

Clinical Trial Protocol title and short title	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
Protocol Number	<i>DNDi-RDV-04-HCV</i>
Phase	Phase I
Indication	HCV
Background and rationale	<p>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 Malaysia and Thailand study (DNDi-SOF/RDV-01-HCV).</p> <p>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. Three hundred and one patients were included in the study and the analysis is underway.</p> <p>During the course of development, a new batch of ravidasvir tablets has been prepared by the proposed commercial manufacturer (Doppel Farmaceutici, Italy) with an Active Pharmaceutical Ingredient (API) manufactured by Pharco B International (Egypt). Tablets manufactured from the Pharco B international API are intended to be used in subsequent clinical trials and be registered as the commercial product.</p> <p>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 Doppel Farmaceutici using CAD Middle East Pharmaceutical Industries LLC (Saudi Arabia) API and tablets from Doppel Farmaceutici using the Pharco B international API are bioequivalent.</p>
Trial Objectives	<p>Primary objectives</p> <p>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 from the Pharco B international API with the clinical trial product ("reference") produced from CAD Middle East Pharmaceutical Industries LLC (Saudi Arabia) API in healthy volunteers, under fasted conditions.</p> <p>Secondary objectives</p> <p>To assess the safety and tolerability of single oral doses of both RDV formulations in healthy volunteers.</p>
Trial Endpoints	<p>Primary Endpoint</p> <p>Plasma RDV C_{max}, area under the plasma concentration-time curve from time of intake until infinity (AUC_{0-∞}), and area under the plasma concentration-time curve from time of intake until the last quantifiable concentration (AUC_{0-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.</p> <p>Secondary Endpoint(s)</p> <p>Pharmacokinetics (PK):</p> <p>Secondary PK endpoints include time to reach the maximum plasma concentration (t_{max}), mean residence time (MRT), elimination rate constant (λ_z), elimination half-life (t_{1/2}, estimated based on λ_z), apparent volume of distribution, terminal phase (V_z/F), and apparent clearance (CL/F).</p> <p>Safety:</p>

	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	<p>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.</p> <p>This replicate design will allow the possibility to scale the acceptance range for C_{max} if the observed intra-subject coefficient of variation for the reference formulation is greater than 30%.</p> <p>A total of 36 healthy subjects will be enrolled.</p>
Main Entry Criteria Inclusion Exclusion	<p>Inclusion criteria</p> <p>Healthy volunteers must meet all of the following inclusion criteria to be eligible for participation in this study:</p> <ul style="list-style-type: none"> • 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, at the date of ICF signature. • Must be a non-smoker or an ex-smoker for more than 90 days. The use of nicotine or nicotine-containing products or electronic cigarettes must be discontinued 90 days prior to the first admission day of the study. • 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 must have a negative serum pregnancy test at Screening and on Day 0. • 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. • Men who participate in this study must not father a child and must agree to use contraceptive protection in the form of a double barrier method (condom or diaphragm) from the moment they sign the Informed Consent Form (ICF) until the Post-Study Safety Assessment. • 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 and documented by the Investigator to have no clinical significance. • Have either a normal 12-lead electrocardiogram (ECG) or one with abnormalities that are considered not clinically significant by the Investigator. QTcF measure should be ≤450 msec (male) or ≤470 msec (female). • Must have negative urine screen for drugs of abuse (including but not limited to 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 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 and have been determined by the Investigator to have clinical significance at Screening will be excluded.
- Pregnant or lactating female healthy volunteers.
- Female healthy volunteers who utilize hormonal contraceptive as one of their birth control methods.
- Have any serious past or active medical condition 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), surgery (e.g stomach bypass) 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 subject compliance. Regular alcohol consumption in males >21 units per week and females >14 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 Units = 125 mL glass of wine, depending on type). As confirmed by a positive alcohol breath test either at screening or at admission day.
- Have donated or lost blood (≥450ml) within three 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 prior to admission with the exception of vitamins (without herbal compounds) and/or paracetamol and/or ibuprofen.
- Have a history of significant drug allergy.
- Have any allergy
- Smokers as confirmed by a breath carbon monoxide (Smokerlyzer) reading of greater than 10 ppm at screening or at admission day, and users of electronic cigarette.
- Unable and/or unwilling to comply with study requirements.
- Believed by the study Investigator to be inappropriate for study participation for any reason

Study Duration

Each subject completing the trial will be evaluated over a study participation for a maximum period of 60 days, including a 28-day screening window and a maximum of 32 days of study observation associated with the first, second, third and last RDV dose exposures.

Test Drugs	<p>Reference product: Ravidasvir 200 mg tablet manufactured by Doppel Farmaceutici, Italy using CAD Middle East Pharmaceutical Industries LLC (Saudi Arabia) API</p> <p>Test product: Ravidasvir 200 mg tablet manufactured by Doppel Farmaceutici, Italy using the Pharco B international (Egypt) API</p>
Statistics Sample size	<p>Assuming, for both C_{max} and AUC_{0-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).</p> <p>Assuming that 15% of the subjects will have unevaluable RDV PK data, a total of 36 subjects will be enrolled.</p>
Statistics Summary of analysis	<p>Summary of analyses</p> <p>The following population sets will be identified:</p> <ul style="list-style-type: none"> • Intent-to-Treat and Safety Population: All subjects who received at least one dose of Investigational Medicinal Product (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. <p>Efficacy analysis</p> <p>Pharmacokinetic Analysis</p> <p>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.</p> <p>Bioequivalence Analysis</p> <p>Analysis of variance (ANOVA) will be performed on log-normal (ln)-transformed C_{max}, AUC_{0-t} and AUC_{0-∞} 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 C_{max}, AUC_{0-t} and AUC_{0-∞} 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.</p> <p>The bioequivalence acceptance range for AUC_{0-t} will be 80%-125%, and that for C_{max} will depend on the observed intra-subject coefficient of variation for the reference formulation (ISCV):</p> <ul style="list-style-type: none"> - If ISCV ≤ 30%, the acceptance range of 80% to 125% will be used. - If ISCV > 30%, the acceptance range will be calculated as follows: $[U, L] = \exp [\pm k \cdot sWR]$, 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 C_{max} 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, most recent version at the time of study start) 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, this will be queried. 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).