CLINICAL STUDY PROTOCOL

A Randomized, Double-blind, Placebo-controlled, Single-center, Phase I, Single-dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of RPH-104 in Healthy Subjects

Name of Sponsor	**TRPHARM İlaç Sanayi Tic. A.Ş.**
Name of Finished Product	Not applicable
Name of Active Ingredient	RPH-104
Title	A Randomized, Double-blind, Placebo-controlled, Single-center, Phase I, Single-dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of RPH-104 in Healthy Subjects
Protocol No:	RPH-104 FIH-01
Study Type:	Interventional
Sites, Countries:	ARGEFAR, Ege University Drug Development and Pharmacokinetics Research and Application Center, İzmir, Turkey
Study Phase:	Phase I (First In Human [FIH] study; human pharmacology)
Subject population	Healthy male and/or female subjects who meet the selection criteria.
Rationale for Study	RPH-104 is a macromolecular compound with a molecular weight of 152.715 kDa (Data on file) and is capable of binding human interleukin-1 beta (IL-1β). It has also been shown in vitro to be a highly potent inhibitor of IL-1β signaling pathway, with low picomolar inhibitor activity. In this First in Human study, RPH-104 will be evaluated primarily for its safety and tolerability. In a phase I study conducted with health volunteers, a similar monoclonal antibody, canakinumab, was investigated in terms of pharmacokinetics and pharmacodynamics besides efficacy and safety. Similarly this aimed to investigate effects of RPH-104 on selected pharmacodynamic parameters, including Anti-Drug Antibodies (ADA) along with obtaining first human data on pharmacokinetics of RPH-104 in humans will be investigated in the same study.
Primary Objective	To evaluate the safety and tolerability of RPH-104 in humans.
Secondary Objectives	The secondary objectives of this study are to investigate: • initial pharmacokinetics (PK) of RPH-104 following sc. injection at different dosages • absolute bioavailability of RPH-104 after sc. injections at different dosages • pharmacodynamic (PD) effects based on laboratory investigations of in vivo biomarkers and functional ex-vivo immune assays. • formation of Anti-drug-antibodies and evaluate its effects on PK modelling
Study Design	Randomized, double-blind, placebo-controlled, single-center, single-dose study design with stepwise increasing five dose groups (4, 20, 40, 80 and 160 mg – fivefold increase / twofold increase / two fold increase / two fold increase)

Number of Subjects	35 healthy male and/or female subjects who meet the eligibility criteria will be included in the study. The statistical analyses in this study will be exploratory in nature since the study is not powered to address any pre-defined statements but to generate valid hypotheses on safety and pharmacokinetic and pharmacodynamics evaluations. A formal sample size calculation as for confirmatory trials was not done. This study is aimed to evaluate the safety and tolerability of RPH-104; a new biologic agent intended to be used in humans, as well as obtaining the initial pharmacokinetic and pharmacodynamics parameters of RPH-104, all resulting p-values and confidence intervals will be interpreted in the exploratory sense only. A sample size of n = 35 subjects was deemed sufficient to get valuable information on the primary and secondary objectives. Seven (7) subjects per dose level of administration with a ratio of 5:2 active to placebo are deemed to be sufficient for obtaining sufficient data on safety and initial pharmacokinetic data in humans.
Duration of Therapy	All subjects included in this study will receive either the active drug or the placebo product as a single dose administration in each dose cohort. There will be no repeat injections and the follow-up duration will be initiated after this single dose administration.
Duration of Follow up	Subjects will be followed for (30) days after administration including inpatient and outpatient period after discharge (ambulatory safety follow-up period). At the end of follow up period, subjects will complete the study by a telephone visit at day 60.
Duration of study	The study will reach completion 8.5 months from the time the study opens to accrual. Planned key milestones include: • First subject first visit: 2016, Q1 • Last subject last visit: 2017, Q2 • Database lock date: 2017, Q3
Study Drugs	**Active:** RPH-104 (TRPHARM İlaç Sanayi Tic. A.Ş.) **Placebo:** Sodium Chloride Sterile Injection BP 0.9% w/v (Each ml contains 0.9% Sodium Chloride in Water for Injections). The placebo will contain no active pharmaceutical ingredients. Placebo will be administered in a blinded manner (e.g., in opaque/blinded syringes with the same appearance as syringes containing RPH-104). Subjects randomized to the placebo arm will be administered placebo by the blinded study site staff via SC injection.
Dosage, route of administration and follow-up period	Subcutaneous administration of the RPH-104 (Investigational Medicinal Product – IMP) or placebo on Day 1 will be performed by a blinded physician, or blinded nurse (under control of a blinded physician), in order to keep the blinding and to ensure the compliance of the volunteers. A second blinded site staff member will witness the administration of the medicinal product Drug administration in a dose cohort will be done with a ratio of 5:2 active to placebo. There will be 3 subgroups in each dose cohort with various active:placebo subject ratios (1:1 in subgroup 1 and 2, and 3:0 in subgroup 3). Each subgroup will be observed for 72 hours

<table>
<tr><td></td><td>post-dose and the next subgroup will be dosed only after positive decision of the Independent Data Monitoring Committee (IDMC). An IDMC meeting will take place for evaluation of safety data after dosing of each subgroup.
Five different dose groups were selected for administration in this First in Human study. Dose of the study drug will be escalated from an initial of 4 mg for the first dose cohort to 20 mg, 40 mg and 80 mg for the 2nd, 3rd, and 4th dose cohorts, respectively. The highest dosage cohort will receive 160 mg.
The dosage scheme and dosage escalation is planned as follows:
<table>
<tr><th>Cohort</th><th>Dose</th><th>Fold Escalation</th></tr>
<tr><td>1</td><td>4 mg</td><td>5x</td></tr>
<tr><td>2</td><td>20 mg</td><td>2x</td></tr>
<tr><td>3</td><td>40 mg</td><td>2x</td></tr>
<tr><td>4</td><td>80 mg</td><td>2x</td></tr>
<tr><td>5</td><td>160 mg</td><td></td></tr>
</table>
All subjects will be hospitalized the day before the dosing, and will be discharged 72 hours post-dose. Observation of the dose leaders will be 72 hours, the remainder of the cohort (3 active subjects) would be dosed after discharge of dose leaders (1 active and 1 placebo subjects). An Independent Data Monitoring Committee (IDMC) meeting will be scheduled after the discharge of each subgroup/cohort. IDMC will evaluate all available medical examination and laboratory data during this meeting.
For all dosage cohorts, RPH-104 and placebo will be drawn from their original vials with 20 gauge (G) 1 ml hypodermic injector and will be applied to subjects after the needle is replaced with a 26 g for subcutaneous injections. Due to the only available concentration of RPH-104 (40 mg/mL, 2 ml vials) 4, 20, 40 and 80 mg dosages will be injected as single sc. injections (0.1, 0.5, 1.0 and 2.0 ml volumes drawn from 40 mg/mL vial). For 160 mg dosage, 2 injections will be performed to the abdominal wall. All injections will be performed subcutaneously to the abdominal wall. The placebo will be administered simultaneously in equal volumes and equal number of injections.</td></tr>
<tr><td>Safety Variables</td><td>- Adverse events (AEs) will be recorded, and coded according to the version of the MedDRA that is current on the date of study initiation.
- Serious adverse events (SAEs)
- Vital signs (including, but not limited, heart rate, respiratory rate, systolic blood pressure [SBP], diastolic blood pressure [DBP], oxygen saturation [pulse oximetry], body temperature)
- Physical examination
- Safety laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis)
- Specialized laboratory data (including, but not limited to, standard 12-lead electrocardiogram [ECG])
- Concomitant medications</td></tr>
<tr><td>Pharmacokinetic (PK) Variables</td><td>- Concentration-time profiles of RPH-104
- Standard non-compartmental PK parameters: Cmax (highest concentration determined in the measuring interval), AUC 0-∞ (area under concentration- from time zero to infinity), AUC 0-t (area under the concentration- time curve from time zero to the last sampling time), tmax (time at which Cmax occurs), tlag (time from</td></tr>
</table>

	administration to first quantifiable concentration), t½ (terminal elimination half-life), λz (terminal elimination rate constant), CL/F (apparent clearance), Vz/F (apparent volume of distribution), F (fractions absorbed) (and hence V and CL) of RPH-104.
Pharmacodynamics (PD) Variables	- Levels of C-reactive protein (CRP), serum amyloid A (SAA), S100 calcium-binding protein A8 (S100A8), interleukin-6 (IL-6), interleukin-1alpha and beta (IL-1 α and β), and interleukin-1 receptor antagonist (IL-1RA) in serum and Anti-RPH-104 antibodies in serum.
Variables to be measured	**Primary variables (Safety variables)** - Nature, frequency, severity and relationship to study drug of recorded AEs; - Vital signs (heart rate, respiratory rate, SBP, DBP, oxygen saturation, body temperature); - Physical examination results; - Results of safety laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis); **Secondary variables (PK-Pharmacokinetic variables)** - Concentration-time profiles of RPH-104; - Standard non-compartmental PK parameters of RPH-104: o Cmax, o AUC 0-∞, o AUC 0-t, o tmax, o tlag, o t½, o λz, o CL/F, o Vz/F, o F; **Pharmacodynamic variables** - Levels of the following parameters, in serum o CRP o SAA o S100A8 o IL-6 o IL-1α o IL-1β o IL-1RA o Anti-Drug Antibodies
Inclusion Criteria	Subjects who meet the following criteria will be eligible for participation in the study: I-1. Subject who is informed and given ample time and opportunity to think about his/her participation and who agrees to give his/her written informed consent. I-2. Subject who is a healthy male or female between 18 and 35 years old (inclusive). I-3. Subject who agrees to use an effective contraceptive method over the entire study

	period and be willing and able to continue contraception for 2 months after the dosing of study treatment. I-4. Subject who has normal body weight as determined by a body mass index (BMI) of between 18 kg/m² and 30 kg/m² (inclusive) and within a body weight of ≥50kg and ≤120kg. I-5. Subject who has a previous and current healthy condition and has no current or past medical history of clinical significance. I-6. Subject who has a good physical and mental health status determined on the basis of the medical history. I-7. Subject who has a good physical and mental health status determined on the basis of the general clinical examination. I-8. Subject who has an electrocardiogram (a standard 12-lead ECG, performed in supine position, after 10 minutes rest, in a controlled, calm environment) with interpretations considered as “normal”; QTc is abnormally prolonged if > 440ms in men or > 460ms in women and QTc is abnormally short if < 350ms. I-9. Subject whose clinical laboratory test results are within the reference range of the laboratory. When one or more laboratory test results are out of reference range and results are not clinically relevant, the subject has to be included in the study after providing written agreement of investigators and an internal medicine specialist independent of the trial team. I-10. Subject who is willing and be able to understand the nature of the study and any hazards of participating in this study and subject who is able to communicate satisfactorily with the Investigator, to participate in and to comply with all study requirements. I-11. Subject who is considered as reliable and capable of adhering to the protocol, according to the judgment of the Investigator.
Exclusion Criteria	Subjects who meet any of the following criteria will be excluded from study: E-1. Subject who previously participated in this study. E-2. Subject who failed Screening due to 1 or more out-of-range value(s) in safety laboratory parameters (e.g., due to a recent mild cold) with clinical relevancy. However, these subjects could be rescreened at least one week after initial screening depending on the clinical evaluation of the investigator for another subgroup/cohort. E-3. Subject who participated in another clinical study of an investigational drug (or a medical device) within the last 3 months or was currently participating in another study of an investigational drug (or a medical device). E-4. Subject who is not willing to abstain from participating in any other study of an investigational drug (or a medical device) until last safety follow-up visit (study termination). E-5. Subject who has a history or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, dermatological, neurological, psychiatric, and hematological (including myelosuppression and bleeding disorders) or

	immunological disorder(s), and/or any condition that could constitute a potential safety risk factor or could alter the absorption, distribution, metabolism or elimination of the study drugs. E-6. Subject who has a history or current condition of a malignancy (including basal cell carcinoma) or autoimmune disease. E-7. Subject who has any clinically significant concomitant chronic or acute illness. E-8. Subject who has a known clinically relevant allergy or known severe adverse reaction to any drug or who has a known or suspected clinically relevant drug hypersensitivity. E-9. Subject who has a known history of chronic latent or persistent opportunistic or severe bacterial, viral, systemic fungal or parasitic infection 2 years prior to Screening, or any recent (within the last 3 months prior to Screening) bacterial, viral, systemic fungal, parasitic infection, or any current sign or symptom that may indicate an infection. E-10. Subject who has positive immunoglobulin-M (IgM) antibodies against Epstein Barr virus-viral capsid antigen (IgM-anti-EBV-VCA) and Cytomegalovirus (CMV). E-11. Subject who has hypercholesterolemia or was dyslipidemic when fasting. E-12. Subject who has a history of significant adverse reaction to biological product(s) or hypersensitivity to protein made from bacterial yeast or mammalian producer cells. E-13. Subject who has a positive Quantiferon TB-Gold (TB) test (or another in vitro test for *Mycobacterium tuberculosis* infection). E-14. Subject who is positive to Human Immunodeficiency Virus-1/2 antibody (HIV-1/2Ab). E-15. Subject who has serum hepatitis, or is a carrier of the Hepatitis B surface antigen (HBsAg), or is Hepatitis C virus antibody (HCV-Ab) positive. E-16. Subject who received (or planned to receive during the study timeframe) vaccines (live or attenuated) within the 3 months, and immunoglobulins (any antibody product) within the 6 months, preceding the study drug administration. E-17. Subject who received any drug treatment in the 14 days preceding the first intake of the study drug with the exception of occasional paracetamol (not exceeding 2g/day with a total of 10g per 14 days) and/or received hepatic enzyme inducers within 2 months before the study drug administration. E-18. Subject who received any antibiotic or antiviral drug(s) within 2 months preceding the Screening Visit. E-19. Subject who has previously received an antibody product within 5-half-lives of the antibody or within 3 months of the start of the study. E-20. Subject smoking more than 5 cigarettes per day according to his/her declaration and unable to stop smoking during the study. E-21. Subject who has a history of chronic alcohol abuse within the last 2 years, or who has a positive alcohol test or who is known to have excessive alcohol intake (weekly intake of more than 14 units alcohol; 1 unit of alcohol equals 1 glass of beer or lager (~330mL), a glass of wine (175mL) or a measure of spirits (25mL)).

	E-22. Subject who has heavy caffeine consumption (including caffeine pills) (>5 units per day; a unit = e.g., 1 cup of coffee, 2 cups of non-green tea or 1 cup of green tea, or 1 caffeine-containing drink (500mL), e.g., cola, energy drinks. E-23. Subject who has a history of drug addiction or a current drug addiction or use. E-24. Subject whose blood pressure and heart rate (measured in supine position, after 10 minutes rest) levels are outside the normal range (SBP: 90 to 145 mmHg; DBP: 40 to 90 mmHg; heart rate: 60 to 90 beats per minute). E-25. Subject who has a symptomatic or asymptomatic orthostatic hypotension at Screening Visit defined as a 20 mmHg or more decrease in SBP, and/or 10mmHg or more decrease in DBP after 1 or 3 minutes standing with the arm relaxed at the side (Time 0 began after the subject was upright). Blood pressure measured after 5 minutes of supine rest will be used as baseline. E-26. Subject, who participated in another clinical study, donated blood or suffered blood loss (equal to or more than 450mL) less than 12 weeks before first administration of the study drug. E-27. Subject who has any psychological or other emotional problems that were likely to invalidate informed consent, or limit the ability of the subject to comply with the protocol requirements. E-28. Subject who has any clinical conditions that, in the opinion of the Investigator, would make the subject unsuitable for the study. E-29. Vulnerable individuals (e.g., persons kept in detention). E-30. Employees of the Investigator or study center, with direct involvement in the proposed study or other studies under the direction of that Investigator or study center, as well as family members (first degree relatives) of the employees or the Investigator. E-31. Subjects who has promiscuous lifestyles. E-32. Subject who does not abstain from alcohol for 48 hours prior to admission on Day -1 and before each study visit. Abstinence could be confirmed with an alcohol test upon admission to each visit. In addition, subjects who does not refrain from consumption of alcohol in daily quantities greater than 1 glass of beer or lager (~330 mL), a glass of wine (175 mL) or a measure of spirits (25 mL) during the ambulatory follow-up phase. E-33. Subject who takes recreational drugs during the entire study. E-34. Subject who does not agree to fast for 10 hours prior to and 2 hours after administration of the study medication. At all times, water will be permitted ad libitum. E-35. Subject who does not agree to refrain from sauna visits, sunbathing, and unusual strenuous physical activity outside of their normal daily routine during the entire duration of the study. E-36. Subject who does not agree to abstain from blood donation during the entire duration of the study.
Statistical Analysis	All subjects receiving the study medication will be included into the safety evaluation.

	Subjects who completed the study according to the protocol (per protocol population) will be included into the statistical evaluation. Subject data of drop-out volunteers or volunteers who were not eligible for the study (missing or inconsistent results) will be reported. Such volunteer data will not be included into descriptive and confirmatory statistics. The arithmetic mean (Mean), the standard deviation (SD), coefficient of variation (CV), minimum (Min), maximum (Max) and median (Med) will be reported for each parameter. For concentration related parameters also the geometric mean (GeoM) will be reported and in accordance with the multiplicative model the coefficient of variation of the geometric mean will be calculated as CV = (exp(σ^2)-1)1/2, with σ^2 = variance of log transformed data. Parameter differences will be tabulated without CV. For tmax preferably the individual subject differences and for all other parameters the subject ratios will be reported. The individual subject values for concentrations and pharmacokinetic parameters will be tabulated with descriptive statistics.