Subjects will be confined during the treatment period and released from the study unit after completion of all Day 6 study procedures.

g. Same procedures should be performed in case of premature determination of the study by any reason.

h. ECG to be recorded pre-dose at 0 (pre-dose) and in 4 hrs after dosing on Day 1 every period

i. Vital signs to be recorded at 0 (pre-dose), 1, 4 and 8 hrs after dosing on Day 1 every period.

j. During subsequent assessment subjects with increased hepatic transaminases not more than 1.5 ULN can be allowed, if the investigator will estimate these changes as clinically non-significant.

4.2.2 Part 2

Table 2 Study Flow Chart for Part 2 of the study

Day Relative to First Dose of Study Drug	**Screening**	**Period 1**							**Period 2**							**Period 3**							**FU visit (phone call)**
	Days -28 to -2	-1	1	2	3	4	5	6	-1	1	2	3	4	5	6	-1	1	2	3	4	5	6[f]	11-13
Informed consent form	x																						
Inclusion/ Exclusion Criteria	x	x	x						x[j]	x[j]						x[j]	x[j]						
Subject Identification card provided	x																						
Demographic Data	x																						
Medical History	x																						
Physical Exam	x	x						x	x						x	x						x	
Body height (cm) and Weight (kg)	x																						
BMI	x																						
HIV/ HBsAg/ HCV	x																						
Drug screen	x	x							x							x							
Laboratory tests[a]	x	x						x	x						x	x						x	
Screening number assignment	x																						
Randomization/ Treatment Number assignment			x																				
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG (12-lead)	x	x	x[g]					x	x	x[g]					x	x	x[g]					x	
Vital Signs (BP, Pulse rate, Body Temperature)	x	x	x[h]					x	x	x[h]					x	x	x[h]					x	
Treatment administration			x	x	x	x	x			x	x	x	x	x			x	x	x	x	x		
PK Blood Sampling																							
NVR PK blood sampling[b]						x	x	x					x	x	x					x	x	x	
Ritonavir PK blood sampling[c]						x	x						x	x						x	x		
Raltegravir PK blood sampling[d]						x	x	x					x	x	x					x	x	x	

Hospitalization[e]		x	x	x	x	x	x	x[e]	x	x	x	x	x	x	x[e]	x	x	x	x	x	x	x[e]	

BP – arterial blood pressure; ECG – electrocardiogram; HIV – human immunodeficiency virus; NVR – narlaprevir; PK – pharmacokinetic

a. Complete Blood Count (CBC), differential chemistry panel, and urinalysis collected in the fasted state (after an overnight fast for morning chemistry sample collections and at least 4 hours without food for other chemistry sample collections). Urinalysis will be performed at Screening only and results will not be captured in the CRF. On treatment days, blood samples should be drawn pre-dose.

b. Narlaprevir blood samples will be collected on Days 4 and 5: pre-dose (0 hr); and on Day 5 at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hrs post-dose (Treatments A and C).

c. A trough sample for ritonavir will be collected a 0 hr (predose) on Days 4 and 5 (Treatments A and C)

d. Raltegravir blood samples will be collected on Days 4 and Day 5: pre-dose (0 hr), and on Day 5 at 0.5, 1, 2, 3, 4, 6, 8, 12 hr post-dose (Treatments B and C).

e. Subjects will be confined during the treatment period and released from the study unit after completion of all Day 6 study procedures.

f. Same procedures should be performed in case of premature determination of the study by any reason.

g. ECG to be recorded pre-dose at 0 (pre-dose) and in 4 hrs after dosing on Day 1 every period

h. Vital signs to be recorded at 0 (pre-dose), 1, 4 and 8 hrs after dosing on Day 1 every period.

j. During subsequent assessment subjects with increased hepatic transaminases not more than 1.5 ULN can be allowed, if the investigator will estimate these changes as clinically non-significant.

Amendment #5

Amendment rationale

The following specification was made in the study protocol:

- Trade name of narlaprevir (Arlansa®) was added to the narlaprevir description.
- Tenofovir disoproxil fumarate manufactured by Gilead Sciences, Inc was replaced with tenofovir disoproxil fumarate (Tenofovir-TL) manufactured by LTD "Drugs Tehnology".
- Information on assessment of hepatic transaminase was added.

Ethical approval

Before implementing this protocol version with Incorporated Amendment #4 it must be reviewed and approved by Health Authorities and Independent Ethics Committee (IECs). In addition the changes herein affect the Informed Consent and the sites are required to update and submit for approval a revised Informed Consent Form that takes into account the changes made in this amended protocol. A signed and dated statement that the protocol, informed consent and other documents have been approved by the IEC must be given to the company-sponsor or it's designee before implementation.

5 INTRODUCTION

5.1 Background

Narlaprevir is a potent, orally administered, serine protease inhibitor specifically designed to inhibit the HCV NS3 (non structural protein 3) protease, preventing cleavage of the HCV polyprotein into functional viral proteins, thereby inhibiting viral replication in infected host cells. Boceprevir and telaprevir are first in class HCV NS3 protease inhibitors that are precursors to Narlaprevir. Combination of boceprevir or telaprevir with pegylated interferon and ribavirin now is not recommended for using due to serious side effects. There remains an unmet medical need to offer new therapies that may eradicate HCV infection and prevent the serious sequelae (cirrhosis, hepatocellular carcinoma, liver failure and transplant) associated with chronic infection.

Narlaprevir was found to be orally bioavailable in pharmacokinetic (PK) studies in animals, including rats, dogs, and monkeys. Following intravenous (IV) administration, narlaprevir is cleared rapidly from plasma with mean effective terminal phase half-life ($t_{1/2}$) values ranging from 0.55 hour to 1.5 hours across species. Narlaprevir interconverts to an inactive diastereomer (SCH 782832) in plasma. The SCH 782832: narlaprevir exposure ratios are species-specific. Cytochrome P450 isoenzyme 3A4 (CYP3A4) is primarily responsible for metabolizing narlaprevir and SCH 782832 into oxidative metabolites [8].

The nonclinical safety profile of narlaprevir has been characterized in a series of toxicology studies, which includes single- and repeated-dose studies (in mice, rats, and dogs), genotoxicity studies, and an in vitro osmotic fragility assay. Other toxicity studies include the evaluation of different formulations, the use of ritonavir (ritonavir) as a means of potentially increasing exposure, an embryo-fetal development studies in rabbits and rats, as well as a number of safety pharmacology assessments in a core battery of systems. Longer-term studies conducted to date included durations from 1 month to 9 months in mice, rats, or dogs. Based on the limited number of preclinical findings identified that tend to be minimal and/or species-specific in nature and/or clinically monitorable, it was recommended that clinical studies with narlaprevir continue.

To date (October 31, 2016) the Phase 1 clinical pharmacology program currently consists of ten completed studies (P04694, P04695, P04959, P04986, P05054, P05065, P05353, P05580, P05778, and CJ05013007). In overall 376 healthy volunteers, 16 cirrhotic patients (11) and 32 HCV-infected subjects (P04695) (1) have been exposed to NVR in phase 1 studies. 93 HCV-infected subjects – in the Phase 2 study and 325 HCV-infected subjects – in Phase 3 study. Narlaprevir has been administered from 50 mg up to 2000 mg alone as a single-dose, and up to multiple doses of 1600 mg three times daily (TID) alone for 6 days or 1200 mg twice daily (BID) with ritonavir for 11 days in healthy subjects, and up to 800 mg TID alone and 400 mg BID with ritonavir in HCV-infected subjects. In the Phase II study NVR was administered at a dosage of 200 mg once daily (QD), 400 mg QD, and 100 mg BID. Achieved plasma narlaprevir concentrations have been well above the anticipated therapeutic requirement [9,10]. Dose-normalized daily exposures of narlaprevir increase markedly when narlaprevir was coadministered with ritonavir, compared with exposures when narlaprevir was administered alone, mainly by inhibiting metabolism of narlaprevir. These data support combination of narlaprevir with a CYP3A4 inhibitor to optimize trough concentrations, as well as provide a more convenient dosing schedule for

patients (QD or BID) [8].

In Phase 1 studies, narlaprevir has been shown to be safe and generally well-tolerated when administered alone and in combination with ritonavir, as well as with or without PegIntron [11]. There have been no dose-related trends in adverse events (AEs) reported with narlaprevir, and the majority of AEs have been mild to moderate in intensity. There have been no clinically significant patterns of changes in vital signs, clinical laboratory values, or electrocardiogram (ECG) recordings. In addition, preliminary viral load data demonstrated potent antiviral activity in HCV genotype 1 (HCV-1)-infected subjects when narlaprevir was administered as monotherapy and in combination with PegIntron [8].

A Phase 2a study (P05104) of narlaprevir is completed in the United States. The primary objective of this study was to identify the optimal schedule and dose regimen of narlaprevir (coadministered with ritonavir) in previously untreated subjects with HCV-1 chronic hepatitis C (CHC) when administered in combination with PegIntron. The study evaluated multiple doses, schedules, and the utility of a 4-week lead-in period with PegIntron and ribavirin prior to the addition of narlaprevir. 111 subjects have been randomized in this study. It has been shown that in the narlaprevir/ritonavir-Treatment Arms, viral load reduction, measured by the proportion of subjects with undetectable HCV RNA, was significantly higher at 4 weeks of treatment with narlaprevir/ritonavir added to peginterferon/ribavirin, compared to the control of peginterferon/ribavirin alone. The addition of narlaprevir/ritonavir to the peginterferon/ribavirin backbone led to a significant increase in SVR compared to the control (28% Control Arm, 65% to 85% narlaprevir/ritonavir-Treatment Arms). Overall, the incremental benefit compared to control was a two-fold to three-fold increase in SVR [8-10].

Narlaprevir was evaluated in large Phase 3, randomized, placebo-controlled, double-blind study CJ05013008 investigating the effectiveness and safety of NVR in 420 naive and previously treated with pegylated interferon alpha and ribavirin with Genotype 1 HCV infected patients without cirrhosis. NVR 200 mg was administered with ritonavir 100 mg once daily, orally, along with pegylated interferon alpha and ribavirin for 12 weeks, with subsequent administration of pegylated interferon and ribavirin only for another 12 weeks to a total treatment course of 24 weeks. Controls were given pegylated interferon and ribavirin for 48 weeks. HCV RNA level was determined by TaqMan HCV Quantitative Test Version 2.0 (Roche Diagnostics) with LOD=LLOQ=15 IU/mL. The average viral load reduction was found to be 5.3 log10 at Week 2 and 5.9 log10 at Week 4 in the NVR group, compared with 1.5 log10 at Week 2 and 2.5 log10 at Week 4 in the control group. SVR24 was achieved in 89,1% (163/183) naive and 69,7 % (69/99) previously treated patients in NVR group and in 59,6 % (53/89) naive and 24,5 % (12/49) previously treated patients in control group. Eleven patients discontinued treatment due to AEs, 7 treated with NVR and 4 with pegylated interferon and ribavirin alone. Five patients from NVR group had SAEs, none was assessed as related to study drug. NVR significantly increases the antiviral activity and effectiveness of pegylated interferon and ribavirin double antiviral therapy in Genotype 1 HCV infected patients without cirrhosis, and produces no additional adverse effects [21].

5.2 Class or Type of Drug Being Studied/Description of Drug

Narlaprevir is a non-ionizable compound containing an alpha-ketoamide moiety. It has a molecular formula of $C_{36}H_{61}N_5O_7S$ and a molecular weight of 707.96 Da. It is the novel serine protease

inhibitor. The mechanism of inhibition involves narlaprevir covalently, yet reversibly, binding to the NS3 protease active site serine (Ser139) through a ketoamide functional group [8, 12].

The investigational drug product is supplied as a 100-mg immediate-release (IR) film-coated tablet. The tablets contain the excipients copovidone, microcrystalline cellulose, lactose monohydrate, sodium lauryl sulfate, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. The tablets are packaged in induction-sealed high-density polyethylene bottles. Experimental and clinical batches are monitored in the ongoing stability program to support appropriate shelf life and storage conditions.

5.3 Preclinical Profile

Nonclinical PK data in support of oral administration of narlaprevir with and without ritonavir were obtained from absorption, distribution, and metabolism studies in rats, dogs, monkeys, and from toxicity/toxicokinetic (TK) studies in mice, rats, and dogs[8].

PK/TK studies in rats and dogs have been conducted using the amorphous form of narlaprevir administered orally as a suspension in 0.4% methylcellulose and IV as a solution in 20% or 40% hydroxypropyl-cyclodextrin. Following oral, single-dose administration, narlaprevir was absorbed and rapidly cleared from plasma. The effective $t_{1/2}$ and mean residence time (MRT) values following IV administration were less than 1 hour. The longer MATs than $t_{1/2}$s indicate that absorption of narlaprevir is slower than its elimination from plasma. Also, as the dose of orally administered drug increased, absolute bioavailability decreased. Administration with food increased bioavailability at high doses (>100 mg/kg). Thus, for the toxicity studies, animals were fed prior to dosing[8].

Narlaprevir interconverts to an inactive diastereomer (SCH 782832) in plasma. Following oral administration of narlaprevir, the SCH 782832: narlaprevir plasma concentration ratios, as well as AUC ratios, were species-specific (humans>dogs>rats>mice). Variation in extent of absorption of narlaprevir and/or rates of metabolism of the individual diastereomers between species may contribute to the ratio differences. Following repeated administration, exposure to narlaprevir and SCH 782832 in male and female mice, rats, and dogs decreased. Exposure to narlaprevir and SCH 782832 in toxicity studies reached a plateau upon administration of increasing doses, particularly in mice and rats, and high exposure multiples relative to the human exposure at an anticipated clinical dose could not be attained[8].

Narlaprevir (1800 mg/kg in mice and rats; 800 mg/kg in dogs) was coadministered with ritonavir (12.5 mg/kg) to mice, rats, and dogs for 2 weeks in part to assess the PK interaction of narlaprevir and ritonavir in these species. The high doses of narlaprevir administered in these studies hindered ritonavir absorption in all three species, therefore hampering the PK increasing effect by ritonavir. Coadministration of narlaprevir and ritonavir decreased maximum observed plasma concentration (Cmax) values for ritonavir by 96% in mice, 100% in rats, and 97% in dogs compared with administration of ritonavir alone. Complete inhibition of ritonavir absorption in rats resulted in no increase in narlaprevir levels[8].

Following IV administration to rats and dogs, narlaprevir had a volume of distribution of 1.6 L/kg and 1.2 L/kg, respectively. These values are all significantly greater than (~13-fold) the blood volume (L/kg) in these species, indicating extravascular distribution of narlaprevir[8]. Range of

14C-narlaprevir Plasma Protein Binding from Various Species 82,4-97,8%[8].

Narlaprevir caused direct inhibition of CYP2D6 and CYP3A4/5 (as measured by dextromethorphan *O*-demethylation and midazolam 1'-hydroxylation, respectively, with HLM) with IC50 values of 88 µM (62,300 ng/mL) and 41 µM (29,000 ng/mL), respectively. Further examination of the direct inhibition of CYP3A4/5 indicated that narlaprevir was a competitive inhibitor of CYP3A4/5 with a Ki* value of 22 µM (15,600 ng/mL). Additionally, upon coadministration with the potent CYP3A4 inhibitor, ritonavir, inhibition of CYP3A4 by narlaprevir would presumably be inconsequential[8].

An extensive nonclinical safety program has been conducted to support the oral administration of narlaprevir. Narlaprevir was found to have a low order of toxicity in single and repeat-dose studies conducted in mice (up to 3 months), rats (up to 6 months), and dogs (up to 9 months). Bacterial mutagenicity, potential carcinogenicity and chromosome aberration studies revealed no evidence of genotoxic potential from narlaprevir batches tested[8].

The major findings observed in repeat-dose toxicity studies were: (1) testicular tubular epithelial degeneration and Sertoli cell cytoplasmic vacuolation in male rodents, (2) a minimal decrease (~7%-8%) in erythrocyte mass (red blood cells [RBCs], hemoglobin, and hematocrit) in female rats, (3) thyroid hyperplasia, hypertrophy, and/or increased thyroid weight in rats, (4) accumulation of eosinophilic precipitates in the gallbladder of mice, (5) hepatocellular cytoplasmic inclusions in mice, and (6) nasal cavity epithelial necrosis in mice. Based on the available nonclinical and clinical data, as well as relevant published literature [3], the Sponsor believes these findings are species-specific for mice and non clinically significant.

The toxicological findings associated with administration of narlaprevir have been well characterized in the nonclinical program, and are not believed to pose a risk to humans. Based on the well characterized findings observed nonclinically in rats, mice, and dogs, and the likelihood that the findings (gallbladder precipitate, thyroid hyperplasia/ hypertrophy, hepatocellular cytoplasmic inclusions, testicular atrophy, nasal epithelial necrosis) observed are species-specific and/or can be readily monitored in the clinic, it is the Sponsor's position that all findings to date in the nonclinical program and additional planned studies support continued clinical development of narlaprevir for the treatment of HCV[8].

5.4 Clinical Profile

5.4.1 Pharmacokinetics

When the tablet formulation of narlaprevir was administered under fed conditions, mean total AUC(I) and C_{max} were increased by 1.8- to 2.8-fold relative to fasted conditions, respectively. No apparent delays in T_{max} under fed conditions were observed compared with fasted conditions. Thus, narlaprevir should be given with food[8].

Narlaprevir is moderately bound to human plasma protein; protein binding ranged from 86.5% to 91.4% in human plasma. narlaprevir has a large volume of distribution, suggesting extensive distribution into tissues[8].

Narlaprevir is extensively metabolized by humans through oxidation, cleavage, and a combination of these processes when narlaprevir was administered alone (P05065). In humans, coadministration of narlaprevir with the potent CYP3A4 inhibitor ritonavir increases exposure to

narlaprevir and SCH 782832[8].

Elimination of narlaprevir was studied in a radiolabeled study in which an oral dose of 400 mg 14C-narlaprevir alone or in combination with ritonavir was administered to healthy subjects (P05065). Co-administration of ritonavir decreased the elimination and substantially increased the half-life of narlaprevir. A mean total of 84.2% of the radioactive dose was recovered 144 hours after a single PO administration of 400 mg [14C] narlaprevir alone as oral suspension. Total radioactivity recovered in urine and feces accounted for 3.14% and 81.1% of the dose, respectively, indicating that renal clearance is a minor elimination pathway for narlaprevir-related entities when narlaprevir is administered alone[8].

Forty-one subjects were enrolled in Study P04695, a randomized, placebo-controlled, evaluator blind study to assess the safety, tolerability, PK, and pharmacodynamics of narlaprevir, in naive or treatment-experienced subjects infected with HCV-1[11,13]. PK results indicated similar PK between healthy and HCV-infected subjects. Narlaprevir was eliminated more slowly when coadministered with ritonavir than when administered alone. Dose-normalized daily exposures of narlaprevir (AUC) on Day 14 (in the presence of PegIntron), when coadministered with ritonavir, increased 7.6- and 7.1- fold in HCV treatment-naive and treatment-experienced subjects, respectively compared with those when narlaprevir was administered alone. PK of narlaprevir (C_{max}, C_{trough}, and area under the plasma concentration-time curve from time 0 to dosing interval [AUC[τ]]) when coadministered with ritonavir were comparable with and without coadministration of PegIntron for both HCV treatment naive and treatment-experienced subjects; therefore, no dose adjustment is warranted when narlaprevir in the presence of ritonavir is coadministered with PegIntron.

32 subjects were enrolled in the Study CJ05013007 (013012cRPh), an open label multicenter study in parallel groups to assess PK of single 200 mg oral dose of narlaprevir (with and without 100 mg oral dose of ritonavir) in patients with hepatic disease and corresponding healthy volunteers. In Part I of the study mean C_{max}, and $AUC_{(0\text{-inf})}$ was 1.6 and 2.7 times higher in patients vs. healthy subjects, respectively. Increased narlaprevir exposure in patients with Child-Pugh Class A was not associated with increased adverse events rate. Simulated steady-state (tau=24 h) C_{max}, and AUC_{tau}, in patients with Child-Pugh class A were 167% and 237% vs. healthy subjects, respectively. Increased NVR exposure in patients with Child-Pugh Class A was not associated with increased adverse events rate. Taking into account significant increase in NVR exposure in patients with Child-Pugh class A cirrhosis vs. healthy volunteers after single dose 200 mg and expected further increase due to RTV coadministration, NVR dose was decreased to 100 mg in the second part of the study. In Part II of the study mean C_{max}, and $AUC_{(0\text{-inf})}$ did not differ significantly in patients with Child-Pugh class A vs. healthy subjects (104% and 107% in patients vs. healthy volunteers, respectively) after single dose NVR 100 mg with RTV 100 mg (Part II of the study). Simulated steady-state (tau=24 h) C_{max}, and AUC_{tau}, in patients with Child-Pugh class A were 105.3% and 107.0%, vs. healthy subjects, respectively[8].

When a single 400-mg dose of 14C-narlaprevir amorphous suspension was given with ritonavir to healthy male subjects, $AUC_{(I)}$ and C_{max} of narlaprevir were increased 10 and four times, respectively, compared with narlaprevir administered alone representing a significant enhancement of narlaprevir exposures under CYP3A4 inhibition by ritonavir[8].

Results from a small drug-drug interaction study evaluating effects of narlaprevir on the PK of midazolam (MDZ, a sensitive substrate of CYP3A4) showed that the AUC of MDZ did not change significantly in four of five female subjects after multiple doses of narlaprevir 400 mg TID (P04694), suggesting that CYP3A4/5 activity was not induced. Mean AUC ratios (%CV) of 1'OH-MDZ to MDZ with and without multiple doses of narlaprevir were similar, 0.3 and 0.25 for five subjects, respectively[8].

5.4.2 Safety and Tolerance

To date (January 10, 2017) the Phase 1 clinical pharmacology program currently consists of ten completed studies (P04694, P04695, P04959, P04986, P05054, P05065, P05353, P05580, P05778, and CJ05013007). In overall 376 healthy volunteers, 16 cirrhotic patients and 32 HCV-infected subjects (P04695) have been exposed to NVR in phase 1 studies [8]. The Phase 2 clinical program currently includes one Phase 2a study (P05104) with 111 randomized subjects who were receiving PegIntron/ribavirin/NVR plus RTV for 12 weeks followed by standard of care PegIntron/ribavirin for either an additional 12 weeks or 36 weeks depending on their HCV-RNA status at 4 weeks of the PegIntron/ribavirin/NVR/RTV combination or PegIntron/ribavirin only (control group) [8]. Open-label extension part of phase 3 study CJ05013008 (PIONEER) is currently ongoing. NVR is administered in combination with RTV (used as a metabolic inhibitor) along with pegylated interferon and ribavirin. In the double-blind part of PIONEER study all eligible patients both treatment naive and treatment failure are randomized into one of the two treatment arms: NVR/RTV plus PEG/RBV and Placebo plus PEG/RBV in a 2:1 ratio. NVR dose was 200 mg per os QD, RTV - 100 mg per os QD. Totally 282 patients were randomized into NVR/RTV group and received at least one dose of NVR [21]. Within of open-label extension part of PIONEER study 43 patients have taken at least one dose of NVR.

Narlaprevir has been administered from 50 mg up to 2000 mg alone as a single-dose, and up to multiple doses of 1600 mg three times daily (TID) alone for 6 days or 1200 mg twice daily (BID) with ritonavir for 11 days in healthy subjects, and up to 800 mg TID alone and 400 mg BID with ritonavir in HCV-infected subjects. In the Phase II study narlaprevir was administered at a dosage of 200 mg once daily (QD), 400 mg QD, and 100 mg BID [8].

Narlaprevir has been shown to be safe and generally well tolerated in healthy subjects when administered as single doses and multiple doses alone and in combination with ritonavir. These early studies have achieved plasma narlaprevir concentrations well above the anticipated therapeutic requirement [8].

Fifty-five percent of healthy subjects dosed with narlaprevir reported at least one treatment-emergent adverse event (TEAE). The percentage of TEAEs reported in placebo-treated subjects, and subjects treated with other drugs only, were similar (56% and 59% respectively). Gastrointestinal disorders (55 subjects, 30%), and nervous system disorders (52 subjects, 28%) were the most frequently reported TEAEs after any narlaprevir administration, with the majority of these events being headache, nausea, and abdominal pain. The majority of TEAEs were considered related to treatment; however, there have been no dose-related trends in AEs reported with narlaprevir, and all AEs but one (generalized edema) were considered mild to moderate in severity regardless of treatment. The severe AE was reported in one female who received 1200 mg BID of narlaprevir with ritonavir for 10 days. The subject was noted to have an elevation of

creatinine at the completion of the study, and at follow up she was found to have severe edema which resolved in approximately 2 weeks without treatment. There have been no clinically significant patterns of changes in vital signs, clinical laboratory values (including inhibin B levels in male subjects), or ECG recordings [8].

Seven healthy subjects administered narlaprevir in the Phase 1 clinical program discontinued due to an AE (P05054, P5580). 2 female subjects experienced moderate nausea and vomiting during treatment with narlaprevir (800 mg BID) with ritonavir (200 mg BID). Five subjects (3 men, 2 female) discontinued treatment with narlaprevir (1500 mg QD) with ritonavir (100 mg QD) due to AEs (1 case of vomiting, 4 cases of increase in serum creatinine). There have been no serious adverse events (SAEs) reported in healthy subjects to date[8].

In Phase 1 Studies in HCV-Infected Subjects **(**Study P04695), narlaprevir was generally safe and well tolerated during 7 days of monotherapy (Period 1) and 14 days of combination therapy with PegIntron (Period 2). A similar number of subjects reported a TEAE during each period (88% Period 1; 97.5% Period 2). The number of AEs reported by placebo-treated (75% to 88%) and narlaprevir-treated (91% to 100%) subjects did not significantly differ. The greatest incidence of TEAEs was gastrointestinal disorders such as diarrhea and nausea (Part 1) and general disorders and administration site conditions, primarily influenza-like illness (Part 2). The most commonly reported individual TEAE in Part 1 was headache (11 subjects, 33%, all of whom received active drug), which was reported in a similar percentage of subjects in three of the four active drug treatment groups (not reported in treatment-experienced subjects receiving narlaprevir 800 mg TID). In Part 2, the most commonly reported individual TEAE was influenza-like illness in 30 (94%) subjects who received narlaprevir and PegIntron with or without ritonavir, and six (75%) subjects who received placebo and PegIntron with or without ritonavir. No dose-related increase in the number of AEs was reported among HCV-infected subjects.[11,13] No significant difference in AEs was noted between subjects that were treatment-naive vs. treatment-experienced. Most events were mild in intensity and considered unlikely related to study drug. There were no deaths, lifethreatening AEs, or discontinuations due to an AE. There were two severe AEs of influenza-like illness which resolved and were considered by the investigator to be probably related to study treatment (PegIntron) [8].

In Study P04695, there were three SAEs reported (one instance of elevated C-reactive protein and two instances of pyrexia) in one HCV-infected subject. This SAE was first reported 3 weeks after completing narlaprevir treatment. The subject was hospitalized for the evaluation of this SAE. At the time of the admission, the subject was receiving pegylated interferon and ribavirin and had a prior history of prolonged fevers while receiving a prior interferon treatment. The Investigator reported the SAE as unlikely related to the blinded study drug and possibly related to the pegylated interferon. No clinically significant patterns of changes in blood chemistry or hematological parameters, vital signs, or ECGs occurred in any treatment group[8].

Phase 2a study P05104 was completed. The most common treatment-emergent AEs included nausea, fatigue, anemia, influenza-like illness, diarrhea, headache and other events that are commonly reported with PR. AEs commonly associated with PR resulted in discontinuation in narlaprevir/ritonavir-treated subjects, including one subjects each with gastrointestinal-symptoms, homicidal ideation, tinnitus, depression, and lethargy. Narlaprevir/ritonavir was not associated with

rash. Serious AEs and discontinuations due to AEs were infrequent in the control and narlaprevir/ritonavir-treatment arms, and no subject died on study. There were no lifethreatening AEs [8-10].

In the study P05104 the adverse event profile and number of discontinuation were consistent with those reported using peginterferon alpha + ribavirin therapy. Nearly all subjects reported AEs that the investigator considered treatment related. Treatment with narlaprevir and ritonavir with peginterferon alpha 2b + ribavirin was generally safe and well tolerated[8-10].

In the double-blind part of phase 3 study CJ05013008 (PIONEER), in which NVR is administered in combination with RTV (used as a metabolic inhibitor) along with pegylated interferon and ribavirin, therapy with NVR and ritonavir was safe and well tolerated. Eleven patients of 420 discontinued treatment due to AEs, 7 treated with NVR and 4 with pegylated interferon and ribavirin alone. Five patients from NVR group had SAEs, none was assessed as related to study drug. In general adverse event profile observed in the study was comparable in NVR/RTV and control group [21].

In single dose PK Study CJ05013007 16 patients with hepatic disease class A by Child-Pugh score and 16 healthy volunteers with normal liver function were included. Open-label extension part of phase 3 study CJ05013008, in which NVR is administered in combination with RTV (used as a metabolic inhibitor) along with pegylated interferon and ribavirin is currently ongoing, and 43 patients received at least one dose of NVR. Studies conducting by JSC R-Pharm (CJ05013008, CJ05013007) have not revealed significant safety concerns [8].

5.5 Rationale

5.5.1 Study Conduct Rationale

In vitro data show that narlaprevir is metabolized by CYP3A4, and there is some evidence of CYP enzyme induction preclinically and CYP3A4 inhibition in human liver microsomes. However, a clinical study of high dose narlaprevir with midazolam showed no clinically relevant effect of narlaprevir on midazolam PK, indicating no relevant induction/inhibition of CYP3A4 by narlaprevir. In vivo, narlaprevir is a sensitive CYP3A4 substrate and co-administration with ritonavir (ritonavir) markedly increases narlaprevir exposure. In addition, in vitro data suggest narlaprevir is a P-gp substrate. Narlaprevir is being developed to be part of a therapeutic regimen that includes ritonavir (ritonavir), a metabolic inhibitor of CYP3A4, to boost the concentration of narlaprevir[8].

This drug interaction study is designed to investigate pharmacokinetic drug-drug interactions between narlaprevir coadministered with ritonavir and antiretroviral drugs (tenofovir disoproxil fumarate and raltegravir), for labeling and clinical dosing guidance purposes.

5.5.2 Study Design Rationale

The current protocol includes 2 parts and additional parts may be added on an ongoing basis as an amendment to the protocol.

Part 1

Part 1 of the study is being conducted to evaluate the pharmacokinetic effect of coadministration of

narlaprevir and tenofovir, as the drugs may be used concomitantly to treat HCV/HIV coinfection.

Tenofovir disoproxil fumarate (tenofovir disoproxil fumarate) is the oral prodrug of tenofovir (tenofovir), a nucleotide reverse transcriptase inhibitor used in the treatment of HIV and hepatitis B. Tenofovir disoproxil fumarate is rapidly absorbed and converted in the plasma to tenofovir; tenofovir is largely eliminated unchanged through renal excretion.

P-glycoprotein (P-gp) is thought to mediate tenofovir disoproxil fumarate absorption from the intestine, as tenofovir disoproxil fumarate efflux has been decreased by several inhibitors including cyclosporin A [1]. As a clinical correlate, HIV protease inhibitors, often coadministered with tenofovir disoproxil fumarate, have variably increased tenofovir plasma concentrations based on their ability to inhibit P-gp mediated efflux, induce P-gp expression and inhibit tenofovir disoproxil fumarate hydrolysis at the level of the intestine [1]. In addition, other transporters are thought to participate in the renal elimination of tenofovir; tenofovir is a substrate for both hOAT1 and hOAT3 and inhibition of either transporter could both alter plasma concentration of tenofovir and decrease elimination.

Narlaprevir has been shown to be a P-gp substrate; it is unknown whether it is a P-gp inhibitor or affects hOAT1 and hOAT3. Thus it is unknown whether narlaprevir could affect tenofovir exposure. As tenofovir disoproxil fumarate has affected HIV protease inhibitor (PI) drug absorption [1]; and these PIs are peptidomimetics similar to narlaprevir, there is also the potential for tenofovir disoproxil fumarate to affect narlaprevir absorption and plasma concentrations.

In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP enzymes. At concentrations substantially higher (~300-fold) than those observed in vivo, tenofovir did not inhibit *in vitro* drug metabolism mediated by any of the following human CYP isoforms: CYP3A4, CYP2D6, CYP2C9, or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP mediated interactions involving tenofovir with other medicinal products is low. [14].

Tenofovir disoproxil fumarate does not significantly affect the pharmacokinetics of HCV PIs boceprevir, telaprevir, or simeprevir [15-17]. The coadministration with simeprevir and boceprevir didn't significantly change exposure parameters of tenofovir. Only coadministration with telaprevir led to 30% increase in AUC and C_{max} of tenofovir, which was not associated with worsened safety profile of this combination. That is why concomitant use of tenofovir disoproxil fumarate with all approved HCV PIs is recommended without any dose adjustment [7,14].

So no major drug-drug interaction is expected between narlaprevir/ritonavir and tenofovir disoproxil fumarate.

This study is designed as a randomized 3-period crossover study and will assess if there is any effect of tenofovir disoproxil fumarate/tenofovir on the pharmacokinetics of narlaprevir and vice versa.

Part 2

Part 2 of the study is being conducted to evaluate the pharmacokinetic effect of coadministration of narlaprevir/ritonavir and raltegravir (raltegravir). A considerable percentage of HIV infected patients

are also infected with HCV. HIV/HCV co-infected patients commonly use HIV and HCV medications simultaneously. Therefore, it is important to know whether drug-drug interactions occur when combining those treatments or not.

Raltegravir is an agent used for the treatment of HIV and is commonly used in HIV/HCV coinfected patients because it does not inhibit or induce CYP enzymes and its primary route of elimination is glucuronidation. Since the current treatment paradigm for HIV involves the administration of anti-HIV agents in combination, to boost efficacy and to control the emergence of resistance, it is currently planned that raltegravir will be administered in combination with other anti-HIV/ HCV drugs, including ritonavir and narlaprevir.

Raltegravir is an HIV integrase inhibitor. In clinical trials in healthy volunteers in the presence of ritonavir, raltegravir pharmacokinetics were just weakly affected and did not require dose adjustment. [2]. In the presence of protease inhibitors (atazanavir and tenofovir) boosted by ritonavir pharmacokinetics of raltegravir changed differently: PK parameters increased in the presence of atazanavir and decreased in the presence of tenofovir. In both cases it was not considered as clinically significant. [2].

Raltegravir does not inhibit (IC_{50}>100 µM) CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A in vitro. Moreover, in vitro, raltegravir did not induce CYP1A2, CYP2B6 or CYP3A4. A midazolam drug interaction study confirmed the low propensity of raltegravir to alter the pharmacokinetics of agents metabolized by CYP3A4 in vivo by demonstrating a lack of effect of raltegravir on the pharmacokinetics of midazolam, a sensitive CYP3A4 substrate. Similarly, raltegravir is not an inhibitor (IC_{50}>50 µM) of UGT1A1 or UGT2B7, and raltegravir does not inhibit P-glycoprotein-mediated transport. Based on these data, raltegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or P-glycoprotein (e.g., protease inhibitors) [18]. Besides raltegravir has a wide therapeutic index and even in 300% raltegravir exposure increase (when coadministered with omeprazole) no safety profile worsening was shown (combination of omeprazole and raltegravir is allowed for use without dose adjustment) [18-20].

Ritonavir is a potent inhibitor of cytochrome 3A (CYP3A) and CYP2D6 and also appears to induce CYP3A and other drug metabolizing enzymes, including glucuronosyl transferases. Based on reported clinical trials no dose adjustment is required for raltegravir with coadministration with ritonavir only [2].

Drug-drug interaction studies were conducted of raltegravir with HCV PIs boceprevir, telaprevir and simeprevir. Boceprevir and simeprevir had no impact on the raltegravir pharmacokinetics (4% and 8% increase in AUC, respectively), while telaprevir coadministered with raltegravir led to 31% increase in raltegravir AUC [18]. All these changes were considered not clinically meaningful [18-20]. Raltegravir had no impact on boceprevir, telaprevir or simeprevir pharmacokinetics. That is why concomitant use of raltegravir with all approved HCV PIs is recommended without any dose adjustment [15-17].

Narlaprevir is not a CYP3A4 inducer/inhibitor, but its effect on the UGT1A1 pathway and other transporters such as P-gp is unknown. It is important to investigate if any drug-drug interaction exist in case of co-administration of raltegravir and narlaprevir / ritonavir combination.

This study is designed as a randomized 3-period crossover study and will assess if there is any effect of raltegravir on the pharmacokinetics of narlaprevir and vice versa.

5.5.3 Dose Rationale

Narlaprevir will be administered at a dose of 200 mg with ritonavir 100 mg QD, the anticipated clinical dose.

All other drugs (Tenofovir disoproxil fumarate and Raltegravir) will be administered at their clinically relevant doses.

6 STUDY OBJECTIVES

6.1 Primary Objectives

The primary objectives of this study are:

Part 1

To evaluate the pharmacokinetic drug-drug interaction between narlaprevir/ritonavir and tenofovir (disoproxil fumarate) in healthy subjects.

Part 2

To evaluate the pharmacokinetic drug-drug interaction between narlaprevir/ritonavir and raltegravir in healthy subjects.

6.2 Secondary Objectives

The secondary objectives of this study are:

Part 1

To evaluate the safety and tolerability of narlaprevir/ritonavir when coadministered with tenofovir in healthy subjects.

Part 2

To evaluate the safety and tolerability of narlaprevir/ritonavir when coadministered with raltegravir in healthy subjects.

7 INVESTIGATIONAL AND ANALYSIS PLAN

7.1 Design of the Study/Methodology

This will be a study in 2 parts conducted in healthy adult subjects, in conformance with Good Clinical Practices. This study will be conducted in 1-2 sites in Russia. This study supposes that 36 subjects should complete the study per protocol. In order to reach this amount all subjects who withdraw the study prematurely will be replaced by new subject. Considering possible 50% drop-out rate maximum 54 subjects will be administered study drug. For enrollment of 54 subjects about

80 healthy volunteers may be screened.

This study may be amended to include additional parts that assess other potential drug interactions and PK considerations that are necessary to support the registration of narlaprevir.

Both parts will be a randomized, 3-period crossover study. Subjects will be screened within 28 days before dosing in this multi-part study. Subjects will be admitted to the study center the evening before the first dose for baseline assessments to confirm eligibility.

Part 1

Subjects will participate in a randomized 3-period crossover study. Every subject will be randomized 1:1:1 to receive one of following treatment sequences: A/B/C, or B/C/A, or C/A/B according to randomization scheme. Only one treatment will be administered per period.

On Day 1 of the first period, subjects will be randomized to one of the treatment sequences and receive the first dose.

Subjects in Part 1 will receive the following:

- Treatment A: narlaprevir 200 mg once daily + ritonavir 100 mg once daily orally for 5 days
- Treatment B: tenofovir disoproxil fumarate 300 mg once daily, orally for 5 days
- Treatment C: narlaprevir 200 mg once daily + ritonavir 100 mg once daily + tenofovir disoproxil fumarate 300 mg once daily, orally for 5 days

All treatments will be administered following a standard breakfast. Subjects will be confined to the study center throughout treatment in each period. Following completion of study procedures for each treatment period, subjects will be discharged from the clinic. After a 7-14 days interval between dosing, subjects will return to start hospitalization for the next treatment period.

Blood and urine samples for determination of narlaprevir, ritonavir (C_{trough}) and tenofovir concentrations will be collected as specified in the Study Flow Chart.

Safety assessments including vital signs, ECGs, and clinical laboratory tests will be performed, and adverse events will be recorded, throughout the study. Subjects will be discharged from the clinic upon completion of all study related procedures in Period 3. Phone call will be conducted after 5-7 days of follow-up period to assess safety data.

Part 2

Subjects will participate in a randomized 3-period crossover study. Every subject will be randomized 1:1:1 to receive one of following treatment sequences: A/B/C, or B/C/A, or C/A/B according to randomization scheme. Only one treatment will be administered per period. On Day 1 of the first period, subjects will be randomized to one of the treatment sequences and receive the first dose.

Subjects in Part 2 will receive the following:

- Treatment A: narlaprevir 200 mg once daily + ritonavir 100 mg QD orally for 5 days
- Treatment B: raltegravir 400 mg twice daily, orally for 5 days

- Treatment C: narlaprevir 200 mg once daily + ritonavir 100 mg QD + raltegravir 400 mg twice daily, orally for 5 days

All treatments will be administered following a standard breakfast and evening dose of raltegravir will be taking after standard dinner. Subjects will be confined to the study center throughout treatment in each period. Following completion of study procedures for each treatment period, subjects will be discharged from the clinic. After a 7-14 days interval between dosing, subjects will return to start hospitalization for the next treatment period.

Blood samples for determination of narlaprevir, ritonavir (C_{trough}) and raltegravir concentrations will be collected as specified in the Study Flow Chart.

Safety assessments including vital signs, ECGs, and clinical laboratory tests will be performed, and adverse events will be recorded, throughout the study. Subjects will be discharged from the clinic upon completion of all study related procedures in Period 3. Phone call will be conducted after 5-7 days of follow-up period to assess safety data.

Screening

Within 28 days prior to treatment, the investigator shall discuss with each subject the nature of the study, its requirements, and its restrictions. Written informed consent will be obtained from each subject prior to any study related procedures being performed, and a signed copy will be given to the volunteer. The inclusion/exclusion criteria will be reviewed, a complete medical history, physical examination, laboratory evaluations and other assessments will be performed as delineated in **Section 4.2** and **Section 7.6**. A screening number will be assigned to each subject on completion of the study-specific informed consent.

Baseline

Subjects will be confined to the study center at least 12 hours prior to dosing. The investigator will review the inclusion/exclusion criteria and record adverse events (AEs) and medications taken within the last 14 days. Laboratory evaluations, vital signs and other assessments will be performed and recorded as delineated in **Section 4.2** and **Section 7.6**.

Treatment Day(s)

Inclusion/exclusion criteria will be reviewed with each subject on the morning of treatment administration. Subjects in both parts of the study will be assigned a randomization number. The randomization number will be used to determine the treatment according to a randomization code (see **Section 7.4.1.3**). Laboratory evaluations, vital signs and other assessments, delineated in **Section 4.2** and **Section 7.6** will be performed and recorded. Serial pharmacokinetic samples will be obtained prior to dosing and as outlined in the Study Flow Chart (**Section 4.2**).

Study Completion/Subject Discharge/Follow-Up

On the last day of their study participation (including premature discontinuation), subjects will be discharged following collection of the last blood sample/assessment. In addition, concomitant medications, adverse events and vital signs will be recorded and a physical exam, and laboratory evaluations, and other assessments required as delineated in **Section 4.2** and **Section 7.6** will be performed.

7.2 Participation in and Completion of the Study

Each subject is considered enrolled in the trial when the subject has provided written informed consent. All subjects will have their information entered into the screening log maintained by the study site. Those subjects, including screened subjects, who experience a serious adverse event, or have a therapeutic intervention (e.g., change in medication administered, dietary therapy, administration of study medication), will have information entered into the case records (e.g., CRF). Those subjects who fail to qualify for further study participation based on the initial interview and initial screening laboratory tests, should have information only recorded in the site screening log.

Each subject is considered to have fulfilled participation in the trial when he/she has completed the last protocol-specified contact (e.g., visits or telephone contacts).

A subject is considered discontinued after he/she has withdrawn consent or has been discontinued under the conditions specified in **Section 7.3.3.**

A subject is considered lost to follow-up, if the investigator is unable to contact the subject. The end of participation for a subject lost to follow-up is the last known contact (e.g., visit or telephone contact).

The overall trial begins when the first subject is enrolled (i.e., signs the informed consent form). The overall trial ends when the last remaining subject has ended participation in the trial, by completing the trial, being discontinued from the trial, or being lost to follow-up.

Follow-up procedures related to pregnancy or (S)AEs may continue beyond the end of the clinical trial.

7.3 Study Population

Healthy adult male and female subjects will be selected for both Parts of the study. It is planned that 36 subjects will complete the study overall. In case of premature withdrawal subjects will be replaced by volunteers from among the subjects who signed the informed consent form. Subjects must meet all the inclusion criteria and none of the exclusion criteria to receive treatment assignment. Considering 50% drop-out rate maximum 54 subjects will be enrolled in the study. 18 subjects should complete each of two parts.

7.3.1 Subject Inclusion Criteria

The subjects must meet **ALL** the criteria listed below for entry at baseline:

1. Subjects must be willing to give written informed consent for the trial and able to adhere to dose and visit schedules.

2. Subjects of either sex and of any race between the ages of 21 and 55 years (both parts), inclusive, having a Body Mass Index (BMI) between 18,5 and 30, inclusive. BMI = weight (kg)/height^2(m).

3. Volunteers should be diagnosed as "healthy": no pathology of the gastrointestinal tract, liver, kidneys, cardiovascular system, central nervous system (previously carried out by standard clinical and lab tests which did not reveal the presence of any diseases. AST and ALT must not exceed the normal range; QTcB for men should be ≤ 450 ms and ≤ 470 ms for women, the interval PR should be ≤ 200 ms).

4. Vital sign measurements (taken after ~3 minutes in a supine or sitting position) must be within the following ranges:

    a. systolic blood pressure, 100 – 130 mm Hg

    b. diastolic blood pressure, 60 -90 mm Hg

    c. pulse rate, 60-80 bpm

5. Female subjects must be:

    a. postmenopausal (defined as 12 months with no menses; age > 40 years and with a FSH level of >40 u/mL).

    b. surgically sterilized at least 3 months prior to baseline (e.g., documented hysterectomy or tubal ligation).

6. Men must agree to use a medically accepted method of contraception (condom and spermicide) during the trial and for 3 months after stopping the medication.

7.3.2 Subject Exclusion Criteria

The subject will be excluded from entry if **ANY** of the criteria listed below are met at baseline:

The subject will be excluded from entry if **ANY** of the criteria listed below are met at baseline:

1. Females with childbearing potential;
2. Subjects who, in the opinion of the investigator, will not be able to participate optimally in the study;
3. Positive results for hepatitis B surface antigen, hepatitis C antibodies or HIV, positive RW results;
4. Allergic reactions in history;
5. Intolerance to medication;

6. Chronic disease of cardiovascular, bronchopulmonary, and/or neuroendocrinal systems, gastrointestinal, liver, pancreas, kidney and/or blood disease;
7. History or presence of impaired renal function, lactase deficiency, lactose intolerance, glucose-galactose malabsorption;
8. History of urinary obstruction or difficulty in voiding;
9. Gastrointestinal surgery in history (except of appendectomy);
10. Acute infections less than 4 weeks before participation in the study;
11. Subjects with a medical history of osteopenia and/or osteoporosis.
12. Regular administration of any medicines less than 4 weeks before participation in the study;
13. Administration of medicines with marked influence on hemodynamics, liver function et al (barbiturates, omeprazole, cimetidine et al) less than 30 days before participation in the study;
14. Blood donation (450 ml or more of blood or plasma) less than 2 months before participation in the study;
15. Intake of more than 10 units of alcohol in a week (1 unit of alcohol is equal to 0.5 L of beer, 200 mL of wine or 50 mL of spirits) or history of drug abuse or alcoholism;
16. Smoking of more than 10 cigarettes or equivalent tobacco use per day;
17. Participation in phase 1 clinical trial less than 3 months before participation in the study;
18. Positive screen for drugs abuse and drug use;
19. Subjects with a medical history of psychiatric or personality disorders that in the opinion of the investigator and sponsor, affects the subject's ability to participate in the trial;
20. Subjects who are part of the study staff personnel or family members of the study staff personnel;

Table 3 Prohibited Medications for Entry into the Study

Prohibited Medications	Washout Period Prior to Dosing
Prescription and non prescription medication except acetaminophen	14 days
Potent inhibitors and inducers of CYP 3A4	14 days
Herbal supplements	14 days
Vitamins at doses that exceed daily replacement requirements	14 days
Oral contraceptives	2 months

Table 4 Human CYP Enzyme Drug-Interactions

Enzyme	Inhibitors	Inducers
CYP3A	cimetidine, clarithromycin, diltiazem, erythromycin, fluoxetine, fluvoxamine, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, paroxetine, ritonavir, saquinavir, telithromycin, venlafaxine, verapamil	carbamazepine, dexamethasone, efavirenz, ifosfamide, nevirapine, modafinil, oxcarbazepine, pioglitazone, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort, troglitazone

7.3.3 Subject Discontinuation Criteria

Subject participation may be terminated during the study for any of the following reasons:

- Serious or severe adverse event (AE);
- Does not meet Inclusion / Exclusion Criteria prior to Treatment Periods 2 and 3 except of clinically not significant increase of ALT or/and AST before Periods 2 and 3 (see Study Flow Charts).
- Failure to comply with the dosing, evaluations, or other requirements of the study;
- Request of the subject (subjects have the right to discontinue treatment at any time for any reason);
- Any situation or condition which may threaten the subject's health or well being by continuing in the study;
- Administrative (e.g., study termination).

At a minimum collect the following information when a subject discontinues:

Table 5 The information that is necessary when a subject discontinues study

1)	The reason the subject discontinued;
2)	The date of the last dose of test products from the trial;
3)	The date of the last assessment and/or contact (telephone or visit) will be arranged as appropriate;

4)	(Serious) Adverse events;
5)	Compliance with the test product administration as specified in this protocol;
6)	Final Assessments;
7)	Every effort should be made to ensure that all procedures and evaluations scheduled for the final trial visit are performed (**Section 4.2**, Trial Flow Chart).

It is the right and the duty of the investigator to interrupt treatment of any subject if he/she feels that study discontinuation is necessary to protect the subject, or that there are unmanageable factors that may interfere significantly with the study procedures and/or the interpretation of results.

If a subject prematurely discontinues, or is discontinued from the study, the primary reason for the discontinuation will be obtained and recorded on the CRF. At the time of discontinuation, every effort (e.g., telephone contact, certified letter) should be made, and documented, to ensure and all procedures and evaluations scheduled for the final study visit are performed (see **Section 4.2**, Study Flow Chart and **Section 7.6**, Study Procedures).

7.3.4 Replacement of Subjects

After consultation between the sponsor and the principal investigator, enrollment may be extended to replace subject(s) discontinued during the study by volunteers from among the subjects who signed the informed consent form.

7.4 Treatments

7.4.1 Study Treatments

7.4.1.1 Treatments Administered

Part 1

- Treatment A: 200 mg of narlaprevir (2 x 100 mg coated tablets), QD, per os (PO) coadministered with 100 mg of ritonavir QD, PO, for 5 days
- Treatment B: 300 mg tenofovir disoproxil fumarate (1 x 300 mg tablet), QD, PO, for 5 days
- Treatment C: 200 mg of narlaprevir (2 x 100 mg coated tablets), QD, PO coadministered with 100 mg of ritonavir QD, PO and 300 mg tenofovir disoproxil fumarate (1 x 300 mg film coated tablets), QD, PO, for 5 days

Part 2

- Treatment A: 200 mg of narlaprevir (2 x 100 mg coated tablets), QD, PO, coadministered with 100 mg of ritonavir QD, PO, for 5 days

- Treatment B: 400 mg raltegravir (1 x 400 mg tablet), BID, PO, for 5 days
- Treatment C: 200 mg of narlaprevir (2 x 100 mg coated tablets), QD, PO coadministered with 100 mg of ritonavir QD, PO and 400 mg raltegravir (1 x 400 mg film coated tablets), BID, PO, for 5 days

For all parts, all doses will be administered following a standard breakfast (for all drugs) and standard dinner (for raltegravir administered twice daily only). Standard breakfast and standard dinner will be similar during the treatment periods and for all patients. Center may refer to recommendations of Diet N 15 for standard meals.

Narlaprevir doses are to be administered at each dose with approximately 200 mL of room temperature noncarbonated drinking water. All treatments should be swallowed whole, not chewed or crushed.

7.4.1.2 Timing of Dose for Each Subject

In Parts 1, 2 the dosing of narlaprevir is once a day in the morning following a standard breakfast.

In **Part 1**, tenofovir disoproxil fumarate and ritonavir should be administered in the morning following a standard breakfast.

In **Part 2**, ritonavir and raltegravir should be administered in the morning following a standard breakfast. Raltegravir should be administered again following standard dinner approximately 12 hours after the morning dose.

Each treatment should be administered, if possible, at approximately the same time each day.

7.4.1.3 Method of Treatment Assignment, Randomization, and/or Stratification

7.4.1.3.1 Screening Number Assignment

A screening number will be assigned to each subject on completion of the study-specific informed consent by the site. Screening numbers will be recorded on the CRF.

7.4.1.3.2 Randomization/Dosing Number Assignment

A subject or randomization number will be assigned to each volunteer by the site using the subject/randomization numbers provided in **Section 7.4.1.3**. prior to the administration of narlaprevir treatment on Day1 of Period 1.

For both parts on Day 1 of Period 1 visit all eligible subjects will be randomized using envelopes with codes into one of the treatment sequences (A/B/C, B/C/A or C/A/B). For both parts responsible statisticians will generate the randomization schedule prior to the start of this study. All randomization information will be stored in a secured area, accessible only by authorized personnel

Part 1

On Day 1 of Period 1, subjects who have met all of the eligibility requirements indicated in **Section 7.3** will be assigned a Subject Randomization Number by the site. Subjects will be assigned Randomization Numbers (1001 and subsequent numbers). This 4-digit randomization number will be used by the clinical site to facilitate the prelabeling of PK samples, and will be the only subject identifier used on all PK sample collections.

Randomization numbers for replacement subjects are included in these numbers. For replacement subject the second digit in 4-digit number is changed from “0” to “1” etc.

Study treatment will be assigned to a subject according to Randomization List.

Part 2

On Day 1 of Period 1, subjects who have met all of the eligibility requirements indicated in **Section 7.3** will be assigned a Randomization Number by the site. Subjects will be assigned Randomization Numbers (2001 and subsequent numbers). This 4-digit randomization number will be used by the clinical site to facilitate the prelabeling of PK samples, and will be the only subject identifier used on all PK sample collections.

Randomization numbers for replacement subjects are included in these numbers. For replacement subject the second digit in 4-digit number is changed from “0” to “1” etc.

Study treatment will be assigned to a subject according to Randomization List.

7.4.1.4 Management of Blinding of Study Treatments

Both parts are open-label.

7.4.1.5 Investigational Product(s)

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, handling, storage, distribution, and usage of these materials in accordance with the protocol and any applicable laws and regulations.

The following Investigational product(s) will be used in the study and will be supplied in sufficient

quantities for subjects and any replacement subjects.

Table 6 Investigational Product(s)

Part	Treatment Group	Drug	Dose (mg)	Dosage strength (mg)	Dosage forms per dose	Dosing periods per day	Sub-jects	Days of Treat-ment	Total dosage forms	Addi-tional Infor-mation
Part 1	A	narlaprevir	200	100	2	1	12	5	120	
	C		200	100	2	1	12	5	120	
	A	ritonavir	100	100	1	1	12	5	60	
	C		100	100	1	1	12	5	60	
	B	tenofovir disoproxil fumarate	300	300	1	1	12	5	60	
	C		300	300	1	1	12	5	60	
Part 2	A	narlaprevir	200	100	2	1	12	5	120	
	C		200	100	2	1	12	5	120	
	A	ritonavir	100	100	1	1	12	5	60	
	C		100	100	1	1	12	5	60	
	B	raltegravir	400	400	1	2	12	5	120	
	C		400	400	1	2	12	5	120	

7.4.1.5.1 Route and administration

All trial medications will be administered with appropriate intervals between subjects to allow for sample collection and any necessary additional clinical observations. All trial medication administrations will be performed by the investigator or responsible designee and will be witnessed by a second person. Trial medication administration will be carried out by a physician with the subject in standing position. Tablet(s) will be taken orally together with 200 mL water after standard breakfast and raltegravir will be taken after dinner in Part 2 of the study. Subjects will have to remain in sitting (semi-recumbent) position for 4 hours after administration (visiting the restrooms under supervision is allowed). In this time, entertainment will not include any exciting or thrilling movies or similar TV programs.

Information on dietary restrictions is given in **Section 7.4.3.**

7.4.1.5.2 Identity of Investigational Product(s)

Narlaprevir

ARLANSA®

Test drug:	**narlaprevir**
Dosage form:	film-coated tablet formulation
Strength:	100 mg
Dose:	200 mg single oral dose
Developer/Manufacturer:	R-Pharm JSC
Manufacturing site:	Hovione FarmaCiencia SA Sete Casas, 2674-506 Loures, Portugal.

The tablets contain the excipients copovidone, microcrystalline cellulose, lactose monohydrate, sodium lauryl sulfate, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. The tablets are packaged in induction-sealed high-density polyethylene bottles.

This packaging configuration provides sufficient protection from light and humidity.

Ritonavir

NORVIR®

Dosage form:	film-coated tablet formulation
Strength:	100 mg
Dose:	100 mg single oral dose
Developer/Manufacturer:	Abbott GmbH & CoKG
	Knollstrasse 50, 67061 Ludwigshafen, Germany

Ritonavir packed in vials containing 30 tablets.

Please refer to Package Insert for additional information on ritonavir (NORVIR®).

Tenofovir disoproxil fumarate

TENOFOVIR-TL

Dosage form:	film-coated tablet
Strength:	300 mg
Developer/Manufacturer:	LTD "Drugs Tehnology"

Tenofovir-TL packed in vials containing 30 tablets.

Please refer to Package Insert for additional information on tenofovir disoprozil fumarate (Tenofovir-TL,,LTD "Drugs Tehnology").

Raltegravir

ISENTRESS®

Dosage form: film-coated tablet

Strength: 400 mg

Developer/Manufacturer: Merck Sharp & Dohme

Insentress packed in unit-of-use bottles of 60 tablets.

Please refer to Package Insert for additional information on raltegravir (ISENTRESS®).

7.4.1.5.3 Source

The sponsor will provide narlaprevir, ritonavir and all other study medication (**Section 7.4.1.5**) for this study. It should be always from the same batch/lot for each particular Study Part.

7.4.1.5.4 Labeling, Storage and Dispensing

The labels will include

- Name of study drug
- Protocol number
- Sponsor name, address and contact phone number
- CRO name, address and contact phone number
- Formulation
- Rout of administration
- Dosage
- Number of Units
- Batch #
- Investigator name
- Site number
- Patient number
- Identification “For clinical trials only”
- Storage conditions
- Note to “Keep out of children reach”
- Expiry date

Local requirements and other information may be added as required. The label should be

produced in a language appropriate for the study site.

Receipt and dispensing of study medication must be recorded by an authorized person at the investigator's site.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, handling, storage, distribution, and usage of these materials in accordance with the protocol and any applicable laws and regulations.

Study drug supplies must be stored at the clinical site in a secure, limited-access location under the storage conditions specified on the medication labels. Clinical sites must maintain temperature logs for study drug storage areas on a daily basis. Study drug(s) will be dispensed by the investigators named on the Authorized Signature Log. The study drug(s) will be dispensed only to study subjects who have provided written informed consent, and have met all entry criteria. Clinical supplies may not be used for any purpose other than that stated in the protocol.

An adequate quantity of study drug will be provided to replace units damaged in shipment/handling, to replace subjects.

7.4.1.5.5 Investigational Product Accountability

Accurate and current accounting of the dispensing and return of investigational product(s) and concomitant medications supplied by the Sponsor will be maintained on an ongoing basis by a member of the trial site staff:

- Investigational medicinal product(s) dispensed to each site will be recorded in the trial-specific Site Investigational Medicinal Product (IMP) Accountability Log (or equivalent document);
- Investigational medicinal product(s) dispensed to each subject will be recorded in the trial-specific Subject IMP Accountability Log (or equivalent document).

The Site IMP Accountability Log and Subject IMP Accountability Log will be verified by the trial monitor. The original Site IMP Accountability Log and Subject IMP Accountability Log will be approved by the investigator and retained at the trial site and a copy supplied to the sponsor or CRO when the trial is complete.

The trial monitor will instruct the site on the return of all investigational product(s) supplies. A final inventory of the total amount of investigational product(s) received at each trial site against the amount used and returned must be recorded in the Site IMP Accountability Log. Inventory records must be readily available for inspection by the trial monitor and/or auditor, and open to government inspection at any time.

7.4.2 Non-Study Treatments

7.4.2.1 Prior and Concomitant Medications

All prior medication taken by the subject 14 days prior to treatment intervention and all concomitant therapy taken by the subject during the study are to be recorded on the CRF. The identity of the therapy, the dose, route, and regimen, the dates started and stopped (or notation of "continuing" if that is the case), and the reason for use must be recorded. The use of any concomitant medication must relate to an AE or the subject's medical history.

7.4.2.2 Medications, Supplements, and Other Substances Prohibited Prior to Baseline and During the Study

The medications prohibited prior to Baseline are listed in the table in **Section 7.3.2** with the subject exclusion criteria.

The subject must not take the treatments listed in table below (other than as specified in the protocol) during the study after Subject Number Assignment or Randomization.

Table 7 - Medications Prohibited During the Study

Medication Name	Duration of Prohibition
Prescription Medications (except those required in the study)	During the Study
Nonprescription Medications (except Acetaminophen)	During the Study
Vitamins, dietary supplements	During the Study
CYP3A4 Inducer (**Section 7.3.2**)	During the Study
CYP3A4 Inhibitor (**Section 7.3.2**)	During the Study
NSAIDS	During the Study

7.4.2.3 Medications Allowed During the Study

The following medications, supplements, and other substances are allowed during the study:

Table 8 Allowed Medications

Medication Names
Acetaminophen (paracetamol)
Medications necessary to treat adverse events or medical emergencies

Note that the use of any concomitant medication must relate to the documented medical history, prophylaxis, or an adverse event of the subject.

7.4.3 Dietary, Tobacco, Alcohol, Caffeine, and Other Restrictions

7.4.3.1 Diet

Meals (breakfast, lunch, dinner and snacks) will be of similar nutritional composition for all subjects/groups on hospitalization days, and will be provided at approximately the same time each day.

In accordance with standards approved in Russian Federation [30], daily meal should include 65 - 117g of proteins for males or 58 – 87g for females (about 30% of daily energy needs), 70 – 154g of fats for males or 60 – 102g for females (about 12% of daily energy needs) and 257 – 586g of carbohydrates that equal to 50—60% of daily energy needs. There are no special requirements for meal composition for study drugs [31]. According to the data in approved drug label information for tenofovir disoproxil fumarate, high fat meal impacts tenofovir pharmacokinetics. Administration of tenofovir disoproxil fumarate with a light meal has no significant effect on the pharmacokinetics of tenofovir compared to fasted administration of the drug. No clinically meaningful effects of meal on raltegravir pharmacokinetics were revealed in PK study [31]. To minimize variation in pharmacokinetics due to food, standard breakfast containing 20% of the total caloric content from fat will be consumed prior to administration of the morning dose of drug(s).

Grapefruit and grapefruit juice must also be excluded from the diet since substances contained in these foods have been reported to inhibit certain drug-metabolizing enzymes.

When meal and blood draw times coincide, blood will be drawn BEFORE the meal is provided.

On days prior to serial PK sampling at approximately 21:00 all subjects should have a light snack (sandwich, piece of fruit, non-caffeinated beverage) after which an overnight fast will be started. Following an overnight fast of at least 10 hours, subjects should start to consume the standard breakfast 30 minutes prior to administration of the drug product. Study subjects should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of the meal. The drug product should be administered with **200 mL of water**. No food should be allowed for at least **4** hours postdose at which time a light lunch will be served. Water can be allowed as desired except for one hour before and after drug administration. Subjects should receive standardized meals scheduled at approximately the same time in each period of the study. Except as required for study procedures, subjects should remain semi- recumbent until **4** hours postdose. For BID treatment subjects should receive a meal or snack prior to the evening dose.

7.4.3.2 Tobacco

The enrollment of nonsmoking volunteers is preferred. If light smokers (≤10 cigarettes/day) or users of equivalent tobacco products (3 pipes/day, 2 cigars/day) are included, they shall have stopped smoking at least 14 days prior to study drug administration. Former smokers will have their tobacco use history quantified and recorded on the medical history section of CRF. Smoking or the use of tobacco products is not allowed during study hospitalization.

7.4.3.3 Alcohol

Subjects will not be permitted to drink alcoholic beverages for 48 hours prior to treatment administration and during the hospitalization period of the study.

7.4.3.4 Caffeine

Subjects will not be permitted to drink caffeine-containing beverages (e.g., coffee, black tea, cola) or use caffeine or xanthine-containing products for 48 hours prior to treatment administration and during the hospitalization period of the study.

7.4.3.5 Exercise

Subjects should refrain from rigorous exercise or physical exertion 48 hours prior to entering into the study and during the study.

7.4.3.6 Other Restrictions

During non-confined study period, subjects should refrain from the use of nutraceuticals, vitamins at doses that exceed daily replacement requirements, and antacids.

7.4.4 Procedures for Monitoring Subject Compliance

At all protocol-specified visits, the investigator or qualified designee is to note in the administration record, and in the appropriate section of the CRF, whether treatment had been taken per protocol in the preceding period. If not, the date(s) and reason for each deviation must be recorded. Space is provided on the CRF, for explanatory comments. In addition, the study staff will maintain an ongoing record of the dispensing, administration and the return of all study medication for each subject on the IMP Accountability Log or equivalent document that will be verified by the study monitor.

7.5 Blood Sampling

Part 1

Approximately 310 mL of blood (± 5%) in overall will be collected from each subject in

- 30 samples/subject, 120-mL in overall for narlaprevir pharmacokinetics
- 4 samples/subject, 16-mL in overall for ritonavir pharmacokinetics
- 26 samples/subject, 104-mL in overall for tenofovir pharmacokinetics
- 1 sample/subject, 15-mL in overall for screening laboratory tests

- 6 samples/subject, 48-mL in overall for clinical laboratory tests

Part 2

Approximately 290 mL of blood (± 5%) in overall will be collected from each subject in

- 30 samples/subject, 120-mL in overall for narlaprevir pharmacokinetics
- 4 samples/subject, 16-mL in overall for ritonavir pharmacokinetics
- 20 samples/subject, 80-mL in overall for raltegravir pharmacokinetics
- 1 sample/subject, 15-mL in overall for screening laboratory tests
- 6 samples/subject, 48-mL in overall for clinical laboratory tests

Blood sampling has to be done at the indicated time points. In case the deviation is more than the criteria mentioned below, a comment has to be given in the comment section of the appropriate CRF page.

Table 9 Allowed time deviation without CRF comments

Time period after dosing	Comment in CRF is needed when deviation is more
0h < scheduled time ≤ 4h	2 min
4h < scheduled time ≤ 24h	10 min
scheduled time > 24h	60 min

Note: For pre-dose samples, a comment is required when the sample is withdrawn after dosing

7.6 Study Procedures

An overview of the study is provided in the Study Design Diagram in **Section 4.1**.The Study Flow Chart in **Section 4.2** summarizes the study procedures and the timing of the procedures to be performed at each visit. Individual study procedures are described below.

For details of the procedures for assessment and reporting of AEs, see **Section 7.7.2.4**, Assessment and Reporting of Adverse Events.

In order to minimize variability of evaluations, it is preferred that the same individuals perform the same types of evaluations on the same equipment for all subjects at each study site.

7.6.1 Explain Study and Obtain Written Informed Consent

The investigator or qualified designee will explain the study and all study requirements to the subject, answer all of his/her questions, and obtain written informed consent before performing any study-related procedure. A copy of the informed consent(s) will be given to the subject.

Issue or Collect Subject Identification Card

The investigator or qualified designee will provide the subject with a Subject Identification Card

after the subject provides written informed consent.

7.6.2 Review Inclusion/Exclusion Criteria Including Concomitant Medications

The inclusion and exclusion criteria will be reviewed by the investigator to ensure that the subject qualifies for the study. All appropriate medication and washout times will be discussed with the subject. All medications used during the 14 days prior to first drug administration or treatment intervention, will be recorded on the CRF.

7.6.3 Demographic Profile

The demographic profile required by the study CRF and permitted by local regulations should be entered. This information may include the subject's age (at baseline), ethnicity, gender and race.

7.6.4 Physical Examination

The investigator will perform a physical examination of the following organ systems at the times specified in **Section 4.2**, Study Flow Chart: Eyes, oropharynx, thyroid, respiratory system, cardiovascular system, abdomen, skin, extremities and reflexes

Clinically significant changes from physical examinations will be recorded as adverse events.

7.6.5 Medical History

A detailed medical history will be obtained by the investigator. Subject history should include information on clinically significant family and personal history, smoking history, history of diseases including past history of hepatitis, allergies or reactions to medications and food, seizures, and previous surgery, trauma, syncope, arrhythmias. Any clinically relevant changes found at any time during the study will be recorded as adverse events on the CRF.

7.6.6 Body Weight (kg) and Height Measurements (cm) Without Shoes

Body weight should be performed on the same scale for the same individual. Measurements should be recorded to the nearest kg and cm and on the CRF.

7.6.7 Body Mass Index (BMI)

BMI should be calculated using the formula and recorded in the source document but not be recorded on the CRF:

BMI = Weight (kg)/Height^2 (m)^2.

7.6.8 Test for HCV, hepatitis B Surface Antigen and HIV Antibodies, RW

Tests will be performed according to standard local procedures. A plan must be in place at the site(s) for the management of a positive test result according to local requirements. Results will be recorded on the CRF.

7.6.9 Screen for Drugs With a High Potential for Abuse

Urine tests for amphetamine, marijuana, morphine/heroin, cocaine, methamphetamine, barbiturates, benzodiazepines, phencyclidine, methadone and ecstasy (MDMA) will be conducted according to standard procedures. Positive results will be recorded on the Comment section of the CRF, and will be reported to the sponsor or CRO.

7.6.10 Clinical Laboratory Safety Tests

The following will be performed according to standard laboratory procedures. Samples should be collected in the fasted state, (after an overnight fast for morning sample collections and at least 4 hours without food for other samples) and prior to study drug administration.

Table 10 Standard laboratory procedures specification

Hematology	Chemistry	Urinalysis
RBC	Sodium	pH
Hematocrit	Potassium	Specific gravity
Hemoglobin	Chloride	Protein
Platelets	Glucose	Glucose
WBC	Blood urea nitrogen (BUN) or UREA	Ketones
Neutrophils	Creatinine	Blood
Lymphocytes	Calcium	Microscopic exam
Monocytes	Inorganic phosphorus	
Basophils	Total protein	
Eosinophils	Albumin	
	AST (SGOT)	
	ALT (SGPT)	
	GGT	
	Total bilirubin	
	Alkaline phosphatase	
	Uric acid	
	LDH	
	Cholesterol	
	Triglycerides	

The laboratory reference ranges should be available at site prior any laboratory testing is performed. If during the trial any laboratory result is outside the reference range and is considered to be clinically significant by the investigator, the test should be repeated at appropriate time

intervals until it returns to baseline or becomes a clinically insignificant finding. Any adverse clinically significant change will be recorded on the CRF as an Adverse Event. Laboratory tests will be recorded on the CRF.

7.6.11 Screening Number Assignment

A screening number will be assigned to each subject on completion of the study-specific informed consent by the site. Screening numbers will be recorded on the CRF as per **Section 7.4.1.3**.

7.6.12 Randomization/Dosing Number Assignment

A subject or randomization number will be assigned to each volunteer by the site using the subject/randomization numbers provided in **Section 7.4.1.3**. prior to the administration of narlaprevir treatment on Day1 of Period 1.

7.6.13 Record Adverse Events and Concomitant Medications

See **Section 7.7.2.4** and **Section 7.7.2.5**, Assessment and Reporting of Adverse Events; **Section 7.4.2**, Non-study Treatments; **Section 7.3.3,** Discontinuation Criteria.

7.6.14 Clinical Assessment of Electrocardiograms

7.6.14.1 Local ECGs

The 12-lead ECG (12-lead at 25 mm/sec reporting rhythm, ventricular rate, PR, QRS, and QT intervals) will be performed by the principal investigator or designee after the subject has been in the supine position for at least 5 minutes.

A commercial 12-lead electrocardiograph should be used. On the electrocardiograph should be recorded the date, time, subject demographics (e.g., age, and sex), subject number, and study-related information (e.g., protocol number and nominal time)

When a study assessment and ECG are in conflict, the ECG should be performed before the meal, pharmacodynamic or pharmacokinetic blood sample or at least 5 minutes afterward. This same timing for obtaining the ECG (i.e., before or after the blood collection) should be used for all ECG recordings. For a given subject all Baseline and post- treatment ECGs should be performed using the same ECG machine. Predose ECGs should be performed within 30 minutes prior to the scheduled time of drug administration.

QTcB will be calculated by Bazett's formula:

$$QTcB = \frac{QT}{\sqrt{RR}}$$

where QTcB is the QT interval corrected for heart rate, and RR is the interval from the onset of one QRS complex to the onset of the next QRS complex, measured in seconds, often derived from the heart rate (HR) as 60/HR (here QT is measured in milliseconds).

7.6.15 Vital Signs

The pretreatment vital signs will be considered the Baseline values. Vital signs will be obtained by the principal investigator or designee. Subjects will be in a seated or supine position for at least 3 minutes.

Systolic and diastolic blood pressure (mm Hg), pulse rate (bpm) and axilar body temperature (°C) and the actual clock time (24:00) will be recorded on the CRF. Any clinically significant change from baseline for vital sign measurement (not associated with another adverse event) will be recorded on the adverse event CRF form.

All blood pressure measurements should be made by consistently using the same arm and type of equipment with an appropriate cuff size. Pulse rate should be obtained manually by radial pulse palpation over a 30 second count or by a validated automated electronic device.

Body temperature should be measured consistently using the same approach.

For detailed schedule of vital signs measurement see **Section 4.2.**

If the scheduled time for vital sign measurements coincides with a blood collection, the vital signs should be performed prior to the blood collection, or at least 15 minutes afterwards. This same timing for obtaining the vital signs (before or after the blood collection) should be used for all vital sign measurements.

7.6.16 Treatment Administration

Refer to **Section 7.4** for Study Treatments to be administered. The time of dose administration should be recorded in CRF for each onsite dose administration.

7.6.17 Blood Samples for Determination of Plasma Concentrations of narlaprevir

4 mL of blood will be collected at the specified time points indicated in **Section 4.2**, Study Flow Chart, into the appropriate tubes (see **Laboratory Manual** for sample acquisition, shipping and labeling instructions).

Sample collection times (actual clock time using 24:00) are to be recorded in the CRF.

Sample collection time deviations will be determined using the actual collection times provided and do not need to be recorded in the CRF. However, any other deviation (e.g., missed sample, broken sample, inappropriate sample handling, etc) must be recorded on the comments page of the CRF.

7.6.18 Blood Samples for Determination of Plasma Concentrations of Ritonavir

4 mL of blood will be collected at the specified time points indicated in **Section 4.2**, Study Flow Chart, into the appropriate tubes (see **Laboratory Manual** for sample acquisition, shipping and labeling instructions). Sample collection times (actual clock time using 24:00) are to be recorded in the CRF.

Sample collection time deviations will be determined using the actual collection times provided and do not need to be recorded in the CRF. However, any other deviation (e.g., missed sample, broken sample, inappropriate sample handling, etc) must be recorded on the comments page of the CRF.

7.6.19 Blood Samples for Determination of Plasma Concentrations of Tenofovir

4 mL of blood will be collected at the specified time points indicated in **Section 4.2**, Study Flow Chart, into the appropriate tubes (see **Laboratory Manual** for sample acquisition, shipping and labeling instructions).

Sample collection times (actual clock time using 24:00) are to be recorded in the CRF.

Sample collection time deviations will be determined using the actual collection times provided and do not need to be recorded in the CRF. However, any other deviation (e.g., missed sample, broken sample, inappropriate sample handling, etc) must be recorded on the comments page of the CRF.

7.6.20 Urine Samples for Determination of Tenofovir Pharmacokinetics

Subjects will be instructed to void prior to dose administration and the urine will be collected as the predose sample. Two 50 mL aliquots of predose urine will be obtained from the well-mixed predose urine collection. All urine will be subsequently collected and pooled according to the collection intervals indicated in **Section 2.2**, Study Flow Chart. At the end of each collection interval, subjects will be instructed to empty their bladder, this urine added to the present pooled urine, and this will mark the end of the present collection interval and the beginning of the next collection interval. The total volume of the urine from postdose collection will be recorded for each subject.

All urine will remain refrigerated or on ice during the collection intervals. Two 50 mL aliquots of urine will be obtained from each well- mixed, pooled urine collection interval and transferred into the appropriate tubes (see **Laboratory Manual** for sample acquisition, shipping and labeling instructions). Two aliquots will be used for profiling (primary and backup).

7.6.21 Blood Samples for Determination of Plasma Concentrations of Raltegravir

4 mL of blood will be collected at the specified time points indicated in **Section 4.2**, Study Flow Chart, into the appropriate tubes (see **Laboratory Manual** for sample acquisition, shipping and labeling instructions).

Sample collection times (actual clock time using 24:00) are to be recorded in the CRF.

Sample collection time deviations will be determined using the actual collection times provided and

do not need to be recorded in the CRF. However, any other deviation (e.g., missed sample, broken sample, inappropriate sample handling, etc) must be recorded on the comments page of the CRF.

7.7 Study Assessments and Analysis

7.7.1 Pharmacokinetics/Pharmacodynamics/Safety

7.7.1.1 Pharmacodynamics

Not applicable for this study.

7.7.1.2 Pharmacokinetics

For detection of study drug concentrations in plasma or urine (for tenofovir) HPLC-MS (High performance liquid chromatography - mass spectrometry) method will be used [32-35]. Details on the planned methods are provided below:

Mobile phase A: 0,2 % formic acid

Mobile phase B: acetonitrile

Sample preparation will be performed by the protein precipitation with an organic solvent.

Chromatographic conditions:

Chromatograph:	High performance liquid chromatograph Shima-dzu LCMS-8040, equipped with two high-pressure pumps, online degasser of mobile phase, column thermostat, autosampler for 192 samples and mass-detector with triple quadrupole or similar device can be used.
Column	Reprosil Pur Basic C18, 1.9 um, 2x50 mm. An alternate column that met the requirements of system can be used
Mobile phase	Mixture of mobile phase A and mobile phase B
Flow velocity	0,5 ml/min for Narlaprevir and Tenofovir; 0,4 ml/min for Ritonavir and Raltegravir
Mass -detector	Ionization method is electrospray (ES+) for Narlaprevir and Tenofovir and positive ionization (MRM (E+)) for Ritonavir and Raltegravir. Detection is carried out by the typical ion-product obtained from the fragmentation of the target substance in the collision cell
Column temperature	25 °C for Narlaprevir and Tenofovir; 40 °C for Ritonavir and Raltegravir
Sample volume	20 ul for Narlaprevir and Tenofovir; 10ul for Ritonavir and Raltegravir

In order to meet the suitability test requirements of the chromatographic system adjustment of the chromatographic conditions will be allowed.

Standard solution should be chromatographed at least 3 times to check the suitability of the system.

The chromatographic system will be considered suitable if the following conditions are met:

- chromatographic column efficiency calculated by the analyte peak on the chromatogram of the standard solution is not less than 2000 theoretical plates;
- asymmetry factor calculated for the analyte peak on the chromatogram of the standard solution is not more than 2.0;
- the retention factor (k ') should be greater than 2.0;

To obtain high accuracy quantitative results with mass-spectrometric detection, analyte labeled with stable isotopes will be used as an internal standard (e.g., narlaprevir d5, tenofovir d9, ritonavir d6, raltegravir d3).

Analyte concentration will be calculated using special software (Analyst for Narlaprevir and Tenofovir and LabSolutions 5.75 for Ritonavir and Raltegravir) with the calibration curve normalized by the chromatographic peak area of the analyte. A linear function normalized as 1/x will be used as calibration curve for Narlaprevir and Tenofovir. A linear function normalized as 1/x2 will be used as calibration curve for Ritonavir and Raltegravir.

Estimated calibration ranges: 10 - 10000 ng/ml for Narlaprevir, 10 - 2000 ng/ml for Tenofovir, 5 - 1000 ng/ml for Ritonavir, 10 - 10000 ng/ml for Raltegravir.

Part 1

Individual plasma narlaprevir and tenofovir concentration data will be used to estimate the following primary pharmacokinetic variables, for the determination of bioavailability comparisons:

$AUC_{(tau)}$	Area under the concentration-time curve during a dosing interval τ at steady state
C_{max}	Maximum observed plasma concentration
T_{max}	Time to maximum observed plasma concentration
C_{min} at steady state	Minimum observed plasma concentration during a dosing interval τ

Tenofovir only:

$Ae_{(24)}$ -	Amount excreted in 24 hours at steady-state CLr- Renal clearance (Ae/AUC) at steady-state

The following additional parameters will be evaluated, if appropriate:

$t_{1/2}$	Terminal phase (elimination) half-life
CL/F	Apparent total body clearance
V/F	Apparent volume of distribution

Predose plasma ritonavir concentration data may be used to estimate C_{trough}.

Part 2

Individual plasma narlaprevir and raltegravir concentration data will be used to estimate the following primary pharmacokinetic variables, for the determination of bioavailability comparisons:

$AUC_{(tau)}$	Area under the concentration-time curve during a dosing interval τ at steady state
C_{max}	Maximum observed plasma concentration
T_{max}	Time to maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration during a dosing interval τ at steady state

The following additional parameters will be evaluated, if appropriate:

$t_{1/2}$	Terminal phase (elimination) half-life
CL/F	Apparent total body clearance
V/F	Apparent volume of distribution

Predose plasma ritonavir concentration data may be used to estimate C_{trough}.

7.7.1.3 Pharmacokinetics-Pharmacodynamics

Not applicable for this study.

7.7.1.4 Interpharmacodynamic (PD-PD) and Safety-PD Analysis

Not applicable for this study.

7.7.2 Safety Monitoring and Assessments

7.7.2.1 Specification of Safety Variables

Adverse events will be tabulated by treatment group, BSOC, and severity. ECGs and clinical

safety laboratory values will be listed by date and time, values and changes from baseline will be tabulated using summary statistics. Vital signs will be listed by day and time.

7.7.2.1.1 Assessment and Reporting of Adverse Events

Adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical-trial subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All adverse events must be recorded into the CRF with the following information:

- the severity grades using the categories mild / moderate / severe;
- its relationship to the study drug(s): unassessable, conditional, unlikely, possible, probable, certain, unrelated
- its duration (onset and stop dates or if ongoing at final exam);
- its outcome
- the actions taken (no actions taken; study drug(s) permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; subject hospitalized/subject's hospitalization prolonged;
- whether it constitutes a serious adverse event (SAE) (see the criteria in the **section 7.7.2.2.1**).

All non-serious AEs must be collected and evaluated from initiation of treatment with study drugs through the last study visit. Non-serious AEs that occur before this time are to be listed in the «Medical History» section of the CRF.

Information about common side effects already known about the study drugs can be found in the Investigator Brochure (for investigational drug) or in the approved Product Information (for marketed medications). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed.

7.7.2.2 Assessment of Adverse Events Severity and Relationship to Treatment

Severity

The investigator should use the following definitions to rate the severity of any adverse event being collected:

- **Mild:** an experience that is usually transient and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. Includes transient laboratory test alterations.
- **Moderate:** an experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.
- **Severe:** an experience that requires therapeutic intervention. The experience interrupts usual daily activities.

Relationship to Treatment

The investigator should use the following definitions for any adverse event being collected to assess the relationship of the adverse event to the use of the study treatment combination:

- Unassessable
- Conditional
- Unlikely
- Possible
- Probable
- Certain
- Unrelated

Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide more plausible explanations
Conditional	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Unrelated	• Another cause of the event is the most plausible; and/or • A clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or • A causal relationship is considered biologically implausible

If an investigator's opinion of possible, unlikely, unrelated to drug was given, an alternate aetiology had to be provided by the investigator for the adverse event (e.g., concomitant treatment, illness, study procedures, etc).

7.7.2.2.1 Monitoring of Adverse Events

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent. An assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drugs, the interventions required to treat it, and the outcome. All adverse events should be treated appropriately. Any actions taken and follow-up results must be recorded on the appropriate page of the CRF and in the subject's source medical documents.

Definition of Serious Adverse Events

Serious Adverse Event (SAE): any untoward medical occurrence or reaction that meets any of the following criteria:

- Results in death;
- Is life-threatening (Life threatening in this context refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe);
- Requires in-subject hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly/birth defect in fetus or child born to a subject administered the drug;
- Other medically important event (Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse).

SAEs must be reported from the time subject's written consent and enrollment to participate in the clinical trial through the time of the last visit. SAEs that occur after this time with suspected association to the investigational drug or clinical trial procedures must also be reported to the company-sponsor.

Information about all SAEs is collected and recorded on the standard form «Serious Adverse Event Report». Investigator must complete the Serious Adverse Event Report Form and send the copy of it to "Almedis" CJSC drug safety responsible person on safety@almedis.ru or by fax +7 495 937 43 19 immediately or within 24 hours. The original copy of the SAE Report Form must be

kept with the subject's documentation at the study site.

All SAEs should be followed up until stable or resolved, i.e. a final outcome is reached. Any follow-up information that is obtained must be forwarded to the company-sponsor observing the same timelines as for initial reports (within 24 hours). Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the subject continued or withdrew from study participation.

All SAEs will be collected and reported to the competent authorities in accordance with the applicable regulations. .Drug safety responsible person or designee is responsible for notification of all principal investigators involved in clinical study about all new relevant Suspected Unexpected Serious Adverse Reactions (SUSARs), which were revealed in ongoing clinical studies of the medicinal product. Investigator notifications are made by fax or e-mail. Cover letter in standard format has to be sent along with SUSARs. After receiving and reading of SUSAR notification, the Investigator or designee have to fax or send by e-mail signed Investigators Notification Form to "Almedis" CJSC DSPV on +7 495 937 43 19, safety@almedis.ru and submit information about SUSAR to the Local Ethics Committee of the medical institution for information.

7.7.2.2.2 Reporting of Pregnancies

Each pregnancy in the female partners of any males who took study drugs in this study must be reported to the company-sponsor within 24 hours of learning of its occurrence. Pregnancy outcomes should be collected.

The Pregnancy Report Form must be used for reporting pregnancies and must be completed for any subject who becomes pregnant after dosing of study drugs. Pregnancy Report Form must be submitted to the company-sponsor according to SAE reporting requirements.

Pregnancy is to be handled as a non-serious event, unless it is falls into one of the following categories:

- Reports of congenital anomalies in the foetus/child;
- Reports of foetal death;
- Spontaneous abortions; and
- Reports of adverse reactions in the neonate that are classified as serious.

7.7.2.2.3 Preplanned Hospitalizations or Procedures

Not applicable

7.7.2.3 Reporting of Investigational Medicinal Product Quality Complaints

Any defect or possible defect in an investigational medicinal product (defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial) must be reported by the investigator to the designated sponsor representative within 24 hours of first becoming aware of the possible defect. This report to the sponsor may be made by telephone, or

by e-mail, or by faxing the quality complaint to the designated sponsor representative. The product and packaging components in question, if available, must be stored in a secure area under specified storage conditions until it is determined whether the product is required to be returned for investigation of the defect. If the product complaint is associated with a SAE, the SAE must be reported separately in accordance with the protocol, and the SAE report should mention the product quality complaint.

7.7.2.4 Monitoring

Before the study initiation a company-sponsor representative will review the protocol and CRF with the investigators. During the study a monitor will visit the clinical sites regularly to check the completeness of subject' source documents, the accuracy of entries on the CRFs, the adherence to the protocol, Good Clinical Practice and local regulatory requirement, the progress of enrollment, and to ensure that study drugs are being stored, dispensed, and accounted for according to specifications. In addition, a monitor will visit the clinical sites to monitor at least the first dosing to check the conduction of study procedures at dosing visits, adherence to the protocol, Good Clinical Practice and local regulatory requirements. Investigators and other appropriate study personnel must be available to assist a monitor during these visits.

The investigator must maintain source documents, including all demographic and medical information, laboratory data, and the results of any other assessments for each subject in the study. The investigator also has to keep signed copy of informed consent for each subject.

The investigator must give a monitor access to all relevant source documents to confirm their consistency with the CRF data. Checks of the consistency of the source data with the CRFs will be performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

7.7.2.4.1 Monitoring Laboratory Assessments

The clinical laboratory values will be reviewed by the investigator for significance and consideration as an AE.

7.7.2.5 Discontinuation, Treatment Interruption Due to Safety Reasons

7.7.2.5.1 Discontinuation

See **Section 7.3.3** for the criteria by which a subject must be discontinued. Should a subject be discontinued from the trial, complete the visit activities as specified for discontinuation in the Trial Flow Chart in **Section 4.2**.

7.7.2.5.2 Temporary Interruption of Treatment for a Subject

A subject may not temporarily interrupt and then restart treatment. The investigator is to discontinue a subject if necessary according to the criteria provided in **Section 7.3.3** .

7.8 Criteria for Early Termination of the Trial

There are no prespecified criteria for terminating the trial early.

8 STATISTICAL ANALYSIS AND REPORTING PLANS

Approximately 36 subjects with 18 in each of two are expected to be randomized/enrolled in the study and receive treatments.

8.1 Data Sets

The pharmacokinetic analysis will only include subjects who received at least one dose of treatment and who have at least one non-missing measurement of concentration. All subjects who are assigned a Randomization Number or Subject Number and who received at least one dose of treatment will be included in the safety analyses.

8.2 Demographic and Other Baseline Characteristics

Demographic variables (e.g., sex, race, age, weight) will be listed and summarized using descriptive statistics for the entire study population and for each part of study.

8.3 Pharmacodynamic and Pharmacokinetic Analyses

8.3.1 Pharmacokinetic Parameters

Mean plasma concentrations of drug along with the derived PK parameters will be summarized by treatment separately for each part (cohort).

The primary PK parameters for Parts 1 and 2 are narlaprevir C_{max} and AUC. All data will be log-transformed before analysis. An ANOVA model on log-transformed PK parameters with treatment, period, sequence treated as fixed effects and subject nested within sequence treated as random effect will be used to obtain an estimate of intra-subject variability. Estimates of the adjusted mean differences and corresponding 90% confidence intervals will be constructed. The resulting estimates will be exponentiated to provide the adjusted geometric mean ratios for the untransformed parameters with the corresponding 90% CIs for the ratios. No formal confirmatory hypothesis testing is planned.

Part 1

Log transformed C_{max} and AUC for narlaprevir and tenofovir will be analyzed separately. For narlaprevir, the primary comparison will be treatment C vs. A; and for tenofovir the primary comparison will be treatment C vs. B.

Part 2

Log transformed C_{max} and AUC for narlaprevir and raltegravir will be analyzed separately. For narlaprevir, the primary comparison will be treatment C vs. A; and for raltegravir the primary comparison will be treatment C vs. B.

8.3.2 Pharmacodynamics

Not applicable for this study.

8.3.3 Pharmacokinetic-Pharmacodynamic Analysis

Not applicable for this study.

8.3.4 Pharmacodynamic-Pharmacodynamic Analysis

Not applicable for this study.

8.4 Determination of Sample Size/Power/Level of Significance

Based on study P04986 (see Investigator Brochure) and reference [32], the inter-subject variability (CV%) for narlaprevir (tablet) Cmax and AUC is estimated to be about 33%; the inter-subject variability (CV%) for narlaprevir Cmax and AUC when coadministered with ritonavir is estimated to be about 20%. Assuming the intra-subject variability (CV%) is about 70% of the inter, the intra-subject variability (CV%) for narlaprevir and narlaprevir coadministered with ritonavir Cmax and AUC is estimated to be about 23% and 14%, respectively.

Part 1

The intra-subject variability (CV%) for tenofovir is assumed approximately 20% (10-15% for AUC24h and 15-20% for Cmax) as a maximum value estimated from the published CIs [22, 23, 24], the expected difference is set to 0 (Ratio = 1.00).

The study with 18 subjects will detect an increase in exposure of 22% or a decrease of 18% between tenofovir coadministered with narlaprevir and ritonavir vs. tenofovir alone with 80% power and alpha=0.1 two sided.

The study with 18 subjects will detect an increase of 15% or a decrease of 13% exposure between narlaprevir coadministered with ritonavir and tenofovir vs. narlaprevir coadministered with ritonavir with 80% power and alpha=0.1 two sided.

Part 2

The sample size for Part 2 will be 18.

For raltegravir, sample size calculations were based on intrasubject CV% of 45% for AUC12h and 60% for Cmax [25-29]. CVs estimated from the published CIs are 35-50% for AUC and 40-70% for Cmax.

The study with 18 subjects will detect an increase of 55% or a decrease of 35% exposure (AUC) as well as detect an increase of 76% or a decrease of 43% Cmax between raltegravir coadministered with narlaprevir and ritonavir vs. raltegravir alone with 80% power and alpha=0.1 two sided.

The study with 18 subjects will detect an increase of 15% or a decrease of 13% exposure between

narlaprevir coadministered with ritonavir and raltegravir vs. narlaprevir coadministered with ritonavir with 80% power and alpha=0.1 two sided.

8.5 Interim Analysis

Data may be analyzed after completion of each part or at the end of the study.

8.6 Safety

8.6.1 Adverse Events

All AEs noted during the study will be listed. Treatment emergent and treatment-related AEs will be tabulated by body system/organ class and preferred term. Summaries of severity and relationship to treatment will also be provided.

8.6.2 Clinical Laboratory Tests

The results of hematology and blood chemistry will be listed for each subject. Laboratory values outside the normal ranges will be flagged. Summary statistics by treatment will be provided for laboratory values at each time point and for change from baseline. Baseline is defined as the predose time point.

8.6.3 Vital Signs

Systolic and diastolic blood pressure, heart rate, and body temperature will be listed for each subject. Summary statistics by treatment at each time point will be provided. Baseline is defined as the predose time point.

8.6.4 Physical Examination

The results of the physical examinations at Screening, and Pre-Dose visits will be listed in the medical history. Post-baseline findings of the physical examinations that meet the criteria of an AE (**Section 7.7.2.2.1**) will be listed in the relevant AE listings.

8.6.5 Electrocardiogram

The results of the ECG will be listed for each subject. If applicable, summary statistics of ECG results will be provided.

8.6.6 Other Safety

Not applicable.

9 ADHERENCE TO ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

This study was designed and shall be implemented and reported in compliance with Good Clinical Practice (GCP), with applicable local regulations (including RF National Standard “Good Clinical Practice”), and with the ethical principles laid down in the Declaration of Helsinki.

9.1 Ethical Conduct of the Study

9.1.1 Independent Ethics Committee or Institutional Review Board

Prior to initiation of the trial at any site, the trial, including the protocol, informed consent, and other trial documents must be approved by an appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The IRB/IEC must be constituted according to applicable regulatory requirements. As appropriate, amendments to the protocol must also be approved by the IRBs/IECs before implementation at the sites, unless warranted to eliminate an immediate hazard. The IRB/IEC approval should be obtained in writing, clearly identifying the trial, the documents reviewed (including informed consent), and the date of the review. The trial as described in the protocol (or amendment), informed consent, and other trial documentation may be implemented only after all the necessary approvals have been obtained and the sponsor has confirmed that it is acceptable for the investigator to do so.

In the event that the IRB/IEC requires changes in the protocol, the sponsor shall be advised and must approve the changes prior to implementation. The investigator shall not modify the trial described in the protocol once finalized and after approval by the IRB/IEC without the prior written approval of sponsor.

If the investigator submits the trial protocol and statement of informed consent to the IRB/IEC, the investigator or qualified designee will forward the approvals to the sponsor.

9.1.2 Subject Information and Consent

The details of the protocol must be provided in written format and discussed with each potential subject, and written informed consent must be obtained for all subjects before any trial-related procedure is performed. In obtaining informed consent, the information must be provided in language and terms understandable to the subject. The subject must give their written consent to participate in the trial. The signed and dated consent form itself must be retained by the investigator as part of the trial records. A copy of the signed and dated consent form must be given to the subject. The consent form must include all of the required elements of informed consent in accordance with ICH Guidelines E6 and local laws. In addition, the sponsor specifically requests that the consent form identify it as the sponsor and state that use of the investigational product(s) is experimental and the side effects of the investigational product(s) are not completely known. The consent form must be approved by the appropriate IRB/IEC and sponsor before trial initiation at a trial site. Any subsequent changes to the approved informed consent form must be reviewed and approved by the appropriate IRB/IEC and sponsor before implementation.

9.1.3 Subject Identification Card

A Subject Identification Card will be provided to each subject to carry on his or her person (e.g., in a wallet) at all times while the subject is participating in the trial, if required in **Section 4.2**. The card is to be shown to caregivers in the event of an emergency.

At a minimum, the card must contain the following information:

1. Protocol number;

2. The subject's protocol identification number;

3. A statement identifying the card-carrier as a participant in a clinical trial (e.g., "This person is participating in a clinical research trial.");

4. A statement indicating the person might be taking an investigational drug (e.g., "This person is taking an experimental drug which could have interactions with other medications, or placebo"); and

5. Contact information in the event of an emergency or hospitalization. The contact information on the card is to be the investigator or a designated site contact, rather an contact from within the sponsor;

The cards may also include other trial-specific information to assist with treatment decisions in the event of an emergency, such as types of concomitant therapies that may, or may not be, permitted as part of emergency treatment. As with any other information provided to subjects, the Subject Identification Card must be approved by the IRB/IEC. Monitors will request that Investigators provide Subject Identification Cards to each subject. Investigators will be asked to request that subjects carry the cards with them while they are participating in the trial.

9.2 Reporting Trial Data to the Sponsor

9.2.1 Data Collection Forms

The sites will be provided with data collection forms (paper Case Report Forms (CRF),); and other appropriate data collection forms as the trial requires. The investigator is to provide subject data according to the given instructions, in the designated data collection form, compliant with GCP practices. The sites will be also provided with instructions for assisting other parties - such as a central laboratory - to collect data. As instructed by the Sponsor, a designated central laboratory may collect data in a database and provide the completed database to sponsor and/or CRO. All data collection forms and the databases from the trial are the exclusive property of sponsor.

The investigator must maintain records and data during the trial in compliance with all applicable legal and regulatory requirements. Each data point must be supported by a source document at the trial site. Any records or documents used as the source of information (called the "subject source data") are to be retained for review by authorized representatives of the sponsor or a regulatory agency.

The investigator will ensure that there are sufficient time, staff, and facilities available for the

duration of the trial to conduct and record the trial as described in the protocol and according to all applicable guidances, laws, and regulations.

All data collection forms (CRFs) should be completed as soon as possible after the evaluation has occurred. All dates appearing on the subject data collection forms for laboratory tests, cultures, and other data collected, must be the dates on which the specimens were obtained, or the procedures performed.

9.2.2 Preparing Case Report Forms for All Subjects

Subject names, initials, or other personal information that is beyond the scope of the trial from any subject should not be collected. Subjects are not to be identified by name or initials on the CRF or any trial documents. The only acceptable identification for a subject that may appear on a CRF or trial document is the unique subject identification number. The investigator must maintain contact information for each participant so that all can be quickly contacted by the investigator, if necessary. All entries into CRFs are the responsibility of the investigator and must be completed by the investigator or a qualified designee.

9.3 Publications and Other Rights

9.3.1 Use of Trial Information in a Publication

The company-sponsor (R-Pharm) has sole ownership of all data, results, reports, and any other information collected and full rights of publication based on data from this study and will maintain full access to the database.

Upon the study completion and finalization of the clinical study report the results of this trial will be submitted for publications. Publications will be based on data from all centers, analyzed as stipulated in the protocol. The investigator agrees not to publish or publicly present any interim results of the study or data gathered from one center or a small group of centers before the global publication without the prior written consent of the sponsor. The investigator further agrees to provide to the sponsor prior to submission for publication or presentation, review copies of abstracts or manuscripts for publication that report any results of the study. The sponsor shall have the right to review and comment with respect to publications, abstracts, slides, and manuscripts with regard to the following concerns:

- Proprietary information that is protected by the provisions contained in;
- The accuracy of the information contained in the publication;
- To ensure that the presentation is fairly balanced and in compliance with applicable regulations;
- Others.

9.4 Trial Documents and Records Retention

During the trial and after termination of the trial – including after early termination of the trial – the investigator must maintain copies of all documents and records relating to the conduct of

the trial. This documentation includes, but is not limited to, protocols, CRFs and other data collection forms, advertising for subject participation, adverse event reports, subject source data, correspondence with health authorities and IRBs/IECs, consent forms, investigator's curricula vitae/biosketch, monitor visit logs, laboratory reference ranges, and laboratory certification or quality control procedures and laboratory director curriculum vitae. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, or as specified below. The sponsor must be consulted if the investigator wishes to assign the files to someone else, remove them to another location, or is unable to retain them for the specified period.

The investigator must retain trial records for the amount of time specified by applicable laws and regulations. At a minimum, trial records must be retained for the amount of time specified by ICH Guidelines or the EU Good Clinical Practices Directive, whichever is longer:

1. The ICH Guidelines specify that records must be retained for a minimum of 2 years after a marketing application for the indication is approved (or not approved) or 2 years after notifying the appropriate regulatory agency that an investigation is discontinued.

2. The EU GCP Directive specifies that trial records must be retained for 5 years after the completion of the trial.

All trial documents shall be made available if required by relevant health authorities, specialists, authorized by sponsor, and audits. The investigator should consult with the sponsor prior to discarding trial and/or subject files.

Sponsor will retain all required documentation pertaining to the trial for the lifetime of the investigational product.

10 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

10.1 Sponsor

The sponsor of this study is the JSC «R-Pharm».

10.2 Investigators

10.2.1 Selecting Investigators

Only investigators qualified by training and experience to perform a clinical investigation with narlaprevir are selected. The sponsor will contact and select all investigators (i.e., the legally responsible party[ies] at each trial site), who, in turn, will select their staff.

10.2.2 Clinical Study Report Coordinator Investigator

A Clinical Study Report (CSR) will be prepared by the sponsor or its qualified designee to describe the results of the trial. One of the investigators shall be selected by the sponsor to provide approval of the final CSR in writing. The investigator chosen to review and approve the CSR is to be called the CSR Coordinating Investigator. The sponsor is to select the CSR Coordinating Investigator from the investigators using the following criteria:

1. Must be the Principal Investigator at a trial site actively enrolling subjects and participating

in the trial;

2. Must be willing and capable of providing approval of the CSR in writing.

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Appendix 1 Known Potential Toxicities of Investigational Products

Ritonavir	Raltegravir	Tenofovir
Very common (may affect more than 1 in 10 people)		
• upper and lower stomach ache		• diarrhoea, being sick (vomiting), feeling sick (nausea), dizziness
• vomiting		Tests may also show:
• diarrhoea (may be severe)		• abnormally low phosphate in the blood
• feeling sick (nausea)		
• flushing, feeling hot		
• headache		
• dizziness		
• pain in the throat		
• cough		
• upset stomach or indigestion		
• a tingling sensation or numbness in the hands, feet or around the lips and mouth		
• feeling weak/tired		
• bad taste in the mouth		
• damage to the nerves that can cause weakness and pain		
• itching		
• rash		
• joint pain and back pain		
Common (may affect up to 1 in 10 people)		
• allergic reactions including skin rashes, severe swelling of the skin and other tissues	• decreased appetite	• headache, stomach pain, feeling tired, feeling bloated, flatulence
• changes in fat distribution	• trouble sleeping; abnormal dreams; nightmare; abnormal behaviour; feelings of deep sadness and unworthiness	Tests may also show:
• increase in cholesterol	• feeling dizzy; headache	liver problems
• inability to sleep (insomnia)	• spinning sensation	
• increase in triglycerides	• bloating; abdominal pain; diarrhoea; excessive gas in the stomach or bowel; feeling sick; vomiting; indigestion; belching	
• anxiety	• certain kinds of rash (more often when used in combination with darunavir)	
• gout	• tiredness, unusual tiredness or weakness; fever	

• increase in urination	• increased liver blood tests; abnormal white blood cells; increased fat levels in blood; increased level of enzyme from salivary glands or pancreas	
• reduced kidney function		
• seizures (fits)		
• low levels of blood platelets		
• thirst (dehydration)		
• abnormally heavy periods		
• wind (flatulence)		
• loss of appetite		
• mouth ulcer		
• muscle aches (pain), tenderness or weakness		
• fever		
• weight loss		
• changes in blood test results (such as blood chemistry and blood count)		
• confusion		
• difficulty paying attention		
• fainting		
• blurred vision		
• swelling of the hands and feet		
• high blood pressure		
• low blood pressure and feeling faint when getting up		
• coldness in the hands and feet		
• acne		