DNDi
Drugs for Neglected Diseases *initiative*

CLINICAL TRIAL PROTOCOL SYNOPSIS

A Phase 1, Open-Label, Four-Period, Two-Sequence, Two-Treatment, Single Dose, Randomized, Crossover Bioequivalence Study of a Test Tablet Formulation of Ravidasvir with the Reference Tablet Formulation of Ravidasvir in Healthy Adult Volunteers Under Fasting Conditions

Name of product(s)	*Reference product: Ravidasvir 200 mg tablet manufactured by European Egyptian Pharmaceutical Industries (EEPI), Egypt* *Test product: Ravidasvir 200 mg tablet manufactured by Doppel Farmaceutici, Italy*
Drug Class	*NS5A Inhibitor*
Phase	*Phase 1*
Indication	*HCV infection*
Clinical Trial Protocol Number	*DNDiHCV002*
Sponsor	*DNDi* *Chemin Louis Dunant 15,* *1202 Geneva, Switzerland* *Phone: +41 22 906 9230*
Principal Investigator	[redacted]
SAC approval	*TBC*
Clinical Trial Protocol Synopsis Version / Date	*Version 1.0 23rd February 2018*

PROTOCOL SYNOPSIS

Background and rationale	Ravidasvir (RDV) is a NS5A inhibitor, which exhibits potent inhibition of HCV replication in HCV replicon assays. Its pharmacological profile is very similar to that of daclatasvir (DCV), the reference pangenotypic NS5A inhibitor. The sofosbuvir and ravidasvir combination showed to be highly efficacious and safe in the Phase 3 study performed in patients infected by HCV genotype 4 in Egypt. Then the Malaysia Thailand study hypothesizes that sofosbuvir plus ravidasvir constitutes a pan-genotypic, potent and safe regimen which can be used in decentralized public health settings under the supervision of appropriately trained health care professionals. Such a combination will not require intensive pre-treatment evaluation or monitoring and can thus be scaled up together with active identification and linkage to care of HCV infected persons. 301 patients were included in the study and the analysis is underway. During the course of development, a new batch of ravidasvir tablets has been prepared by the proposed commercial manufacturer (Doppel Farmaceutici, Italy). Tablets manufactured by Doppel Farmaceutici are intended to be used in subsequent clinical trials and be registered as the commercial product. The purpose of this Phase 1, Open-Label, Four-Period, Two-Sequence, Two-Treatment, Single Dose, Randomized, Crossover Bioequivalence Study is to assess if ravidasvir 200 mg tablets supplied by EEPI and tablets from Doppel Farmaceutici are bioequivalent.
Trial Objectives	**Primary objectives:** To compare the rate and extent of absorption for RDV when administered as a single 200 mg oral dose of the proposed commercial product (“test”) produced by Doppel Farmaceutici with the clinical trial product (“reference”) manufactured by EEPI in healthy volunteers, under fasted conditions. **Secondary objectives** To evaluate the safety and tolerability of single oral doses of RDV in healthy volunteers.

Trial Endpoints	**Primary Endpoint** Plasma RDV Cmax, area under the plasma concentration-time curve from time of intake until infinity (AUC0-∞), and area under the plasma concentration-time curve from time of intake until the last quantifiable concentration (AUC0-t) will be calculated based on plasma RDV concentrations at pre-dose (time 0 hours) and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 24, 36, and 48 hours post-dose. **Secondary Endpoint(s)** ***Pharmacokinetics:*** Secondary PK endpoints include time to reach the maximum plasma concentration (tmax), mean residence time (MRT), elimination rate constant (λz), elimination half-life (t1/2, estimated based on λz), apparent volume of distribution, terminal phase (Vz/F), and apparent clearance (CL/F). ***Safety:*** Safety and tolerability will be assessed by monitoring clinical adverse events (AEs), vital signs, 12-lead ECGs, safety-related clinical laboratory tests (clinical chemistry, haematology, and urinalysis), and physical examinations.
Trial Design	This is an open-label, single-center, single-dose, randomized two-way crossover (2 treatments, 4 periods and 2 sequences) study of a test tablet formulation of ravidasvir with the reference tablet formulation of ravidasvir in healthy adult volunteers under fasting conditions. This replicate design will allow the possibility to scale the acceptance range for Cmax if the observed intra-subject coefficient of variation for the reference formulation is greater than 30%. A total of 36 healthy subjects will be enrolled.
Main Entry Criteria Inclusion Exclusion	**Inclusion criteria** Healthy volunteers must meet all of the following inclusion criteria (as applicable) to be eligible for participation in this study: • Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures. • Must be between 18 and 55 years of age, inclusive. • Must be a non-smoker. The use of nicotine or nicotine-containing products must be discontinued 90 days prior to the first dose of study drug. Users of electronic cigarette are not allowed to participate in this study. A smokerlyzer test will be performed to estimate the amount of carbon monoxide in the breath. • Must have a calculated body mass index (BMI) of 18.0 to 29.9 kg/m2. • Must be HIV-1 antibody negative. • Must be hepatitis B (HBV) surface antigen negative.

	• Must be hepatitis C (HCV) antibody negative. • Females of childbearing potential must have a negative serum pregnancy test at Screening and on Day 0, D7, D14, D21 and D29 (post-study safety assessment). • Females of childbearing potential must agree to utilize highly effective contraception methods (with the exception of hormonal contraceptive) from 3 weeks prior to baseline (Day 0) throughout the duration of study treatment and for 30 days following the last dose of study drug. Female healthy volunteers who utilize hormonal contraceptive as one of their birth control methods are not allowed to participate in this study. • Healthy volunteers must, in the opinion of the Investigator, be in good health based upon medical history, physical examination (including vital signs), and screening laboratory evaluations (haematology, chemistry, and urinalysis) must fall within the normal range of the local laboratory's reference ranges unless the results have been determined by the Investigator to have no clinical significance. • Have either a normal 12-lead electrocardiogram (ECG) or one with abnormalities that are considered clinically insignificant by the Investigator. • Must have negative urine screen for drugs of abuse (including ketamine, amphetamines, tetrahydrocannabinol, morphine, methamphetamine, and benzodiazepines) • Must be willing and able to comply with all study requirements. **Exclusion criteria** Healthy volunteers who meet any of the following exclusion criteria (as applicable) are not to be enrolled in this study: • Healthy volunteers with any hematologic or urinary analyte that is outside the normal limits of the study laboratory at Screening will be excluded • Pregnant or lactating female healthy volunteers. • Have any serious or active medical or psychiatric illness which, in the opinion of the Investigator, would interfere with subject treatment, assessment, or compliance with the protocol. This would include renal, cardiac, hematologic, hepatic, pulmonary (including chronic asthma), endocrine (e.g., diabetes), central or peripheral nervous, gastrointestinal (including an ulcer), vascular, metabolic (thyroid disorders, adrenal disease), or immunodeficiency disorders, active infection, or malignancy that is clinically significant or requiring treatment. • Have participated in an investigational trial involving administration of any investigational compound within 90 days prior to the study dosing or 5-times the half-life of the drug tested in the previous clinical trial, whichever is longer (time calculated relative to the last dose in the previous clinical trial). • Current alcohol or substance abuse judged by the Investigator to potentially interfere with healthy volunteer compliance.

	• Have poor venous access and unable to donate blood. • Have donated blood (<500ml) within two months of study dosing. • Have donated plasma within 7 days of study dosing. • Have difficulty in swallowing solids like tablets. • Have taken any prescription medications or over-the-counter medications including herbal products within 1 week of commencing study drug dosing with the exception of vitamins and/or acetaminophen and/or ibuprofen. • Female healthy volunteers who utilize hormonal contraceptive as one of their birth control methods. • Have a history of significant drug allergy. • Smokers and users of electronic cigarette. • Unable to comply with study requirements. • Believed by the study Investigator to be inappropriate for study participation for any reason
Study Duration and Study treatments	Screening will take place within 28 days before Study Day 1. Eligible healthy volunteers will come to the Clinical Study Unit in the late afternoon/evening of Day 0 (the day before the first dose of study medication). On Day 1, the 36 healthy volunteers will receive in a randomized fashion (1:1), a single oral dose of RDV in the form of the reference tablet formulation or the test tablet formulation of RDV, under fasted conditions[1]. Intensive PK sampling and clinical and laboratory safety monitoring will be conducted post-dose during Days 1-3 (please see schedule of events). Healthy volunteers are expected to remain at the research facility until the 48-hour post-dose PK sample is obtained and safety assessments (on Day 3) are performed. Subsequently, after a washout period (Days 4-6)[2], healthy volunteers will return to the Clinical Study Unit in the late afternoon/evening of Day 7 to be re-confined for receipt of their second study medication on Day 8 (the alternate formulation to their first study medication), under fasted conditions. Intensive PK sampling and clinical and laboratory safety monitoring will be conducted post-dose during Days 8-10 (please see schedule of events). Healthy volunteers are expected to remain at the research facility until the 48-hour post-dose PK sample is obtained and safety assessments (on Day 10) are performed. Subsequently, after an additional washout period (Days 11-13), healthy volunteers

[1] No evidence of food effect with RVD

[2] At least 5 times the half-life: in IB PPI-668, average T1/2s consistent among dose groups, ranged from 6.26 to 7.10 hr. D4-6 are the days spent at home, but the tablet was taken on D1 and next on Day 8. The total washout period is 7 days.

will return to the Clinical Study Unit in the late afternoon/evening of Day 14 to be re-confined for receipt of their third study medication on Day 15 (the same formulation as their first study medication), under fasted conditions.

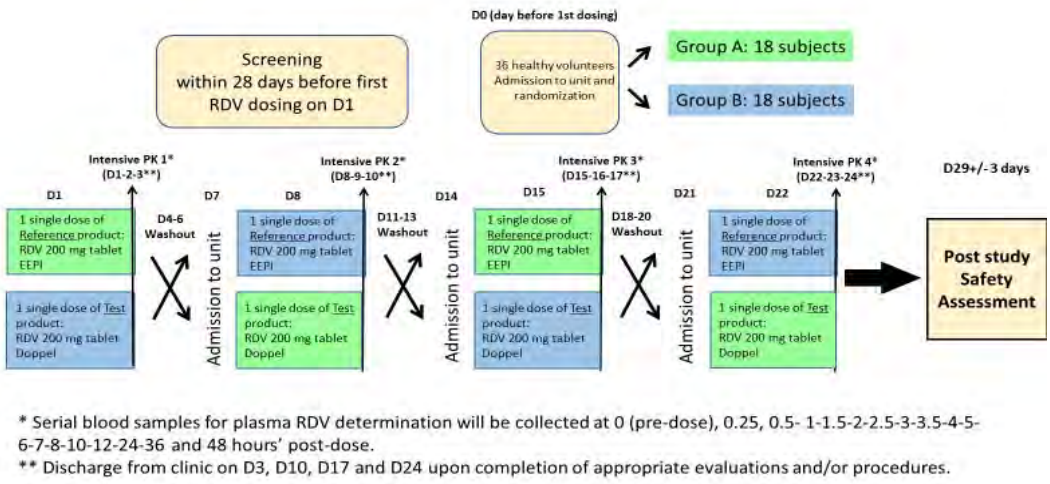
Intensive PK sampling and clinical and laboratory safety monitoring will be conducted post-dose during Days 15-17 (please see schedule of events). Healthy volunteers are expected to remain at the research facility until the 48-hour post-dose PK sample is obtained and safety assessments (on Day 17) are performed.

After an additional washout period (Days 18-20), healthy volunteers will return to the Clinical Study Unit in the late afternoon/evening of Day 21 to be re-confined for receipt of their fourth (last) study medication on Day 22 (the same formulation to their second study medication), under fasted conditions.

Intensive PK sampling and clinical and laboratory safety monitoring will be conducted post-dose during Days 22-24 (please see schedule of events). Healthy volunteers are expected to remain in-house at the research facility until the 48-hour post-dose PK sample is obtained and safety assessments (on Day 24) are performed[3] .Study medication will be administered with 240 ml of water at approximately 08:00 hours on Day 1, 8, 15 and 22 after an overnight fast of at least 10 hours. Food will be withheld for at least 4 hours after dosing. Standardized lunch and dinner will be served at approximately 4 hours and 11 hours post-dose while standardized snacks will be served at 7 hours and 13 hours post-dose (see detailed schedule of event in Appendix II).

A safety follow-up visit will be conducted on Day 29 ±3 days of the last period, or at the time of early termination (if applicable).

Figure 1- Overall study design



[3] All practical aspects of the management of healthy volunteers as well as inclusion/exclusion criteria and schedule of events were re-evaluated with the Phase 1 clinical unit (in house follow-up time, safety follow-up visit, non-smoking, pregnancy tests, contraception, breath alcohol test, ambulatory visits …)

Test Drugs	Reference product: Ravidasvir 200 mg tablet manufactured by European Egyptian Pharmaceutical Industries (EEPI), Egypt Test product: Ravidasvir 200 mg tablet manufactured by Doppel Farmaceutici, Italy
Statistics Sample size	Assuming, for both Cmax and AUC0-t, observed intra-subject coefficients of variation of 32% and observed geometric mean ratios of 105%, an overall sample size of 30 evaluable subjects will provide over 90% power to detect that the 90% confidence intervals of both geometric mean ratios lie within the acceptance range of 80% to 125% (two one-sided tests procedure with a type I error of 0.05). Assuming that 15% of the subjects with have unevaluable RDV PK data, a total of 36 subjects will be enrolled.
Statistics Summary of analysis	**Summary of analyses** The following population sets will be identified: • Intent-to-Treat and Safety Population: All subjects who received at least one dose of IMP. • Pharmacokinetic Population: Includes all the subjects who completed the study and did not have any protocol deviation or events implying a bias for the PK evaluation. **Efficacy analysis** **Pharmacokinetic Analysis** PK parameters of plasma RDV will be calculated using non-compartmental methods and summarized by treatment sequence using descriptive statistics. Plasma RDV concentrations at each time point will be listed and summarized by treatment sequence. Plasma RDV versus time profiles will be plotted for each subject; similar summary plots will be constructed for each treatment sequence. **Bioequivalence Analysis** Analysis of variance (ANOVA) will be performed on log-normal (ln)-transformed Cmax, AUC0-t and AUC0-∞ values to evaluate the bioequivalence of the test tablet formulation relative to the reference tablet formulation. The ANOVA models will contain the following variables, all treated as fixed effects: sequence, subject within sequence, period and treatment. The ratios of the least squares (LS) geometric means and 90% confidence intervals for plasma RDV Cmax, AUC0-t and AUC0-∞ will be calculated. The intra-subject coefficient of variation will be calculated by fitting an ANOVA model with sequence, subject within sequence and period, after removing data from the test formulation. The bioequivalence acceptance range for AUC0-t will be 80%-125%, and that for Cmax will depend on the observed intra-subject coefficient of variation for the reference formulation (ISCV): - If ISCV ≤ 30%, the acceptance range of 80% to 125% will be used. - If ISCV > 30%, the acceptance range will be calculated as follows: *[U, L] = exp [± k · sWR],*

	where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and sWR is the within-subject standard deviation of the log-transformed values of Cmax of the reference formulation. - Bioequivalence will be declared if the back-transformed 90% confidence intervals of the geometric mean ratios for both AUC_{0-t} and C_{max} lie within the acceptance ranges specified above. **Safety analysis** Adverse events will be tabulated by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and by organ system and severity. The subset of AEs that are considered by the Investigator to have a relationship to study medication will be considered to be treatment-related AEs. If the Investigator does not specify the relationship of the AE to study medication, the AE will be considered to be treatment-related. The number and percentage of AEs and treatment-related AEs, overall and by body system, will be tabulated per treatment. AEs will also be summarized by severity, using the severity grading scale. Other safety analysis will be conducted (clinical laboratory tests, vital signs, ECG).

Schedule of events

	Screening	**Study Period 01, 02, 03 and 04** [1]				**Post study Safety Assessment**
Day	Within -28 days before first RDV dosing	D0, D7, D14 and D21	D1, D8, D15 and D22	D2, D9, D16 and D23	D3, D10, D17 and D24	D29 ± 3 days
Ward confinement		X[2]	X	X		
Outpatient visit	X					
Informed consent (ICF)	X					
Assessment of inclusion/exclusion criteria	X					
Confirmation of inclusion/exclusion criteria (for Day 0), or suitability for the healthy volunteer to continue the study will be assessed (for Day 7, 14 and 21).		X				
Demographic and baseline data collection	X					
Body weight, height, BMI	X					
Medical history assessment and update	X	X				
Complete physical examination	X					X
Brief physical examination		X			X	
Biochemistry blood sample	X	X				X
Haematology Blood sample	X	X				X
Serology test (HIV, HBV, HCV)	X					
Urine analysis (Dipstick)	X					X

Day	Within -28 days before first RDV dosing	D0, D7, D14 and D21	D1, D8, D15 and D22	D2, D9, D16 and D23	D3, D10, D17 and D24	D29 ± 3 days
Drugs of abuse urine test	X	X				
Alcohol breath test	X	X				
12-lead ECG	X					X
Serum pregnancy test (if required)	X	X				X
Vital signs (HR, BP, RR, oral temperature)	X	X	X		X	X
Concomitant medications / Medication history	X	X	X	X	X	X
Compliance check		X				
Randomization (D0 only)		X				
Dosing			X			
PK blood sampling			X	X	X	
Standardized meal			X[3]	X[3]	X[3]	
Adverse Events monitoring	X	X	X	X	X	X
Protocol Restriction		X	X	X	X	X

1. Period 01, 02, 03 and 04 will be separated by a washout period of at least 7 days.

2. Healthy volunteers will be admitted into the CRW unit the afternoon before the dosing day, at least 10 hours before dosing time

3. Standardized meals will be served at 4,7,11 and 13 hours post dose. Standardized meals will be served on Day 2, D9, D16 and Day 23 and standardized breakfast will be served on D3, D10, D17 and Day 24, before the healthy volunteer is discharged from the unit upon completion of appropriate evaluations and/or procedures.

Notes

a. Prospective healthy volunteers should be screened no more than 28 days prior to administration of the first dose of study drugs.
b. Haematology: CBC with differential and platelet count.
c. Serum chemistry: alkaline phosphatase, AST, ALT, total bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium and sodium.
d. Pregnancy tests only for females of child-bearing potential: negative serum pregnancy test at Screening and on Day 0, D7, D14, D21 and D29 (post-study safety assessment).
e. One dose of study drug (200 mg RDV tablet) on morning of Day 1, Day 8, Day 15, and Day 22, after overnight fast of at least 10 hr.
f. Serial blood samples for plasma RDV determination will be collected at 0 (predose), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 24, 36, and 48 hours' post-dose.
g. Discharge from clinic on D3, D10, D17 and D24 upon completion of appropriate evaluations and/or procedures.
h. Protocol restrictions to be maintained in washout as well

Study Timelines

Final protocol available	March 2018
Study treatment supply available	March 2018
FSFV	Mid - May 2018 (D1)
Duration of recruitment period	Approx. 3 weeks
Duration of follow-up period (if applicable)	7 days +/- 3 days
LSLV	Mid - June 2018 (D29)
Study Analysis	September 2018
Final study report	October 2018

STUDY SCOPE

Target countries	Malaysia
Enrollment target	At least 30 healthy subjects completing the study with evaluable RDV PK data for both RDV formulations will be required. This is expected to require enrolment of up to 36 subjects
Number of sites	1 site
Number of healthy volunteers per site	36 healthy volunteers will be enrolled with the aim of at least 30 healthy volunteers completing the study
DSMB involvement	No Data Safety Monitoring Board involvement is expected
Partners involvement	Data management, Biostatistics activity and PK analysis will be performed by AMS PHPT: AMS-PHPT Research Platform Data Management Center 187/10 Changklan Rd., Changklan, Muang, Chiang Mai 50100 Thailand
Other study special needs	Not applicable

Study Treatments Supply

Study treatments	Ravidasvir tablets are white to off-white, oval, biconvex tablets. Each tablet contains 200 mg ravidasvir (as its dihydrochloride salt) as well as the inactive ingredients microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and isomalt. Ravidasvir tablets are supplied in High Density Polyethylene (HDPE) bottles each containing 28 tablets. The proposed commercial product ("test") is manufactured by Doppel Farmaceutici (Rozzano, Italy), while the clinical trial product ("reference") is manufactured by European Egyptian Pharmaceutical Industries (EEPI, Alexandria, Italy). The qualitative and quantitative composition of the test and reference products are identical.
Labeling instructions	All study drug supplies will be prepared and labelled according to the requirements of local law and legislation. Each bottle will be labelled with the following information: • Name of sponsor (DNDi) • Name, address and telephone number of investigator • Drug name, dosage form and quantity • Route of administration • Batch number • Clinical protocol number/code • Directions for use – refer to study protocol • "For clinical trial use only" • Storage conditions • Expiry date
Other information	Do not store above 30°C. There are no other special handling precautions