CLINICAL STUDY PROTOCOL

Investigational product provided by the Sponsor:	RPH-104/L04018
Study Sponsor	**R-Pharm International LLC**
Legal address	123154, Russian Federation, Moscow, 19 Berzarina St., bld. 1, floor 1, office V, room 9 Phone: +7 (495) 956-79-37
Study Protocol Code:	CL04018054
Study title:	An Open-label, Single-dose, Active-controlled Randomized Phase IIa Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of RPH-104 (L04018) Administered at Different Doses to Patients With Acute Gout Attack
Study phase:	IIa
Protocol version:	7.0
Study Protocol Date:	November 19, 2020

CONFIDENTIALITY STATEMENT

SIGNATURE PAGE 1 (STUDY SPONSOR)

By signing this statement, the person signing this document approves the study protocol, version 7.0 of November 19, 2020, and confirms that it has been created in accordance with the Ethical Principles of the Declaration of Helsinki, current edition of the ICH GCP E6 Good Clinical Practice Guidelines and applicable legislations. According to the Power of Attorney No. 25 dated May 14, 2018 issued by R-Pharm International LLC:

Signature: _____

Mikhail Yuryevich Samsonov, Cand. Med. Sci.

Date: _____

SIGNATURE PAGE 2 (PRINCIPAL INVESTIGATOR)

By signing this page, the Investigator approves the Study Protocol, version 7.0 of November 19, 2020, and assumes an obligation to conduct the study at his/her study site in accordance with all requirements of the Protocol, including all the data confidentiality requirements, as well as the ethical principles of the Declaration of Helsinki, ICH GCP E6 Good Clinical Practice guidelines, and local regulatory requirements.

Healthcare institution/study site address: _____

_____

Signature: _____

Full name and position: _____

_____

Date: _____

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Study Sponsor: R-PHARM INTERNATIONAL LLC

The study is conducted by R-Pharm JSC.

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When reporting serious adverse events, one must be guided by the procedures described in Section 12.5. Investigators should inform the Sponsor of the development of serious adverse events within 24 hours of receipt of relevant information. The completed SAE notification form must be sent to the following number/ email address:

Contact information for SAE reporting
(24-hour)
Fax: +7 (495) 956-79-38
Safety@Rpharm.ru

Study sites

The study will involve up to 19 sites in the Russian Federation.

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Central laboratories

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2) Central Laboratory for assessment of other samples

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LIST OF ABBREVIATIONS

ANCOVA	Analysis of covariance
AUC(0-∞)	Area under the concentration of active substance–time curve in the time interval from zero (before taking the drug) to infinity
AUC(0-t)	Area under the concentration of active substance–time curve in the time interval from zero (before taking the drug) to the last detected concentration of the drug
Cmax	Maximum concentration of the active substance
CTCAE	Common Terminology Criteria for Adverse Events
GCP	Good Clinical Practice
HAQ	Health assessment questionnaire
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
LLoQ	Lower limit of quantification
LOCF	Last observation carried forward
T½	Half-life related to the terminal phase of the PK curve
tmax	Time to maximum concentration of the active substance
SUSAR	Suspected unexpected serious adverse reaction
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
APTT	Activated partial thromboplastin time
VAS	Visual Analogue Scale
ULN	Upper Limit of Normal
HIV	Human Immunodeficiency Virus
WHO	World Health Organization
GGT	Gamma-glutamyl transpeptidase
IL	Interleukin
BMI	Body mass index
CRF	Case Report Form
LDH	Lactate dehydrogenase
HDL	High-density lipoproteins
LDL	Low-density lipoproteins
INR	International normalized ratio
INN	International nonproprietary name
ADR	Adverse Drug Reaction
NSAID	Nonsteroidal anti-inflammatory drug
AE	Adverse event
SAE	Serious adverse event
ESR	Erythrocyte sedimentation rate
(hs) CRP	(high-sensitivity) C-reactive protein
PK	Pharmacokinetics
TNF	Tumor necrosis factor
HCG	Human chorionic gonadotropin

ALP	Alkaline phosphatase
ECG	Electrocardiogram

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2 PROTOCOL SYNOPSIS

Sponsor Name: R-Pharm International LLC			
Investigational medicinal product provided by the Sponsor: RPH-104/L04018			
Name of the active ingredient: RPH-104/L04018			
Study title:	An Open-label, Single-dose, Active-controlled Randomized Phase IIa Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of RPH-104 (L04018) Administered at Different Doses to Patients With Acute Gout Attack		
Study sites:	Approximately 19 sites in the Russian Federation		
Clinical study phase:	IIa		
Study goal and objectives:	**Study goal:** To evaluate the efficacy, pharmacokinetics, pharmacodynamics, safety and tolerability of RPH-104 following a single injection in adult patients with an acute gout attack. **Objectives:** • To investigate the efficacy of RPH-104 in the treatment of an acute gout attack following a single subcutaneous injection at doses of 4, 20, 40, 80 and 160 mg; • To investigate the pharmacokinetics of RPH-104 following its single subcutaneous injection; • To investigate the effect of RPH-104 following its single subcutaneous injection on concentrations of high-sensitivity C-reactive protein (hs-CRP), serum amyloid protein, blood cytokines (IL-1α, IL-1β, IL-1RA, IL-6, IL-8, TNF-α); • To investigate the safety parameters of RPH-104 in adult patients with an acute gout attack.		
Study methods:	A multicenter, randomized, parallel group, single-dose, phase IIa, open-label study of the sponsor's investigational product to evaluate its efficacy, pharmacokinetics, pharmacodynamics, and safety. It is planned to enroll patients in two periods: in the first period, it is planned to randomize 7 patients for treatment with the reference product Voltaren® (diclofenac) and 15 patients for treatment with RPH-104 4 mg; in the second period, it is planned to randomize 7 patients into the reference product Voltaren® (diclofenac) group and 56 patients into the RPH-104 groups at doses of 20 mg, 40 mg, 80 mg and 160 mg, 14 patients in each group.		
Number of patients:			
Number of patients participating in the study enrollment procedures:	up to 135		
Patients treated with investigational product therapy:	85		
In each treatment	treatment with RPH-104: 15 patients – 4 mg, 14 patients – doses of 20 mg, 40		

Sponsor Name: R-Pharm International LLC	
Investigational medicinal product provided by the Sponsor: RPH-104/L04018	
Name of the active ingredient: RPH-104/L04018	
group:	mg, 80 mg, 160 mg therapy with Voltaren® (diclofenac): 14 patients
Primary diagnosis:	Acute gout attack
Main eligibility criteria:	Male and female patients aged 18 to 80 years with an acute gout attack that occurred within not more than 120 hours (5 days) before randomization, with at least one painful joint at screening with pain intensity of 50 mm and more on a 100 mm visual analogue scale (VAS) for pain intensity assessment.
Investigational product provided by the Sponsor:	RPH-104, solution for subcutaneous injection, 40 mg/ml
Doses:	4, 20, 40, 80, 160 mg
Route of administration:	For doses 4, 20, 40, 80 mg – subcutaneously, once. A 160 mg dose is divided into two injections, 80 mg each at different injection sites.
Reference product:	Voltaren® (diclofenac), enteric-coated tablets
Doses:	50 mg and 25 mg
Route of administration:	Orally, 50 mg 3 times a day for 3 days, then 25 mg 3 times a day for 9 days (total 12 days).
Rescue therapy:	Patients who do not tolerate pain receive the rescue medication 2 hours after the first use of the investigational product to intensify therapy. The rescue medication is triamcinolone 40 mg intramuscularly. If an attack recurs after the use of the rescue medication, treatment is carried out in accordance with the standard practice of the hospital.
Concomitant therapy:	In order to prevent damage to the gastric and duodenal mucosa caused by Voltaren® (diclofenac), all patients receiving Voltaren® (diclofenac) will simultaneously take Ortanol® (omeprazole) as follows: 20 mg, orally daily before breakfast throughout the course of Voltaren® (diclofenac) treatment. On the first day of therapy in the study, it is possible to take it regardless of meals and at a later time. Method of administration of Ortanol® (omeprazole): orally, with a sufficient amount of liquid.
Duration of treatment:	Treatment with RPH-104: single dose (a 160 mg dose is divided into two injections, 80 mg each at different injection sites. therapy with Voltaren® (diclofenac): 12 days
Evaluation criteria:	
Primary efficacy variable	Change in pain intensity in the assessed joint at 72 hours after start of the investigational product therapy compared to baseline, as measured on the visual analogue scale (VAS).
Other efficacy variables:	• Change in pain intensity in the assessed joint at 15, 30, 45 minutes, 1, 1.5, 2, 4, 8, 24, 48, 72 hours, on days 5, 6, 10, 15, 18, 22, 29 and 45 after start of the investigational product therapy compared to baseline (as measured on VAS). • Proportion of patients who rated the response to the investigational product therapy as "Excellent" or "Good" at 15, 30, 45 minutes, 1, 1.5

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Name of the active ingredient: RPH-104/L04018		

	hours, 2, 4, 8, 24, 48, 72 hours, on days 5, 6, 10 15, 18, 22, 29, and 45 after initiation of the investigational product therapy; • Change in the degree of swelling, tenderness, erythema in the assessed joint at 24, 48, 72 hours, on days 5, 6, 10, 15, 18, 22, 29 and 45 after start of the investigational product therapy compared to baseline; • Change in movement restriction in the assessed joint at 24, 48, 72 hours, on days 5, 6, 10, 15, 18, 22, 29 and 45 after start of the investigational product therapy compared to baseline; • Time to 50% reduction in pain intensity in the assessed joint relative to the baseline level according to the VAS; • Time to use of the rescue medication; • The proportion of patients who received the rescue medication within 72 hours of starting the investigational product therapy and over the entire treatment period; • Changes in the health assessment questionnaire (HAQ) scores 15, 29, and 45 days after start of the investigational product therapy compared to baseline.
Pharmacokinetic variables:	Blood samples for pharmacokinetic assessment will be collected from patients who have received RPH-104 at the following times: before RPH-104 administration, at 2, 8, 24, 48, 72, 96, 120, 216, 336, 408, 504, 672, 1056 hours after the investigational product administration. Pharmacokinetic parameters of subcutaneous RPH-104: AUC0-t, AUC0-∞, Cmax, tmax, t1/2, Kel.
Immunogenicity vairables:	Blood samples for immunogenicity assessment will be collected from patients treated with RPH-104 at the following time points: before administration of RPH-104, on Day 15, Day 45. Anti-RPH-104 antibody concentrations will be assessed.
Pharmacokinetic variables:	• Change in serum hs-CRP levels at 24, 72 hours, 5, 6, 15, 29 and 45 days after start of the investigational product therapy compared to baseline. • Change in serum amyloid protein A levels at 24, 72 hours, 5, 6, 15, 29 and 45 days after start of the investigational product therapy compared to baseline. • Change in serum cytokine (IL-1α, IL-1β, IL-1RA, IL-6, IL-8, TNF-α) levels at 24, 72 hours, 5, 6, 15, 29 and 45 days after start of the investigational product therapy compared to baseline.
Safety variables:	Adverse events, laboratory results, vital signs, physical examination findings, ECG findings.
Statistical methods:	*Data analysis* Descriptive statistics of continuous variables will be presented using means,

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Investigational medicinal product provided by the Sponsor: RPH-104/L04018		
Name of the active ingredient: RPH-104/L04018		

median, 25th and 75th percentiles, standard deviation, minimum, maximum, number of observations available. Categorical data will be presented as absolute and relative values for each category. Time to event parameters will be plotted using Kaplan-Meier curves.

Efficacy analysis

The primary efficacy variable will be analyzed by analysis of covariance using baseline and treatment group as covariates. Other continuous efficacy variables will be analyzed using repeated measures ANOVA. Efficacy variables representing time to event will be compared using a log rank test.

The pharmacokinetic, pharmacodynamic and immunogenicity parameters of RPH-104, as well as safety of the therapy with the investigational products will be assessed using descriptive statistics methods.

Interim data analysis

Due to the low patient recruitment rate in the study and the adverse impact of the COVID-19 pandemic on the recruitment, at the decision of the sponsor, an interim analysis of the data of 47 patients included in the study as of November 2020 will be carried out in order to assess the feasibility of continuing recruitment and further conducting the study. All patients whose data will be included in the interim analysis completed their participation in the study; follow-up is not required in the study. The interim analysis will include the efficacy, safety, pharmacokinetics and pharmacodynamics data available and verified at the time of analysis. No changes in the declared statistical methods in connection with the interim analysis are planned. The dose dependence of the pharmacokinetics and pharmacodynamics of the investigational product, as well as the main efficacy measures (reduction in pain intensity) will be studied using descriptive statistics, a confidence interval approach, and graphical methods. The safety analysis will be carried out using descriptive statistics methods. Formal testing of hypotheses is not planned in the study. In view of the exploratory nature of the study, no corrections for multiple comparisons are planned.

Sample size justification

Fourteen (14) patients per group will allow constructing 95% confidence intervals around the mean change in pain intensity on a visual analogue scale at 72 hours after the start of the investigational product use in each group with an accuracy of 30 mm change in pain intensity.

In addition, this sample size will allow establishing statistically significant differences between the groups in pairwise comparisons, without control for type I error for multiple comparisons, taking into account the type I error α = 5%, if the difference between the compared groups is $\geq$ 20 mm. The sample size was calculated assuming a standard deviation of 26 mm for change in pain intensity at 72 hours.

3 STUDY FLOW CHART

Table 3.1 Schedule of the study procedures

	Прескрининг1	**Day 1**					**D2**	**D3**	**D4**	**D5**	**D6**	**D10**	**D15**	**D18**	**D22**	**D29**	**D45**	**D60**	**BRM**	**FUV**
Procedure/time (hours)		**Screening[2]**	**0**	**2**	**4**	**8**	**24**	**48**	**72**	**96**	**120**	**216** ± 1 day	**336** ± 1 day	**408** ± 1 day	**504** ± 1 day	**672** ± 1 day	**1056** ± 1 day	± 7 days		
Time window for evaluation of PK, PD, overall pain intensity in the assessed joint, and patient global assessment of efficacy				±10 minutes			±2 hours		±3 hours											
Visit (V); Telephone call (T)	V	B27					V	V	V	V	V	B3	V	B3	B3	V	V	T		
Handing over the patient information sheet with information about the study to the patient, informing the patient about the study procedures and possible participation	X																			
Signing of the Informed Consent Form	X1	X4																		
Medical history collection		X																		
Tuberculosis risk assessment questionnaire		X																		
Recording concomitant/previous therapy[24]		X	X Throughout the study																	X
Collection of demographics[5]		X																		
Efficacy and pharmacodynamic assessment																				
Pain intensity in the assessed joint[6]		X7	X8	X	X29	X	X	X	X	X	X	X26	X	X26	X26	X	X		X25	
Patient global assessment of efficacy[6]			X8	X	X29	X	X	X	X	X	X	X26	X	X26	X26	X	X		X25	
Health assessment questionnaire (HAQ) [6]		X																		
Assessment of the degree of swelling, tenderness, erythema		X					X	X	X	X	X	X	X	X	X	X	X			

	Прескрининг1	Day 1					D2	D3	D4	D5	D6	D10	D15	D18	D22	D29	D45	D60	BRM	FUV
Procedure/time (hours)		**Screening**[2]	**0**	**2**	**4**	**8**	**24**	**48**	**72**	**96**	**120**	**216** ± 1 day	**336** ± 1 day	**408** ± 1 day	**504** ± 1 day	**672** ± 1 day	**1056** ± 1 day	± 7 days		
Time window for evaluation of PK, PD, overall pain intensity in the assessed joint, and patient global assessment of efficacy				±10 minutes			±2 hours		±3 hours											
and movement restriction in the assessed joint by physician[9]																				
High-sensitivity (hs) CRP[10]		X					X		X	X	X		X			X	X			
Serum amyloid protein A[10]		X					X		X	X	X		X			X	X			
Cytokines (IL-1α, IL-1β, IL-1RA, IL-6, IL-8, TNF-α) [10]		X					X		X	X	X		X			X	X			
Recording the timing of rescue therapy																			X25	
Diagnosis of infections: HIV, HBsAg, HCV Ab [10,11]		X																		
Diagnosis of tuberculosis (T-SPOT.TB) [10]		X22																		
Blood samples for pharmacokinetic assessment [10, 12]			X	X		X	X	X	X	X	X	X	X	X	X	X	X			X
Anti-drug antibodies [10, 12]			X														X			X
Serum pregnancy test for women of childbearing potential		X															X			X
Clinical laboratory tests[13]		X14								X			X				X			X
Urinalysis with sediment microscopy (site laboratory)[23]		X								X			X				X			X
Physical examination[15]		X											X				X			X
Vital signs[16]		X					X		X	X	X		X		X	X	X			X
Weighing										X			X				X			X
12-lead ECG		X14								X							X			X
Chest X-ray in 2 views		X14,17																		
Adverse event recording		X18	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

	Прескрининг1	**Day 1**					**D2**	**D3**	**D4**	**D5**	**D6**	**D10**	**D15**	**D18**	**D22**	**D29**	**D45**	**D60**	**BRM**	**FUV**
Procedure/time (hours)		**Screening[2]**	**0**	**2**	**4**	**8**	**24**	**48**	**72**	**96**	**120**	**216** ± 1 day	**336** ± 1 day	**408** ± 1 day	**504** ± 1 day	**672** ± 1 day	**1056** ± 1 day	± 7 days		
Time window for evaluation of PK, PD, overall pain intensity in the assessed joint, and patient global assessment of efficacy				±10 minutes			±2 hours		±3 hours											
Eligibility assessment		X																		
Randomization			X																	
Subcutaneous administration of RPH-104[12]			X																	
Assessment of injection site reactions [12, 19]			X[19]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
First dosing Dispensing of Voltaren® (diclofenac) and Ortanol® (omeprazole) [20]			X[28]																	
Dispensing of Voltaren® (diclofenac) and Ortanol® (omeprazole) for self-administration [20]			X[28]																	
Use of rescue medication Kenalog[25]				X																
Handing over the Patient Diary[21,30]			X				X	X	X	X	X	X	X	X	X	X				
Patient diary collection							X	X	X	X	X	X	X	X	X	X	X			

D – day, CRP – C-reactive protein, PK – Pharmacokinetics, PD – pharmacodynamics (in this study, these are hsCRP, serum amyloid protein A, cytokines), BRM – before the administration of rescue medication, FUV – follow-up visit for early discontinuation of the patient from study

1. At pre-screening, the patient is informed about the study procedures, signs the informed consent to participate in the pre-screening, and is given the patient information sheet with informed consent form describing the main study for familiarization.
2. Screening procedures must be performed within 24 hours and the patient is randomized during this time. If necessary (in exceptional cases), the screening period can be extended, while randomization had to be carried out no later than 120 hours (5 days) after the onset of an attack.

3. Visits to the study site on Study Days 10, 18 and 22 are required for patients receiving RPH-104; Patients receiving Voltaren® (diclofenac) do not have to come to the study site, but they must fill out the patient diary and patient questionnaires on these days (pain in the assessed joint, patient global assessment of efficacy).
4. Informed consent to participate in the study must be obtained and the informed consent form for participation in the study be signed prior to starting any study procedure.
5. This includes date of birth, sex, race, weight, height, body mass index, and information on alcohol consumption.
6. The patient is given questionnaires at the visits to record pain intensity in the assessed joint on the visual analogue scale (VAS), patient global assessment of efficacy, and scores of the health assessment questionnaire.
7. The VAS must be completed twice: the first time at the screening to assess the patient's eligibility and the second time before randomization to obtain a baseline value. Re-assessment of pain intensity in the assessed joint must be performed immediately (within 1 hour) before randomization.
8. Assessment of pain intensity and global efficacy assessment must be performed prior to taking blood samples. It is necessary to hand over a questionnaire to the patient for assessment of pain intensity and global efficacy assessment after 15, 30, 45 minutes, (interval ± 5 min) 1 and 1.5 hours (interval ± 10 min) after the use of the investigational products.
9. The physician assesses the degree of swelling, tenderness, erythema and movement restriction in the assessed joint using the categorical scales specified in this protocol.
10. hs-CRP, serum amyloid protein A, cytokines, HIV, HBsAg, HCV Ab, T-SPOT.TB tests, pharmacokinetics and anti-drug antibodies (including the test for neutralizing antibodies) are performed in central laboratories.
11. For the diagnosis of infections (HIV, HBsAg, HCV Ab), blood serum samples will be sent to the central laboratory. In addition, rapid tests for the diagnosis of HIV, hepatitis B and C are performed at the screening. Rapid test results should be evaluated prior to patient randomization. Patients suspected of having HIV, hepatitis B or C on the basis of rapid test results should not be randomized.
12. Administration of RPH-104, assessment of injection site reactions, blood sampling to assess the pharmacokinetics of the investigational product and anti-drug antibodies will be performed only for patients randomized to receive RPH-104.
13. These include: complete blood count (hemoglobin, hematocrit, erythrocytes, platelets, total WBC count with WBC differential in %, absolute neutrophil count), blood chemistry: sodium, potassium, chlorine, magnesium, calcium, phosphorus, bicarbonates, BUN (or urea), uric acid, total protein, albumin, glucose, creatinine with estimation of creatinine clearance using the Cockcroft-Gault formula, bilirubin (total and direct), AST, ALT, alkaline phosphatase, LDH, amylase, lipase, GGT, creatine kinase, MB-creatine kinase; blood lipids (cholesterol, triglycerides, LDL, HDL); coagulation tests (fibrinogen, INR, aPTT). Complete blood count and creatinine test at screening and on Study Days 5, 15, 45 and with early discontinuation of the patient from the study are performed at the local laboratory of the study site. Blood chemistry tests with blood lipids and coagulation tests are performed in the central laboratory.
14. The results of ECG, chest x-ray in 2 views, creatinine level, absolute neutrophil count, leukocyte and platelet counts should be assessed prior to patient randomization. To be included in the study, the patient has to meet the study eligibility criteria based on these data.

15. Physical examination includes: assessment of overall health, skin (presence of rash or lesions), head, mouth, eyes, ears, throat, nose, lungs (auscultation), heart (auscultation for murmurs, gallop rhythm, pericardial friction rubs), lower extremities (peripheral edema, presence of varicose veins), abdomen (palpation and auscultation), nervous system (mental status, gait, reflexes, motor and sensory functions, coordination) and lymph nodes.
16. This includes: body temperature, blood pressure, respiratory rate and heart rate in a sitting position after 5 minutes at rest.
17. Chest X-ray in 2 views is performed at screening if the patient does not have results of chest X-ray in 2 views or fluorography of the chest in 2 views or chest CT performed within 3 months before the expected date of the first injection of the investigational product;
18. Serious adverse events are recorded from the time of signing the informed consent to participate in the study. Other adverse events are recorded from the time of administration to the patient (the first intake by the patient) of the investigational product.
19. In patients receiving RPH-104, the assessment of injection site reactions is carried out 15, 30, 45 minutes (interval ± 5 min) after administration and then in accordance with the table of study procedures. The physician assesses the presence of tenderness, redness, swelling, induration, hemorrhage and itching at the RPH-104 injection site. The patient is assessed for these reactions at each visit. They are recorded as adverse events.
20. Voltaren® (diclofenac) and Ortanol® (omeprazole) are dispensed only for patients receiving Voltaren® (diclofenac).
21. In the diaries, patients record information about the development of adverse events and changes in concomitant therapy (discontinuation or dose change) or use of new concomitant therapy. Patients receiving Voltaren® (diclofenac) are also given additional diaries to record information about the use of Voltaren® (diclofenac). The diaries are filled in by patients when they are outside the study site.
22. Blood sampling for T-SPOT.TB test should be carried out either at screening, or during the time the patient is in the hospital.
23. Urine analysis includes: color, transparency, specific gravity, pH level, glucose, protein, ketone bodies, bilirubin, urobilinogen, nitrites. Analysis of urine sediment includes: leukocyte count, erythrocyte count, epithelial cell count with cell type, and bacterial count.
24. Information is collected about all previous therapy for the primary disease—gout, information about other prior therapy is collected for a period of 30 days before the start of screening.
25. Patients who do not tolerate pain receive the rescue medication after 2 hours and until Day 45 of the study after the first use of rescue medication Kenalog® (triamcinolone) to intensify therapy. If it is necessary to use the rescue medication, immediately before its use, an unscheduled assessment of pain severity using a visual analogue scale (VAS) and global assessment of efficacy is to be performed and the time of use of the rescue medication is to be registered.
26. If patients receiving Voltaren® (diclofenac) miss visits on Day 10, 18 and 22, they record pain intensity in the assessed joint and the patient global assessment of efficacy at home. For this purpose, they are given patient questionnaires to take home at Visits on Days 6 (1 score) and 15 (2 scores).
27. By the decision of the investigator, after the use of the investigational products, patients can be hospitalized and remain under observation in the hospital. All procedures in accordance with the visit schedule for these patients are carried out in a hospital setting. Patients who, in the investigator's opinion, are not eligible for hospitalization, are followed up for at least 3 hours after the investigational product administration, after which they can leave the study site and continue to participate in the study with all assessments performed on an outpatient basis.

28. At the visit on Day 1, all patients in the Voltaren® (diclofenac) group are given the drug for dosing at the study site; patients who are hospitalized by the decision of the investigator are given the drug in a hospital setting before being discharged; subsequently, these patients are given the drug in an amount sufficient for self-administration at home in accordance with the study protocol. Patients who are not eligible for hospitalization receive the drug for self-administration on Day 1 after the rest of the procedures and assessments.
29. Patients receiving Voltaren® (diclofenac) on an outpatient basis are allowed to leave the study site 3 hours after taking the drug. In this case, they are given patient questionnaires (measurement of pain in the assessed joint, patient global assessment of efficacy) to fill at home 4 and 8 hours after taking the drug.
30. New patient diaries are issued as needed.

4 STUDY RATIONALE AND GOAL

The present study is a phase IIa study. This study aims to evaluate the efficacy, pharmacokinetics, pharmacodynamics, safety and tolerability of RPH-104 following a single injection in adult patients with an acute gout attack.

To clarify certain aspects of conducting a clinical trial, the following changes have been made to this protocol compared to the previous version 6.0 of June 6, 2019:

- An interim analysis of data from patients randomized as of November 2020 was included.

Rationale for change: Due to the low rate of enrollment in the study (between March 2018 and November 2020, 47 patients [~55% of the planned sample size] were enrolled in the study) and the negative impact on enrollment of the COVID-19 pandemic, the sponsor decided to conduct an interim analysis of the data of 47 patients included in the study as of November 2020 in order to assess the feasibility of continuing the recruitment and further conducting the study. All patients whose data will be included in the interim analysis completed their participation in the study; follow-up is not required in the study. The interim analysis will include the efficacy, safety, pharmacokinetics and pharmacodynamics data available and verified at the time of analysis. An interim report based on the results of the analysis may become final. In case of early termination of the study, the sponsor will send respective notifications to the investigators and the regulatory authorities.

4.1 General information about the disease

Gout is a metabolic disease characterized by the deposition of urate crystals in the form of sodium monourate or uric acid in different tissues of the body.

An increase in the blood concentration of uric acid (hyperuricemia) underlies the development of gout. Increased blood concentrations lead to the formation of needle-shaped crystals of sodium salt of uric acid in the joints. Macrophages recognized and uptake these crystals, then they are attacked by neutrophils. The subsequent release of IL-1β provokes inflammation, vasodilation and attraction of immune cells to the focus [1].

Clinically, gout manifests by recurrent acute arthritis: a reddened, tender, hot, and swollen joint. Pain usually develops quickly, in less than 12 hours. The first metatarsophalangeal joint is affected in about half of patients. Gout can also lead to the development of gouty nodules (tophi) and kidney damage. The disease more frequently affects men.

Gout treatment is based on alleviating acute attacks, management of hyperuricemia and prevention of flares. First-line therapy for acute attacks includes non-steroidal anti-inflammatory drugs, steroids and colchicine, as well as various methods of prevention of flares during periods of remission 2, 3, 4]. Despite the effectiveness of these methods, 69% of patients experience another gout attack within a year; furthermore, tolerability of these drugs is limited, especially in patients with concomitant hepatic, kidney, and heart disease, diabetes and hypertension. Therefore, in recent years, studies of drugs with an alternative mechanism of action were ongoing, in particular, of IL-1 inhibitors [5].

In this study, Voltaren® (diclofenac) was selected as a reference drug to alleviate a gout attack. The reason for choosing Voltaren® (diclofenac) was the presence of the indication ‘treatment of a gout attack’ in the Voltaren® (diclofenac) labeling, as well as in accordance with the National Rheumatology Guidelines [6] and due to the widespread use of Voltaren® (diclofenac) in clinical practice.

4.2 Description of investigational products and concomitant therapy

4.2.1 Treatment with RPH-104 (investigational product provided by the sponsor)

RPH-104 is a hybrid protein that selectively binds IL-1β at femtomolar concentrations [7]. Two active fragments of the molecule are responsible for RPH-104 binding to IL-1β: an extracellular portion of human IL-1 receptor, type 1 and a portion of IL-1 receptor accessory protein (IL-1-RAcP) that is an IL-1 co-receptor.

Structurally, the RPH-104 molecule comprises two polypeptide chains: the first one consists of the extracellular portion of IL-1 receptor and a mutant Fc-fragment of human IgG1; the second one consists of the IL-1-RAcP portion and a mutant Fc-fragment of human IgG1.

A tissue cross-reactivity study performed using tissue samples from humans and cynomolgus monkeys showed specific staining of the following structures of both types with the RPH-104–biotin complex: cytoplasm and membrane of macrophages and histiocytes of lymph nodes, hepatic epithelium and Kupffer cells. Based on the study findings, it has been concluded that staining of human and cynomolgus monkeys tissues with the RPH-104–biotin complex is highly similar.

The toxicity of RPH-104 has been studied following single and repeated dosing to cynomolgus monkeys. The study showed that a single subcutaneous injection of RPH-104 at doses of 5, 50, and 200 mg/kg and a single intravenous administration of RPH-104 at doses of 5 and 200 mg/kg were well tolerated by animals and did not cause adverse events. RPH-104 was also well tolerated by the animals following repeated subcutaneous injections to monkeys at doses of 5, 50, and 100 mg/kg, once a week for 4 weeks. Based on the study findings, it was concluded that NOAEL for RPH-104 administered weekly for 4 weeks is 100 mg/kg. Anti-drug antibodies were detected in 68% of monkeys at the end of the administration period. The drug was not immunotoxic in monkeys.

The first clinical study of RPH-104 aimed at investigation of the tolerability, safety, pharmacokinetics, pharmacodynamics and immunogenicity of single subcutaneous 4-, 20-, 40-, 80- and 160-mg doses of RPH-104 in healthy volunteers was completed in 2018. The results of this clinical study showed that RPH-104 was well tolerated by healthy volunteers at all doses tested. A list of adverse events observed in subjects in this study is presented in Table 4.2.

More detailed information about RPH-104 is contained in the current version of the Investigator's Brochure.

4.2.2 Voltaren® (diclofenac) – reference product

Voltaren® (diclofenac) is a non-steroidal anti-inflammatory drug (NSAID). Voltaren® (diclofenac) has pronounced anti-inflammatory, analgesic and antipyretic effects. The main mechanism of action of Voltaren® (diclofenac) is the inhibition of the synthesis of prostaglandins, which play an important role in the development of inflammation, pain and fever.

Pharmacokinetics

After oral administration of coated tablets, Voltaren® (diclofenac) is completely absorbed in the intestine. After a single dose of 50 mg of the drug, the maximum concentration in the blood is observed after 2 hours and is 1.5 μg/mL. If Voltaren® (diclofenac) tablets are taken during or after a meal, the rate of absorption may slow down, but the amount of absorbed Voltaren® (diclofenac) does not change.

Diclofenac is 99.7% bound to plasma proteins, predominantly with albumin (99.4%). Voltaren® (diclofenac) enters the synovial fluid, where maximum concentrations are measured 2-4 hours later than in blood. Two hours after reaching the maximum concentration in the blood, the

concentration of Voltaren® (diclofenac) in the synovial fluid is higher than in the blood, and its values remain higher over a period of up to 12 hours.

Voltaren® (diclofenac) is metabolized in the liver. About 60% of the administered dose of the drug is excreted in the urine as glucuronic conjugates of the unchanged active substance, as well as in the form of metabolites, most of which are glucuronic conjugates. Less than 1% of the dose taken is excreted unchanged. The rest of Voltaren® (diclofenac) is excreted in the form of metabolites via bile with feces.

Pharmacokinetic properties in special populations

After oral administration, there are no differences in absorption, metabolism and excretion of the drug associated with the age of patients.

In patients with renal impairment, no accumulation of Voltaren® (diclofenac) was noted when used at usual doses. In patients with chronic hepatitis or compensated liver cirrhosis, pharmacokinetic properties of Voltaren® (diclofenac) are similar to those without liver disease.

Indications

- Inflammatory and degenerative diseases of the musculoskeletal system, including rheumatoid, juvenile, chronic arthritis; ankylosing spondylitis and other spondyloarthropathies; osteoarthritis; gouty arthritis; bursitis, tendovaginitis;
- Spinal pain syndromes (lumbago, sciatica, ossalgia, neuralgia, myalgia, arthralgia, radiculitis);
- Post-traumatic postoperative pain accompanied by inflammation (e.g. in dentistry and orthopedics);
- Algodismenorrhea;
- Pelvic inflammatory disease (including adnexitis);
- Infectious and inflammatory diseases of ENT organs, accompanied with severe pain (as part of complex therapy): pharyngitis, tonsillitis, otitis media.

For more information about Voltaren® (diclofenac), see the instructions for medical use. When evaluating the relationship of adverse events with Voltaren® (diclofenac), the investigator should take into account all information about Voltaren® (diclofenac) from the instructions for medical use.

4.2.3 Ortanol® (omeprazole) – concomitant medication

Ortanol® (omeprazole) is a proton pump inhibitor. In this study, this drug will be used in combination with Voltaren® (diclofenac) to prevent damage to the gastric and duodenal mucosa caused by the NSAID, Voltaren® (diclofenac). The indication and route of administration of Ortanol® (omeprazole) in this study correspond to the information in the instructions for medical use.

Ortanol® (omeprazole) is contraindicated in the following conditions: hypersensitivity to Ortanol® (omeprazole) or other components of the drug; age under 4 years (or weight below 31 kg) in the treatment of duodenal ulcers and under 2 years with a weight below 20 kg for the treatment of reflux esophagitis, symptomatic treatment of heartburn and acid regurgitation in gastroesophageal reflux disease; concomitant use with nelfinavir, erlotinib and posaconazole; rare hereditary forms of lactose intolerance, deficiency of lactase, sucrase/isomaltase or malabsorption of glucose/galactose.

For more information about Ortanol® (omeprazole), see the instructions for medical use.

4.2.4 Triamcinolone acetonide (rescue medication)

In this study, triamcinolone acetonide has been selected as a rescue medication to be administered in the form of intramuscular injection 40 mg. The rescue medication was selected on the basis of national recommendations for its use for the relief of an acute gout attack [6]. The intramuscular route of administration has been selected on the basis that the study will include, among other things, patients with a polyarticular form of gout who are indicated for systemic therapy. The dose for use was selected on the basis of the US instructions for medical use of triamcinolone acetonide, valid at the time of writing the protocol [14] and the experience with this drug in clinical trials to relieve an acute gout attack [10]. If triamcinolone acetonide is ineffective, the Investigator may select another drug for the patient in accordance with standard hospital practice.

4.3 Preclinical and clinical trial results essential for this study

This Study Protocol presents a brief description of the results of the most important studies. Detailed information on the results of preclinical and clinical studies of RPH-104 is contained in the latest version of the Investigator's Brochure.

4.3.1 Preclinical studies

Mechanism of action studies.

In vitro studies have investigated the kinetics of binding of RPH-104 to human type 1 IL-1 receptor ligands: IL-1α, IL-1β, and an interleukin 1 receptor antagonist (IL-1RA). The studies have shown that the mean dissociation constant for these ligands is 18 nM, 11.8 fM and 21.6 pM for IL-1α, IL-1β and IL-1RA, respectively. Thus, it has been found that the affinity of RPH-104 to IL-1α, IL-1β and IL-1RA differs significantly. The affinity of RPH-104 for IL-1β is approximately 2000 times higher than the affinity of RPH-104 for IL-1RA and approximately 1,000,000 higher than the affinity of RPH-104 for IL-1α.

4.3.2 Clinical pharmacology trials

Pharmacokinetics of RPH-104 in humans

At the time of writing this protocol, data on the pharmacokinetics of RPH-104 were available for a single subcutaneous injection in healthy volunteers at doses of 4 and 20 mg. The results of evaluation of pharmacokinetic RPH-104 parameters from phase 1 studies in healthy volunteers are provided in Table 4.1 below.

Table 4.1 Pharmacokinetic parameters of RPH-104 after a single subcutaneous injection in healthy volunteers

PK parameters/RPH-104 dose	4 mg (N=5)	20 mg (N=5)	40 mg (N=3)	80 mg (N=5)	160 mg (N=5)
C_{max} (ng/mL)	198 ± 89.1	1280 ± 402	1650 ± 257	5120 ± 1410	10300 ± 4470
AUC(0-t) (h*ng/mL)	74500 ± 24700	430000 ± 95700	661000 ± 158000	1610000 ± 317000	3390000 ± 1450000
AUC(0-∞) (h*ng/mL)	87100 ± 28300	505000 ± 105000	804000 ± 196000	1850000 ± 353000	3990000 ± 1810000
$t_{1/2}$ (h)	245 ± 9.50	249 ± 6.08	255 ± 43.1	235 ± 22.8	243 ± 40.4
tmax (h)	96 (94.4 – 192)	96 (48. – 96.2)	120 (96 – 192)	96 (72 – 120)	120 (72 – 120)

Note: data are presented as means ± standard deviation, except for tmax values, where the median is presented (minimum value – maximum value)

As can be seen from the presented table, the maximum concentration of RPH-104 appears in the blood on average approximately 4-5 days after the subcutaneous administration of RPH-104. The

study results showed that RPH-104 at doses ranging from 4 to 160 mg has linear pharmacokinetics and its half-life is approximately equal to 10 days.

4.3.3 Adverse events during RPH-104 therapy

The study of single doses of RPH-104 in healthy volunteers was conducted as a randomized, double-blind, single-center study with a gradual increase in the dose of RPH-104 in each subsequent cohort. Each cohort included 7 volunteers who were randomized in a 5:2 ratio to receive a single pre-specified dose of RPH-104 or placebo. Volunteers were followed up for 60 days, of which 3 days the volunteers spent in the hospital, 27 days the volunteers came for visits to the study site, and at the end of the follow-up period (day 60) they received a call to collect information on adverse events (AEs).

In order to assess the safety of RPH-104 therapy, information on adverse events, vital signs, physical examination, clinical laboratory tests (complete blood count, blood chemistry tests, coagulation tests and urinalysis), ECG were evaluated in volunteers. The decision to include volunteers in each subsequent cohort was made by an independent data monitoring committee, based on an assessment of the therapy safety data and pharmacokinetic data in the previous cohort. A total of 35 healthy volunteers took part in the study [13].

A list of all reported adverse events is presented in Table 4.2 below. No serious adverse events were reported. A total of 70 adverse events were recorded. In the 4 mg and 20 mg dose groups, of 5 subjects treated with RPH-104, 3 subjects (60%) experienced gastrointestinal disturbances. In the 20 mg dosing group, AEs of nervous system disorders were reported with the same frequency (60%). In the 40 mg dosing group, the most commonly reported AEs were infections (40%). Five subjects (100%) who received RPH-104 80 mg and 3 subjects (60%) who received 160 mg had headache. All reported AEs in all dosing groups were mild and resolved completely. The most common AEs in both RPH-104 and placebo subjects were headache (44%-30%), nausea (12%-30%) and nasopharyngitis (8%-20%), respectively. There was no significant difference in AEs between the placebo and RPH-10 groups.

Table 4.2 Adverse events reported in a phase 1 study of RPH-104 in healthy volunteers

n (%)

	Dose group 1 (4 mg)		Dose group 2 (20 mg)		Dose group 3 (40 mg)		Dose group 4 (80 mg)		Dose group 5 (160 mg)	
System Organ Class Preferred term	**RPH-104 N=5**	**Placebo N=2**	**RPH-104 N=5**	**Placebo N=2**	**RPH-104 N=5**	**Placebo N=2**	**RPH-104 N=5**	**Placebo N=2**	**RPH-104 N=5**	**Placebo N=2**
Any Adverse Events	**5 (100%)**	**1 (50%)**	**3 (60%)**	**2 (100%)**	**4 (80%)**	**2 (100%)**	**5 (100%)**	**1 (50%)**	**5 (100%)**	**1 (50%)**
Nervous system disorders	**1 (20%)**	**1 (50%)**	**3 (60%)**	**1 (50%)**	**1 (20%)**	**2 (100%)**	**5 (100%)**	**-**	**3 (60%)**	**-**
Headache	1 (20%)	-	1 (20%)	1 (50%)	1 (20%)	2 (100%)	5 (100%)	-	3 (60%)	-
Dizziness	-	1 (50%)	1 (20%)	-	-	1 (50%)	-	-	-	-
Fainting	-	-	1 (20%)	-	-	-	-	-	-	-
Attention disorder	-	-	1 (20%)	-	-	-	-	-	-	-
Gastrointestinal Disorders	**3 (60%)**	**1 (50%)**	**3 (60%)**	**1 (50%)**	**1 (20%)**	**1 (50%)**	**-**	**1 (50%)**	**1 (20%)**	**-**
Nausea	1 (20%)	1 (50%)	2 (40%)	1 (50%)	-	-	-	1 (50%)	-	-
Vomiting	1 (20%)	-	-	-	1 (20%)	-	-	-	-	-
Diarrhea	-	-	1 (20%)	-	-	-	-	-	1 (20%)	-
Dysphagia	1 (20%)	-		-	-	-	-	-	-	-
Abdominal pain	-	-	1 (20%)	-	-	1 (50%)	-	-	-	-
Aphthous ulcer	-	-	-	-	-	-	-	-	-	-
Infections and infestations	**2 (40%)**	**1 (50%)**	**-**	**-**	**2 (40%)**	**1 (50%)**	**-**	**-**	**2 (40%)**	**1 (50%)**
Nasopharyngitis	-	-	-	-	-	1 (50%)	-	-	2 (40%)	1 (50%)
Gingivitis	2 (40%)	-	-	-	-	-	-	-	-	-
Pyuria	1 (20%)	-	-	-	-	-	-	-	-	-
Pharyngitis	-	-	-	-	1 (20%)	-	-	-	-	-
Upper respiratory tract infection	-	-	-	-	1 (20%)	-	-	-	-	-
Bacteriuria	-	1 (50%)	-	-	-	-	-	-	-	-
Asymptomatic bacteriuria	-	1 (50%)	-	-	-	-	-	-	-	-
General disorders and administration site conditions	**2 (40%)**	**-**	**-**	**-**	**-**	**1 (50%)**	**-**	**1 (50%)**	**1 (20%)**	**-**
Asthenia	2 (40%)	-	-	-	-	-	-	1 (50%)	-	-
Soft tissue inflammation	-	-	-	-	-	-	-	-	1 (20%)	-
Hyperthermia	-	-	-	-	-	1 (50%)	-	-	-	-

Musculoskeletal and connective tissue disorders	**-**	**-**	**1 (20%)**	**-**	**-**	**1 (50%)**	**1 (20%)**	**1 (50%)**	**-**	**-**
Arthralgia	-	-	1 (20%)	-	-	-	1 (20%)	1 (50%)	-	-
Myalgia	-	-	-	-	-	1 (50%)	-	-	-	-
Muscle spasm	-	-	1 (20%)	-	-	-	-	-	-	-
Skin and subcutaneous tissue disorders	**1 (20%)**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**1 (20%)**	**-**
Hyperhidrosis	-	-	-	-	-	-	-	-	1 (20%)	-
Ecchymosis	1 (20%)	-	-	-	-	-	-	-	-	-
Investigations	**-**	**-**	**-**	**-**	**1 (20%)**	**-**	**-**	**-**	**1 (20%)**	**-**
Blood creatine phosphokinase increased	-	-	-	-	1 (20%)	-	-	-	1 (20%)	-
Ear and labyrinth disorders	**-**	**-**	**1 (20%)**	**1 (50%)**	**-**	**-**	**-**	**-**	**-**	**-**
Pain in the external ear	-	-	1 (20%)	-	-	-	-	-	-	-
Ear itching	-	-	-	1 (50%)	-	-	-	-	-	-
Pollakiuria	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**2 (40%)**	**-**
Pollakiuria	-	-	-	-	-	-	-	-	2 (40%)	-
Cardiac disorders	**-**	**-**	**-**	**1 (50%)**	**-**	**-**	**-**	**-**	**-**	**-**
Right bundle branch block	-	-	-	1 (50%)	-	-	-	-	-	-
Respiratory, thoracic and mediastinal disorders	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**1 (20%)**	**-**
Cough	-	-	-	-	-	-	-	-	1 (20%)	-
Psychiatric disorders	**1 (20%)**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Emotional reactivity	1 (20%)	-	-	-	-	-	-	-	-	-
Reproductive system and breast disorders	**-**	**1 (50%)**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Dysmenorrhoea	-	1 (50%)	-	-	-	-	-	-	-	-

4.4 Concise description of known risks and potential benefits associated with the use of the investigational product

Given the available information on the use of RPH-104 in healthy volunteers, it can be expected that a single subcutaneous administration of the drug in patients with gout in doses up to 160 mg inclusive will not cause severe adverse drug reactions in patients.

The patient may benefit from the use of RPH-104 , for example, pain and other manifestations of gouty arthritis exacerbation may decrease or disappear or the risk of gouty arthritis exacerbation may decrease.

Voltaren® (diclofenac) may cause side effects. For more information about the side effects of Voltaren® (diclofenac), see the instructions for medical use. In order to prevent one of these side effects: damage to the gastric or duodenal mucous membrane, patients using Voltaren® (diclofenac) will receive the concomitant drug Ortanol® (omeprazole). The patient may benefit from the use of Voltaren® (diclofenac), for example, pain and other manifestations of gouty arthritis exacerbation may decrease or disappear.

None of the investigational products is likely to help achieve a sufficient analgesic effect in 100% of patients who receive these drugs in this study. In this regard, this study provides for the use of a rescue medication, triamcinolone acetonide, which is effective in a subset of patients with an acute gout attack (see Section 4.2.4). If triamcinolone acetonide is ineffective, other drugs for the treatment of a gout attack may be used. In addition, at the discretion of the patient, he/she may withdraw from the study at any time.

4.5 Justification for the sample size

The assumption about the efficacy of RPH-104 in patients with an acute gout attack was based on the similarity in the mechanism of action of RPH-104 and Canakinumab (Ilaris®). Canakinumab (fully human anti-IL-1β monoclonal antibody) is approved in the EU and Russia for the treatment of patients with acute gouty arthritis and intolerance of other inflammatory therapies [8, 9]. The results of double-blind, randomized trials of canakinumab versus triamcinolone showed that patients with an acute gout attack treated with canakinumab had lower pain intensity 72 hours after starting therapy and a lower risk of new gout attacks, compared with patients who received triamcinolone [11].

Justification of the patient's age. According to epidemiological data, the prevalence of gout increases with age and reaches a plateau at 80 years [21,22]. Patients aged 70-79 years are 5 times more likely to suffer from gouty arthritis compared with patients under 50 years old [23]. The incidence of gout has a linear dependence on age, reaching the peak of the disease in the age of 80-84 years [21, 22]. The age of patients included in the study of drugs (NSAIDs, type 2 cyclooxygenase inhibitors, glucocorticosteroids, IL-1 inhibitors) for treatment of an acute gout attack was 18 years or older or was limited to 80 years [24, 25, 26, 27]. Given the epidemiological data on gout, as well as information on the age of patients included in various studies of treatment of acute gout attacks, the age of patients in this study is limited to 18-80 years ($\geq$ 18 and $\leq$ 80 years).

4.6 Justification for the method of administration, dosing, dosing regimen, and treatment course

It is expected that in this study, subcutaneous administration of RPH-104 at doses from 4 to 160 mg may reduce pain intensity in patients with an acute gout attack.

The rationale for effective doses of RPH-104 is based on the following assumptions:

1. The blood IL-1β level in patients with gout does not exceed 100 pg/mL [11],
2. The blood IL-1β level in healthy volunteers is about 0.3 pg/mL [13].

3. Dissociation constant of RPH-104 and IL-1β does not exceed 43.9 fM [7].
4. The molecular weight of RPH-104 is 152.7 kDa,
5. The molecular weight of IL-1β is 17.5 kDa.
6. The dissociation constant of RPH-104 and IL-1β relationship to the concentrations of RPH-104, IL-1β, and RPH-104:IL-1beta complex is described by the following equation:

$$Kd = \frac{[\text{RPH-104}]^* [\text{IL-1}\beta]}{[\text{RPH-104:IL-1}\beta]}$$

where [RPH-104], [IL-1beta], and [RPH-104:IL-1β] are the molar concentrations for RPH-104, IL-1β, and the RPH-104:IL-1β complex, respectively.

Thus, based on the above equation, the calculated concentration of RPH-104 in the blood capable of reducing the free blood IL-1β level from 100 pg/mL to 0.3 pg/mL is 20 pM or 3 ng/mL. It is expected that this concentration of RPH-104 may reduce pain in patients with gout.

According to a Phase 1 study in healthy volunteers, a blood concentration of RPH-104 of 3 ng/mL will be reached approximately 2 hours after subcutaneous injection of RPH-104 4 mg and less than 30 minutes after subcutaneous injection of RPH-104 20 mg and higher.

The results of the phase 1 study of RPH-104 showed that a single subcutaneous injection of RPH-104 at doses from 4 to 160 mg was well tolerated by healthy volunteers (see Section 4.3.3). Based on these results, it is assumed that RPH-104 will be well tolerated by patients following a single subcutaneous injection at doses ranging from 4 to 160 mg in this clinical study.

The duration of use of Voltaren® (diclofenac) was selected based on the ACR guidelines for the management of acute gout attacks, according to which the use of NSAIDs at a full dose (if necessary) is indicated until the gout attack completely resolves [17]. According to the classification criteria for gout, a gout attack can last for up to 14 days, consequently, drugs that relieve a gout attack are indicated during this time [17]. A stepwise approach to relieve a gout attack is used with NSAIDs. In this case, NSAIDs are used at a full dose during the first 3 days, then at a lower dose in the next 7 days [19]. According to an article on a phase III study of rilonacept, for the relief of an acute gout attack, the reference product from NSAIDs was used at the full dose for 3 days (150 mg per day), then at a lower dose (75 mg per day) for 9 days [19]. In accordance with the Voltaren® (diclofenac) labeling, the recommended initial dose of the drug is 150 mg per day and 75-100 mg per day for long-term therapy [20]. In this study, Voltaren® (diclofenac) will be used as a reference product in the first 3 days at the full dose of 150 mg per day, then at a lower dose of 75 mg per day for the next 9 days.

4.7 Conformity of the principles of this study to international, regional, and other standards

This study is conducted in accordance with this protocol, the ethical principles set forth in the Declaration of Helsinki of the World Medical Association (last revision), and the current edition of Good Clinical Practice (ICH GCP E6), the legislation and standards of the Russian Federation: the Constitution of the Russian Federation; the current edition of Federal Law No. 61-FZ of the Russian Federation of April 12, 2010 *On the circulation of medicinal products*; the current edition of Federal Law No. 323-FZ of the Russian Federation of November 21, 2011 *On the basics of protecting the health of citizens in the Russian Federation*; Decree No. 714 of the Government of the Russian Federation of September 13, 2010 *On Approval of Model Rules for Compulsory Life and Health Insurance of a Patient Participating in Clinical Trials of a Medicinal Product*" (as amended on September 4, 2012); Decree No. 393 of the Government of the Russian Federation of May 18, 2011 *On Amendments to the Model Rules for Compulsory*

Life and Health Insurance of a Patient Participating in Clinical Trials of a Medicinal Product; Order No. 703n of the Ministry of Health and Social Development of Russia of August 23, 2010 *On Approval of the Notification Form for the Completion, Suspension or Termination of a Clinical Trial of a Medicinal Product for Medical Use*; Order No. 774n of the Ministry of Health and Social Development of Russia of August 31, 2010 *On the Ethics Council*, Order No. 200n of the Ministry of Health of Russia of April 1, 2016 *On Approval of Good Clinical Practice Guidelines*, GOST R52379-2005 *Good Clinical Practice* and other applicable legislative acts.

5 STUDY GOAL AND OBJECTIVES

5.1 Study goal

To evaluate the efficacy, pharmacokinetics, pharmacodynamics, safety and tolerability of RPH-104 following a single injection in adult patients with an acute gout attack.

5.2 Study objectives

- To investigate the efficacy of RPH-104 in the treatment of acute gouty arthritis following a single subcutaneous injection at doses of 4, 20, 40, 80 and 160 mg;
- To investigate the pharmacokinetics of RPH-104 following its single subcutaneous injection;
- To investigate the effect of RPH-104 following its single subcutaneous injection on concentrations of high-sensitivity C-reactive protein (hs-CRP), serum amyloid A protein, blood cytokines (IL-1α, IL-1β, IL-1RA, IL-6, IL-8, TNF-α);
- To investigate the safety parameters of RPH-104 in adult patients with an acute gout attack.

6 STUDY DESIGN

6.1 Primary and secondary endpoints

6.1.1 Primary efficacy variable

Change in pain intensity in the assessed joint at 72 hours after start of the investigational product therapy compared to baseline, as measured on the visual analogue scale (VAS).

6.1.2 Other efficacy variables

- Change in pain intensity in the assessed joint at 15, 30, 45 minutes, 1, 1.5, 2, 4, 8, 24, 48, 72 hours, on days 5, 6, 10, 15, 18, 22, 29 and 45 after start of the investigational product therapy compared to baseline (as measured on VAS).
- Proportion of patients who rated the response to the investigational product therapy as "Excellent" or "Good" at 15, 30, 45 minutes, 1, 1.5 hours, 2, 4, 8, 24, 48, 72 hours, on days 5, 6, 10 15, 18, 22, 29, and 45 after initiation of the investigational product therapy;
- Change in the degree of swelling, tenderness, erythema in the assessed joint at 24, 48, 72 hours, on days 5, 6, 10, 15, 18, 22, 29 and 45 after start of the investigational product therapy compared to baseline;
- Change in movement restriction in the assessed joint at 24, 48, 72 hours, on days 5, 6, 10, 15, 18, 22, 29 and 45 after start of the investigational product therapy compared to baseline;
- Time to 50% reduction in pain intensity in the assessed joint relative to the baseline level according to the VAS;
- Time to use of the rescue medication;

- The proportion of patients who received the rescue medication within 72 hours of starting the investigational product therapy and over the entire treatment period;
- Changes in the health assessment questionnaire scores 15, 29, and 45 days after start of the investigational product therapy compared to baseline.

6.1.3 Pharmacokinetic variables

Pharmacokinetic parameters of subcutaneous RPH-104: AUC0-t, AUC0-∞, Cmax, tmax, t1/2, Kel.

6.1.4 Pharmacodynamic variables

- Change in serum hs-CRP levels at 24, 72 hours, 5, 6, 15, 29 and 45 days after start of the investigational product therapy compared to baseline.
- Change in serum amyloid protein A levels at 24, 72 hours, 5, 6, 15, 29 and 45 days after start of the investigational product therapy compared to baseline.
- Change in serum cytokine (IL-1α, IL-1β, IL-1RA, IL-6, IL-8, TNF-α) levels at 24, 72 hours, 5, 6, 15, 29 and 45 days after start of the investigational product therapy compared to baseline.

6.1.5 Safety variables

Frequency and severity of adverse events, laboratory results, vital signs, physical examination findings, ECG findings.

6.1.6 Immunogenicity assessment

Blood samples for immunogenicity assessment will be collected from patients treated with RPH-104 at the following time points: before administration of RPH-104, on Day 15, Day 45. Concentrations of anti-RPH-104 antibodies will be assessed, including an assessment for neutralizing antibodies.

6.2 Study design and study design flowchart

This clinical study is a multicenter, open-label, single-dose, parallel-group, two-period, randomized, phase IIa study to assess the efficacy, pharmacokinetics, pharmacodynamics, safety and tolerability of the investigational product RPH-104.

In study Period 1, eligible patients are enrolled in a group of 22 patients and randomized to receive either RPH-104 4 mg or Voltaren® (diclofenac) in a 15:7 ratio (15 RPH-104 : 7 Voltaren® (diclofenac)). Patients using Voltaren® (diclofenac) will receive the concomitant drug Ortanol® (omeprazole) in order to prevent damage to the gastric or duodenal mucous membrane.

Upon completion of the enrollment of 22 patients, study Period 2 starts. In Period 2, newly enrolled patients are randomly assigned to one of 5 treatment groups: RPH-104 20 mg, 40 mg, 80 mg and 160 mg and active control (Voltaren® (diclofenac)). It is planned to include 14 patients in the RPH-104 groups in Period 2, and 7 patients in the Voltaren® (diclofenac) group.

The enrollment of patients in Period 1 and Period 2 is sequential. There is no pause between the enrollment of patients in Period 1 and Period 2. Thus, patient enrollment for study Period 2 begins immediately after all Period 1 patients are enrolled. Information on the planned total number of patients in the treatment groups is presented in Table 6.1.

Table 6.1 Number of patients by treatment groups

Treatment group	Study therapy	No. of patients
RPH-104 4 mg	RPH-104, 4 mg, SC, single dose	15
RPH-104 20 mg	RPH-104, 20 mg, SC, single dose	14
RPH-104 40 mg	RPH-104, 40 mg, SC, single dose	14
RPH-104 80 mg	RPH-104, 80 mg, SC, single dose	14
RPH-104 160 mg	RPH-104, 160 mg, SC, divided into 2 injections, 80 mg each at different injection sites	14
Voltaren® (diclofenac)	Voltaren® (diclofenac) 50 mg 3 times a day for 3 days, then 25 mg 3 times a day for 9 days	7 in Period 1 and Period 2 each, total of 14 patients
Total		85

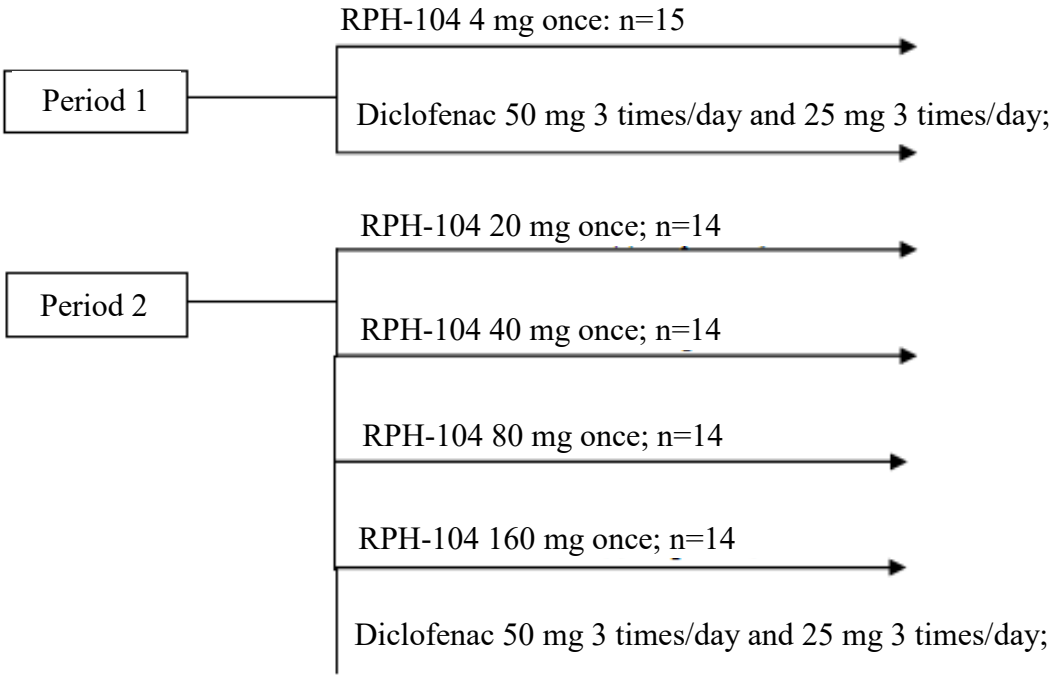
Information about the investigational product used for the treatment of acute gout in the patients in this study (RPH-104 or Voltaren® (diclofenac)) and the dose of RPH-104 is unblinded to the patients and physicians. Patients who do not tolerate pain receive the rescue medication after 2 hours and until Day 45 of the study after the first use of rescue medication to intensify therapy. The rescue medication is triamcinolone 40 mg intramuscularly. If an attack recurred after the use of the rescue medication, treatment of acute gout attack is carried out in accordance with the standard practice of the hospital.

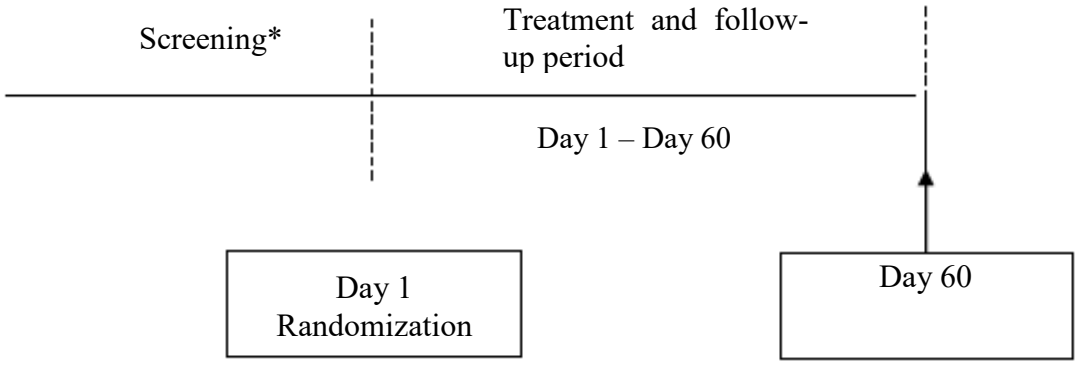
The primary efficacy variable is assessed 72 hours after initiation of the investigational product use. Secondary efficacy variables are evaluated over a 45 day period of therapy and follow-up.

The safety of the investigational product is assessed over a 60-day period of therapy and follow-up.

The study flow diagram is shown in Figure 6.1. The total duration of the study for one patient does not exceed 70 days.

RPH-104 4 mg once: n=15





* Screening procedures must be performed within 24 hours and the patient is randomized during this time. If necessary (in exceptional cases), the screening period can be extended, while randomization must be carried out no later than120 hours (5 days) after the onset of an attack.

Figure 6.1 Flow diagram of the study design.

6.3 Subjectivity minimization measures

6.3.1 Randomization

In Period 1, eligible patients are randomized to receive either RPH-104 4 mg or Voltaren® (diclofenac) in a 15:7 ration, i.e. 15 RPH-104 : 7 Voltaren® (diclofenac)).

In Period 2, eligible patients are randomized to receive either RPH-104 20 mg, 40 mg, 80 mg and 160 mg or Voltaren® (diclofenac) in a 2:2:2:2:1 ratio, respectively.

A summary of the treatment groups and the number of patients per group is provided in Table 6.1.

The randomization will be carried out on the basis of a pre-generated randomization list with a random sequence of randomization of patients generated by the software.

The patient will be randomized by assigning the patient a number and a short name of the therapy group, for example, RPH-104 4 mg. An Interactive Web Response System (IWRS) with technical support service will be used to randomize the patient. Randomization is carried out by the investigator Information about the patient group assigned at randomization is to be recorded in the source documentation.

6.3.2 Blinding

This is an open-label study. Information about the drug for the treatment of acute gout attacks is unblinded to patients and investigators. In this study, there are subjective criteria for assessing the efficacy of study therapy, and information about the drug taken may affect the evaluation of the efficacy of the investigational product by the investigator and the patient. However, since this study is exploratory and is conducted with the aim of assessing the possibility of treating patients with an acute gout attack with RPH-104 in principle, the open-label design of the study is considered acceptable. The efficacy data from this study are not intended to be used to determine the sample size in blind studies.

7 SELECTION OF THE PATIENT POPULATION

In this study, up to 135 adult patients with an acute gout attack will sign the main informed consent form and undergo screening procedures.

At screening, it is planned to select 85 patients meeting all the eligibility criteria for the study described in this section for further participation in the study and initiation of treatment with the investigational product.

7.1 Principal diagnosis

Adult patients with an acute gout attack are eligible for the study.

7.2 Inclusion criteria

To initiate treatment of patients with the investigational product and to carry out the investigation procedures specified by the protocol after the screening visit, patients had to meet all the inclusion criteria:

1. The patient gave his / her informed consent to participation in this study; the Informed Consent Form was signed both by the patient and the Investigator;
2. Male and female patients aged 18 to 80 years inclusive;
3. Established diagnosis of gout according to the criteria established by the American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) in 2015;
4. Pain in at least one joint at the screening and immediately prior to initiation of therapy with the investigational products, with intensity of 50 mm to 100 mm on the Visual Analogue Scale (VAS);
5. Development of acute gout attack within 120 hours (5 days) prior to the randomization date;
6. A history of 1 or more acute gout attacks prior to the Screening Visit;
7. Patients receiving uric acid-lowering agents had to continue receiving these drugs at a stable dose for at least 4 weeks prior to enrolment to the study and throughout the study; the patients not receiving uric acid-lowering drugs might start receiving this treatment after the end of the study;
8. Body mass index ≤ 40 kg/m^2;
9. QTcF interval ≤ 450 msec for menand ≤ 470 msec for women on ECG at screening;
10. For women with childbearing potential: negative serum pregnancy test at screening;

11. Consent of women of childbearing potential and men who have female partners of childbearing potential to abstain from sexual intercourse or to use effective methods of contraception throughout the study and for 60 days after RPH-104 administration (if the patient receives RPH-104), as described in Section 9.9;
12. The patient's ability to fulfil the requirements of the Study Protocol, as judged by the Investigator.

7.3 Exclusion criteria

Patients are not eligible for the study after the screening period if they meet any of the following criteria:

1. The patient received therapy with ibuprofen at a dose of up to 400 mg inclusive within 4 hours or >400 mg within 8 hours prior to the randomization;
2. The patient received therapy with diclofenac at a dose of up to 50 mg inclusive within 8 hours or >50 mg within 24 hours prior to the randomization;
3. The patient received any other non-steroidal anti-inflammatory drug (NSAID) within 24 hours prior to the randomization;
4. The patient received opioids within 48 hours prior to the randomization;
5. The patient received metamizole or metamizole-containing drugs within 12 hours prior to the randomization;
6. The patient received any analgesic drug (including paracetamol) within 6 hours prior to the randomization;
7. The patient received a long-acting NSAID (half-life ≥24 hours) within 5 half-life periods or 1 month prior to the randomization, whichever is longer;
8. The patient received naproxen, meloxicam, nabumetone, celecoxib, etoricoxib or extended-release indomethacin within 5 days prior to the randomization;
9. The patient received corticosteroids (including intra-articular and inhaled) within 4 weeks prior to the randomization;
10. The patient received colchicine within 7 days prior to the randomization;
11. Intolerance of or contraindications to NSAIDs;
12. Contraindications to Ortanol® capsules 20 mg;
13. Chronic heart failure, NYHA functional class II-IV;
14. A history of or current clinically significant ventricular arrhythmias or clinically significant atrial tachyarrhythmias;
15. Unstable angina or stable exercise-induced angina, functional class III or IV;
16. Secondary gout, chemotherapy-induced gout, lead- or transplantation-induced gout;
17. Rheumatoid arthritis, confirmed or suspected infectious septic arthritis or any other type of acute inflammatory arthritis;
18. Clinically significant renal impairment determined based on creatinine clearance (estimated using the Cockcroft-Gault formula) <60 mL/min, or patients on hemodialysis;
19. Blood coagulation disorders; a history of gastrointestinal bleedings or perforation;
20. Pregnant or breast-feeding women;

21. Elective surgery or major surgical intervention (minor surgical procedures, such as catheter placement or bone marrow biopsy, are not exclusion criteria) within 14 days before the first dose of the investigational medicinal product;
22. Current or suspected HIV-infection, HBsAg, Hepatitis C Virus antibodies (HCVAb), other acute or chronic bacterial, fungal or viral infections at the time of enrolment to the study;
23. Presence of any risk factors for tuberculosis based on the results of assessment using the Tuberculosis Risk Assessment Questionnaire at the screening or confirmed tuberculosis or any other infectious disease of the lungs or bronchi based on chest X-ray (2 views) findings performed within 3 months prior to the screening visit, or the need for anti-TB medications, such as isoniazid during the study;
24. Neutropenia, leukopenia, or thrombocytopenia determined based on the following laboratory parameters assessed at screening:
    a. Absolute neutrophil count (ANC) below 1.5 x 10^9/L;
    б. White blood cell count below 4.0 x 10^9/L;
    в. Platelet count below 150 x 10^9/L;
25. Immunization with live vaccines within 3 months prior to the subject's enrolment to the study or planned vaccination within 60 days after the expected date of the first dose of the investigational product;
26. A history of allergic reactions to biological drugs, Voltaren® (diclofenac) or Ortanol® (omeprazole);
27. Contraindications to subcutaneous, intramuscular, intravenous or intra-articular injections;
28. A history of malignancy (except for patients with localized *in situ* basal cell carcinoma of the skin or *in situ* cervical cancer, who could be enrolled to the study immediately after the treatment for this disease), unless it is in remission for ≥5 years, as well as patients who are investigated for cancer or patients with a suspected malignancy;
29. A condition or disease, which, in the Investigator's opinion, could jeopardize the patient's safety or affect the investigational product safety assessment;
30. Any other conditions and diseases, such as uncontrolled diabetes mellitus, uncontrolled hypertension, congestive heart failure, exacerbation of peptic ulcer disease, clinically significant liver diseases, kidney diseases, uncontrolled thyroid dysfunction, unhealed wounds, ulcers or bone fractures, psychiatric disorders, uncontrolled epilepsy, drug dependence, which could prevent the patient from complying with this Study Protocol;
31. Use of biologicals or investigational medicinal products within 5 half-life periods of these drugs or 3 month prior to the randomization, whichever is longer;
32. Blood donation or blood loss of ≥400 mL within 8 weeks prior to the randomization.
33. The patient was already randomized in this clinical study.

8 WITHDRAWAL FROM THE STUDY AND PREMATURE TERMINATION OF THE STUDY

If a decision has been made to withdraw a patient early from the study following the study drug administration, the investigator must schedule a follow-up visit for the patient within 7 days, if possible. If this is not possible, the patient must be invited for a follow-up visit as soon as possible in the period exceeding 7 days. At this visit, it is necessary to carry out all the assessments specified for this visit (see Section 10.3).

If a patient is excluded from the study due to an AE or a laboratory abnormality, the patient must be monitored until the AE resolved or his/her condition stabilized.

8.1 Early withdrawal from the study

The withdrawal criteria are:

- Withdrawal of informed consent.
- Patient's death.
- Patient's pregnancy.
- A significant protocol deviation, which, in the opinion of the Investigator, and upon agreement with the Sponsor, could result in an incorrect interpretation of the study results.

The use of a rescue medication, prohibited drugs, and missing certain procedures or individual visits are generally not the reasons for discontinuation of the patient from the study. In these cases, the patient should be offered to continue the visits and examinations in accordance with the clinical study protocol.

The Investigator should make all reasonable efforts to determine the reason of the patient's withdrawal from the study. The date and reason for the patient's early withdrawal from the study had to be clearly described in the CRF for any patient who received at least one dose of the investigational product.

If a patient is withdrawn from the study due to pregnancy, the Investigator provides the Sponsor with information concerning the pregnancy outcome (see Section 12.7).

Regardless of the reasons for early withdrawal from the study, no replacement of withdrawn patients is to be made.

8.2 Premature termination of the study at an individual study site and premature termination of the study in general

The sponsor reserves the right to terminate the study at an individual study site or at all sites at any time due to reasons of medical and/or administrative nature.

In case of premature study termination, the Investigator should, regardless of the reason for this decision, immediately notify all patients and ensure their follow-up and further treatment. The sponsoring company will notify in writing the Investigator and regulatory authorities about the termination of the study, indicating the reasons for this decision.

In case of premature termination of the study, the Investigator should, if possible, conduct the procedures and evaluations scheduled for the follow-up visit for early withdrawal in all patients who have not completed their participation in the study by this time (see Section 10.3).

9 PATIENT TREATMENT

9.1 Description of investigational products and concomitant therapy

Investigational product provided by the Sponsor

RPH-104 solution for subcutaneous injection, 40 mg/mL is provided by the Sponsor of the study.

Name	RPH-104/L04018
Dosage form	RPH-104 solution for subcutaneous injection, 40 mg/ml, 2 mL
Active substance	RPH-104/L04018
Excipients	Sucrose, Polyethylene glycol (PEG) 3350, sodium chloride, L-histidine
Appearance	A clear or slightly opalescent solution
Packaging	4 mL glass vial with RPH-104 solution for subcutaneous injection, 2 mL
Manufacturer	Branch of R-Pharm JSC, Yaroslavl Factory of Finished Dosage Forms, 150061, Yaroslavl, Gromova str. 15 phone/fax +7 (4852) 40-30-20.

Reference product

Voltaren® (diclofenac) enteric-coated tablets, 25 and 50 mg is provided by the study Sponsor.

Marketing authorization holder (owner): Novartis Pharma Limited, Switzerland.

Trade name: Voltaren® tablets 25 mg and 50 mg

Name	Voltaren®
INN	diclofenac
Dosage form	Enteric coated tablets 25 mg and 50 mg
Active substance	diclofenac sodium
Excipients	anhydrous colloidal silicon dioxide, microcrystalline cellulose, lactose monohydrate, magnesium stearate, corn starch, povidone K30, sodium carboxymethyl starch
Coating composition:	For 25 mg: hypromellose, macrogolglycerol hydroxystearate, dye iron oxide yellow, talc, titanium dioxide For 50 mg: hypromellose, macrogolglycerol hydroxystearate, dye iron oxide yellow, dye iron oxide red, talc, titanium dioxide
Enteric coating composition	copolymer of methacrylic acid and ethyl acrylate (1:1), macrogol 8000, silicone antifoam emulsion SE2, talc
Colored coating composition	For 25 mg: hypromellose, macrogolglycerol hydroxystearate, dye iron oxide yellow, talc, titanium dioxide For 50 mg: hypromellose, macrogolglycerol hydroxystearate, dye iron oxide yellow, dye iron oxide red, talc, titanium dioxide
Appearance	For 25 mg: yellow, round, biconvex, bevelled-edged enteric-coated tablets embedded with "CG" on one side of the tablet and "BZ" on the other For 50 mg: light brown, round, biconvex, bevelled-edged enteric-coated tablets embedded with "CG" on one side of the tablet and "GT" on the other
Packaging	For 25 mg and 50 mg: 2 10-tablet blisters per carton

	3 10-tablet blisters per carton
Manufacturer	NOVARTIS Saglik Gida ve Tarim Urunlery Sanayi ve Ticaret, A.S., Turkey

Concomitant drug for patients receiving Voltaren® (diclofenac)

Ortanol® (omeprazole) 20 mg capsule is provided by the study sponsor.

Marketing authorization holder (owner): Sandoz dd, Slovenia.

Trade name: Ortanol®, capsules, 20 mg

Name	Ortanol®
INN	omeprazole
Dosage form	Capsule
Active substance	omeprazole
Excipients	Low-substituted hydroxypropyl cellulose, MCC, anhydrous lactose, croscarmellose sodium, povidone, polysorbate 80, hypromellose phthalate, dibutyl sebacate, talc
Capsule coating	Hypromellose, carrageenan, potassium chloride, titanium dioxide, iron (III) oxide yellow (for 40 mg), iron (III) oxide red (for 40 mg), water, printing ink: iron (III) oxide black (E172), shellac, anhydrous ethanol, anhydrous isopropanol, propylene glycol, butanol, ammonium hydroxide, potassium hydroxide, purified water
Appearance	Hard capsules No. 2, white body and cap inscribed with "OME 20" in black ink on both parts of the capsule
Packaging	7 capsules per blister, 4 blisters per carton
Manufacturer	Lek Pharmaceuticals dd, Slovenia

9.2 Packaging and labelling

Investigational product RPH-104 solution for subcutaneous injection, 40 mg/mL, 2 mL will be supplied in 4 mL vials. 1 vial per carton.

Voltaren® (diclofenac) will be supplied as 25 and 50 mg film-coated tablets in the manufacturer's original packaging.

Ortanol® (omeprazole) will be supplied in the form of 20 mg capsules in the manufacturer's original packaging.

The investigational product RPH-104, Voltaren® (diclofenac), Ortanol® (omeprazole) and Kenalog® (triamcinolone) are labeled in accordance with the requirements of the Russian legislation.

9.3 Storage conditions

Storage of products used in this study is the responsibility of an authorized employee or pharmacist of the study site. RPH-104 must be stored under the following conditions:

- At 2°C to 8°C. Do not freeze.

Voltaren® (diclofenac) and Ortanol® (omeprazole) should be stored under the following conditions:

- In a dry, dark place, below 25 °C.

Kenalog® (triamcinolone) must be stored under the following conditions:

- In a dark place, at 8°C to 25°C. Do not freeze.

The drugs must be stored in commercial packaging in a secured place with limited access. An authorized employee or pharmacist of the study site should monitor the temperature regime in the refrigerator in which the drugs are stored, and record the temperature on weekdays, taking into account the minimum and maximum temperatures from the previous measurement.

9.4 Accounting and destruction of investigational products and concomitant therapy

The authorized employee or pharmacist of the study site is responsible for the receipt of all study drugs at the study site. Upon delivery of a product lot to the study site, the authorized employee examines the cargo and fills out the reception confirmation form. A copy of this form should be retained at the study site, and the original should be sent to the Sponsor or an organization designated by the Sponsor.

During the study, the investigational products RPH-104, Voltaren® (diclofenac), Kenalog® (triamcinolone) and the concomitant drug Ortanol® (omeprazole) should be accounted for. The patient must return all Voltaren® (diclofenac), Kenalog® (triamcinolone) and Ortanol® (omeprazole) issued to the patient and unused and all packages from used Voltaren® (diclofenac), Kenalog® (triamcinolone) and Ortanol® (omeprazole) to the investigator. Returned Voltaren® (diclofenac), Kenalog® (triamcinolone) and Ortanol® (omeprazole) are accountable. Voltaren® (diclofenac), Kenalog® (triamcinolone) and Ortanol® (omeprazole) returned by the patient cannot be re-dispensed.

Returned unused Voltaren® (diclofenac), Kenalog® (triamcinolone) and Ortanol® (omeprazole) and used Voltaren® (diclofenac), Kenalog® (triamcinolone) and Ortanol® (omeprazole) packages must be retained at the Study Center until specifically instructed by the Sponsor.

The procedure for destruction of the investigational products will be determined by the Study Sponsor.

9.5 Dose, method of administration, dosing regimen, and duration of therapy

9.5.1 Use of the investigational product RPH-104

RPH-104 is administered to patients randomized to one of the RPH-104 groups. The dose of RPH-104 for administration to a patient is selected based on information on the patient's therapy group.

To administer RPH-104 4 mg to a patient, 0.1 mL of RPH-104 solution is injected to the patient. To administer RPH-104 20 mg to a patient, 0.5 mL of RPH-104 solution is injected to the patient. To administer RPH-104 40 mg, 1 mL of RPH-104 solution is injected to the patient. To administer RPH-104 80 mg, 2 mL of RPH-104 solution is injected to the patient. To administer RPH-104 160 mg, the patient received two injections of 2 mL RPH-104 solution at different injection sites (Table 9.1).

RPH-104 is injected subcutaneously into the anterior abdominal region in one of the areas indicated in Figure 9.1.

Table 9.1 Injected volume of RPH-104 to patients

Treatment group	Volume of RPH-104 solution for administration to the patient
RPH-104 4 mg	0.1 mL
RPH-104 20mg	0.5 mL
RPH-104 40 mg	1 mL
RPH-104 80mg	2 mL
RPH-104 160 mg	Two 2 mL injections at different injection sites

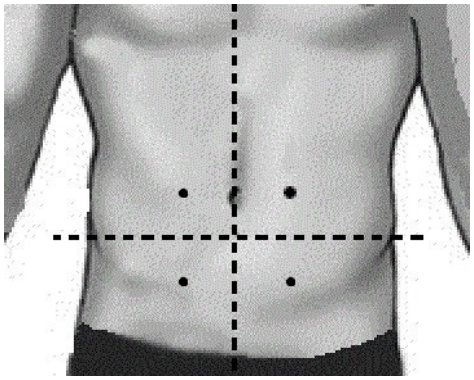


Figure 9.1 Areas of the anterior abdominal wall where RPH-104 should be administered.

9.5.2 Voltaren® (diclofenac) intake

Voltaren® (diclofenac) is given to patients randomized to the Voltaren® (diclofenac) group.

On the first day of therapy, Voltaren® (diclofenac) is dispensed in an amount sufficient to take the drug until the end of the therapy period. The patient takes the first dose of the drug at the study site. Patients who, by the decision of the Investigator, continue to participate on an outpatient basis subsequently take the drug at home on their own in accordance with the study protocol. Hospitalized patients continue to take the drug in a hospital setting until discharge.

Patients take Voltaren® (diclofenac) orally, at a dose of 50 mg 3 times a day for 3 days, then 25 mg 3 times a day for 9 days (12 days in total).

Voltaren® (diclofenac) will be used with Ortanol® (omeprazole), see Section 9.8.1.

9.5.3 Duration of treatment

In all cases, RPH-104 is administered as a single injection; in the case of a 160-mg dose, the drug is administered as two consecutive 80 mg injections at different injection sites.

The duration of therapy with Voltaren® (diclofenac) is 12 days.

The duration of use of Voltaren® (diclofenac) was selected based on the ACR guidelines for the management of acute gout attacks, according to which the use of NSAIDs at a full dose (if necessary) is indicated until the gout attack completely resolves [17]. According to the classification criteria for gout, a gout attack can last for up to 14 days, consequently, drugs that

relieve a gout attack are indicated during this time [18]. A stepwise approach to relieve a gout attack is used with NSAIDs. In this case, NSAIDs are used at a full dose during the first 3 days, then at a lower dose in the next 7 days [19]. According to an article on a phase III study of rilonacept, for the relief of an acute gout attack, the reference product from NSAIDs was used at the full dose for 3 days (150 mg per day), then at a lower dose (75 mg per day) for 9 days [20]. In accordance with the Voltaren® (diclofenac) labeling, the recommended initial dose of the drug is 150 mg per day and 75-100 mg per day for long-term therapy. In this study, Voltaren® (diclofenac) will be used as a reference product in the first 3 days at the full dose of 150 mg per day, then at a lower dose of 75 mg per day for the next 9 days.

By the decision of the investigator, patients can be hospitalized after the use of the investigational products. Patients who, in the investigator's opinion, are not eligible for hospitalization, are followed up for at least 3 hours after the investigational product administration, after which they can leave the study site and continue to participate in the study with all assessments performed on an outpatient basis.

9.6 Overdose with the sponsor's investigational product

Cases of RPH-104 overdose are not known. Symptomatic treatment should be used in the event of an overdose.

9.7 Compliance assessment

Patients treated with Voltaren® (diclofenac) are given diaries to record the date, time and dose of Voltaren® (diclofenac) taken. All missed doses should be recorded in the Patient's Diary.

The information on the number of Voltaren® (diclofenac) tablets dispensed to and received from the patient, as well as information from the patient's diary is recorded. It is automatically calculated using the formula: the number of tablets taken by the patient/the number of tablets that the patient had to take * 100%.

If, based on the results of compliance assessment, the patient took less than 80% of the prescribed dose of Voltaren® (diclofenac), the investigator must discuss with the sponsor the appropriateness of the patient's further participation in the study and the possible premature discontinuation of the patient from the study.

9.8 Previous and concomitant therapies

9.8.1 Orthanol® (omeprazole)

In order to prevent damage to the gastric and duodenal mucosa caused by Voltaren® (diclofenac), all patients receiving Voltaren® (diclofenac) will simultaneously take Ortanol® (omeprazole) as follows: 20 mg, orally daily before breakfast throughout the course of Voltaren® (diclofenac) treatment.

Method of administration of Ortanol® (omeprazole): orally, with a sufficient amount of liquid. The capsule must be swallowed whole. If the patient cannot swallow the capsule whole, it is possible to dissolve its contents in a small amount of water or fruit juice (for example, apple or orange). The capsule may not be dissolved in carbonated drinks or used with milk. The resulting solution of the drug should be drunk immediately after preparation, washed down with an additional ½ glass of water.

On the first day of therapy in the study, it is possible to take it regardless of meals and at a later time.

9.8.2 Rescue therapy for a gout attack

Patients who do not tolerate pain will receive the rescue medication 2 hours after the first use of the investigational product to intensify therapy. The rescue medication is triamcinolone 40 mg

intramuscularly. Before administration of the rescue medication, pain relief efficacy in the assessed joint must be evaluated on VAS and the patient global assessment of efficacy must be performed using a categorical scale and the time of administration of the rescue medication must be recorded.

Triamcinolone suspension for injection is provided by the study sponsor.

Name	Kenalog®
INN	Triamcinolone
Dosage form	Suspension for injection
Active substance	Triamcinolone acetonide
Excipients	Benzyl alcohol, sodium chloride, carmellose sodium, polysorbate 80, hydrochloric acid, sodium hydroxide, water for injection
Packaging	Ampoules, 40 mg/mL, 1 mL No. 5 (1 blister, 5 ampoules per blister)
Manufacturer	JSC KRKA, dd. Novo mesto, Slovenia

If an attack recurs after the use of the rescue medication, treatment is carried out in accordance with the standard practice of the hospital.

9.8.3 Recording information on prior and concomitant therapy

Prior therapy

The following information about the therapy that the patient has previously received for gout (all prior therapy for gout during the gout therapy period), as well as other prior therapy within 30 days prior to screening is recorded in the CRF:

- The names of the drugs, their doses, and the dates of use;
- The names of any investigational medicinal products used by the patient with treatment dates.

To do this, the information should be transferred from the patient's chart or case record into the CRF.

Concomitant therapy

Information about all concomitant therapies received by the patient from the signing of the Informed Consent Form until the completion of the study by the patient must be recorded in the source documentation and in the CRF for each patient (including information on the date of the start and end of concomitant therapy or a mark on the continuation of concomitant therapy at the last visit).

9.8.4 Allowed concomitant therapy

Uric acid-lowering agents

Uric acid-lowering agents are allowed provided that patients have received a stable dose of these drugs for at least 4 weeks prior to the intended date of randomization, and the dose of these drugs remains stable throughout the study.

9.8.5 Prohibited concomitant therapy

The following therapy is prohibited from the moment of signing the informed consent (start of screening) until the end of the study (except in cases of inefficacy of sequential therapy with the investigational product and the rescue medication):

- Analgesics/NSAIDs (including selective type 2 cyclooxygenase inhibitors, analgesic antipyretics and opioids); The exception is acetylsalicylic acid at a dose of <325 mg/day, when the patient is taking it as an antiplatelet agent;
- Systemic or intra-articular corticosteroids, inhaled corticosteroids, excluding rescue medications;
- Colchicine;
- Any other biological products, excluding the investigational product;
- Any investigational medicinal product or medical device other than RPH-104;
- Herbal preparations are prohibited within 2 weeks before the first RPH-104 dose and throughout the study.
- It is prohibited to prescribe uric acid-lowering agents for the first time.

Vaccination with live vaccines is prohibited during the study participation or within 60 days after RPH-104 administration.

9.9 Contraception during the study

Women with child-bearing potential, as well as men who have female partners with child-bearing potential, should use highly effective methods of contraception for the entire duration of the study, and also for 60 days after the administration of RPH-104.

Highly effective methods of contraception:

1. Complete sexual abstinence if it is preferred by the patient and is the patient's normal lifestyle. Therefore, periodic sexual abstinence during ovulation based on symptoms, body temperature measurements, during the post-ovulation period, calendar-based methods, interrupted sexual intercourse, and combinations of these methods are not acceptable contraception methods.
2. Female surgical contraception: bilateral oophorectomy, tubal ligation carried out at least 6 weeks before the administration of the investigational medicinal product.
3. Vasectomy in men carried out at least 6 months before the administration of the investigational medicinal product, with a documented absence of sperm in ejaculate.
4. Use of an intrauterine contraceptive—intrauterine device (IUD): IUD made of copper or IUD with progesterone.
5. Double barrier method (condom and intrauterine spermicide, spermicidal cervical caps or spermicidal diaphragms).

10 CLINICAL EVALUATION PLAN AND STUDY VISITS

The time frames established by the Study Protocol should be observed for all the visits described below.

The study site personnel should make all efforts to conduct the assigned schedule of procedures and visits exactly as required by the Study Protocol.

All deviations from the study flow chart and procedures scheduled for the visits should be documented in the CRF.

10.1 Pre-screening

A pre-screening visit is carried out for patients with gout who visit the physician-investigator as part of routine patient follow-up and do not experience an acute gout attack. At this visit, the

patient is informed about the study procedures and the patient signs the Informed Consent to participate in the screening. The patient receives a copy of the Patient Information Sheet with Informed Consent Form for review and making a decision about participation in the study in the event of an acute gout attack.

10.2 Screening and treatment period

Screening procedures must be performed within 24 hours and the patient is randomized during this time. If necessary (in exceptional cases), the screening period can be extended, while randomization must be carried out no later than 120 hours (5 days) after the onset of an attack.

Patients randomized to the Voltaren® (diclofenac) group do not have to come to the study site on study days 10, 18 and 22, but they should complete the diary, if applicable, and the patient questionnaire on these days.

Screening day (screening procedures and baseline assessments)

The patients are invited to participate in the study and are given a copy of the Patient Information Sheet with Informed Consent Form for review and making a decision about their participation. The patient's written informed consent to participation in the study must be obtained before any procedures scheduled in this study, including the screening procedures, are carried out.

Patients who have read the Patient Information Sheet and signed the Informed Consent Form will be assigned numbers by the online randomization system in the order in which they visit the study site during the screening visit procedures. The number for each patient will consist of two parts: the first two digits will indicate the site number, the next three digits will indicate the assigned serial number of the patient. The individual patient number is retained for subsequent randomization.

Example of patient number assignment: At site 1, the first patient who signs the informed consent form will be assigned number 01001, which will be retained through randomization. The second patient who signs the informed consent form is assigned number 01002. Let us assume that the second patient was not randomized. Then he drops out of the study with number 01002. The third patient receives number 01003. The number assigned to the patient will be indicated on all study documents and in the source documentation.

If a patient is withdrawn from the study during the screening period (an exclusion criterion identified, patient's refusal to participate, etc.), the reason for withdrawal should be specified in the screening log. In this case, the patient can take part in the study again.

After signing the informed consent form for participation in the clinical study, the following procedures are performed at screening:

- Confirmation of the diagnosis, documenting the information about the primary disease;

  NOTE. The diagnosis of gout can be made at a visit to the study site during a current gout attack based on the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) criteria of 2015 with the total score of 8. Uric acid level as the diagnostic criterion can be determined earlier, regardless of when. The highest uric acid levels ever measured must be used.

- Collection of demographic data, medical history, information about previous and concomitant therapy;
- Patient assessment using the TB risk assessment questionnaire;
- Measurement of height and weighing, calculation of body mass index (body mass index must be assessed before randomization);

- Dispensing questionnaires to the patient to record the following:
  - Pain intensity in the assessed joint according to VAS (screening score);
  - Health assessment questionnaire score (baseline value);
- Physician assessment of the degree of swelling, tenderness, erythema and movement restriction in the assessed joint (baseline value);
- Blood sampling for the following analyses:
  - Diagnosis of infections: HIV, HBsAg and HCV Ab (rapid tests, the results must be evaluated before randomization);
  - Diagnosis of infections: HIV, HBsAg, HCV Ab (central laboratory);
  - Complete blood count with WBC differential (absolute neutrophil count, leukocyte and platelet counts must be assessed prior to patient randomization);
  - Blood creatinine level (local laboratory, creatinine levels must be assessed prior to patient randomization);
  - Diagnosis of tuberculosis: T-SPOT.TB test performed at screening or during the hospital stay (central laboratory);
  - Calculation of creatinine clearance (automatically in CRF using the Cockcroft-Gault formula);
  - Blood chemistry with blood lipids (central laboratory);
  - Blood clotting tests (central laboratory);
  - Baseline sample for hs-CRP (central laboratory);
  - Baseline sample for serum amyloid protein A (central laboratory);
  - Baseline sample for cytokines (central laboratory);
  - Serum pregnancy test for women of childbearing potential (the results must be assessed prior to patient randomization);
- Urinalysis;
- Physical examination (the results must be assessed prior to patient randomization);
- Vital signs (the results must be assessed prior to patient randomization);
- 12-lead ECG (the results must be assessed prior to patient randomization);
- Chest X-ray in 2 views (the results must be assessed prior to patient randomization);
- Serious adverse event recording;
- Eligibility assessment.

For patients meeting the eligibility criteria, the following procedures are performed immediately prior to randomization:

- Handing over to the patient a questionnaire for recording pain intensity in the assessed joint according to the VAS (baseline value recorded immediately (within 1 hour) before randomization).

Day 1 (randomization and initiation of therapy)

Patients meeting the eligibility criteria are randomized to receive therapy with either of the investigational products, RPH-104 or Voltaren® (diclofenac).

After randomization, the patients undergo the following procedures:

- Blood collection for the following tests (only for patients randomized to the RPH-104 group, prior to drug administration):
    - Baseline blood sample to study the RPH-104 pharmacokinetics (central laboratory);
    - Baseline blood sample to study anti-RPH-104 antibody levels (central laboratory);
- Subcutaneous injection of RPH-104 (only for patients randomized to RPH-104 groups);

NOTE. The time of administration of RPH-104 is recorded in the source documentation and CRF. Sampling time for subsequent blood samples to assess pharmacokinetics, pain intensity in the assessed joint, and patient global assessment of efficacy are counted from this time. The acceptable time intervals for these procedures are indicated in the Study Procedure Table (see Section 3).

Evaluation of pain intensity in the assessed joint and patient global assessment of efficacy are performed before pharmacokinetic blood sampling in accordance with the pre-specified time intervals for these procedures.

- Dispensing Voltaren® (diclofenac) and Ortanol® (omeprazole) to the patient in an amount sufficient for use until the end of the treatment period (only for patients randomized to the Voltaren® (diclofenac) group);

NOTE. Subcutaneous injection of RPH-104 or the first dose of Voltaren® (diclofenac) must be given within 30 minutes after randomization.

By the decision of the investigator, after the use of the investigational products, patients can be hospitalized and remain under observation in the hospital or continue to participate in the study on an outpatient basis.

After administration of the investigational products, outpatients remain under the supervision of the investigator for at least 3 hours, after which they are allowed to leave the study site. These patients should return to the study site for all analyses and assessments in accordance with the study procedure schedule (Table 3.1).

- Dispensing questionnaires to the patient to record the following:
    - Pain intensity in the assessed joint according to VAS (at 15, 30, 45 minutes, 1, 1.5 h after the use of the investigational product);
    - Patient global assessment of the efficacy using a categorical scale (at 15, 30, 45 minutes, 1, 1.5 h);
- Evaluation of RPH-104 injection site reactions 15 minutes after injection (only for patients who received RPH-104);
- Collecting information on concomitant therapy and adverse events;
- Handing over the Patient Diary.

Day 1 (2 and 8 hours after the start of therapy) *– only for patients randomized to RPH-104 groups*

- Dispensing questionnaires to the patient to record the following:
  - Pain intensity in the assessed joint according to VAS;
  - Patient global assessment of the efficacy using a categorical scale.
- Blood sampling for the following analyses:
  - Assessment of RPH-104 pharmacokinetics (central laboratory);
- Evaluation of RPH-104 injection site reactions;
- Collection of information on concomitant therapy and adverse events.

Day 1 (4 hours after the start of therapy) *– only for patients randomized to RPH-104 groups*

- Dispensing questionnaires to the patient to record the following:
  - Pain intensity in the assessed joint according to VAS;
  - Patient global assessment of the efficacy using a categorical scale;
- Evaluation of RPH-104 injection site reactions;
- Collection of information on concomitant therapy and adverse events.

Day 2 (24 hours after the start of therapy)

- Assessment of vital signs;
- Dispensing questionnaires to the patient to record the following:
  - Pain intensity in the assessed joint according to VAS;
  - Patient global assessment of the efficacy using a categorical scale.
- Blood sampling for the following analyses:
  - Assessment of RPH-104 pharmacokinetics (only for patients randomized to the RPH-104 groups, central laboratory);
  - hs-CRP (central laboratory);
  - Serum amyloid protein A (central laboratory);
  - Cytokines (central laboratory);
- Assessment of the degree of swelling, tenderness, erythema and movement restriction in the assessed joint;
- Evaluation of RPH-104 injection site reactions (only for patients who received RPH-104);
- Collection of information on concomitant therapy and adverse events;
- Patient diary collection and registration of entered data;
- Handing over the Patient Diary.

Day 3 (48 hours after the start of therapy)

- Dispensing questionnaires to the patient to record the following:
  - Pain intensity in the assessed joint according to VAS;
  - Patient global assessment of the efficacy using a categorical scale.
- Blood sampling for the following analyses:
  - Assessment of RPH-104 pharmacokinetics (only for patients randomized to the RPH-104 groups, central laboratory);
- Assessment of the degree of swelling, tenderness, erythema and movement restriction in the assessed joint;
- Evaluation of RPH-104 injection site reactions (only for patients who received RPH-104);
- Collecting information on concomitant therapy and adverse events;
- Patient diary collection and registration of entered data;
- Handing over the Patient Diary.

Day 4 (72 hours after the start of therapy)

- Assessment of vital signs;
- Dispensing questionnaires to the patient to record the following:
  - Pain intensity in the assessed joint according to VAS;
  - Patient global assessment of the efficacy using a categorical scale.
- Blood sampling for the following analyses:
  - Assessment of RPH-104 pharmacokinetics (only for patients randomized to the RPH-104 groups, central laboratory);
  - hs-CRP (central laboratory);
  - Serum amyloid protein A (central laboratory);
  - Cytokines (central laboratory);
- Assessment of the degree of swelling, tenderness, erythema and movement restriction in the assessed joint;
- Evaluation of RPH-104 injection site reactions (only for patients who received RPH-104);
- Collecting information on concomitant therapy and adverse events;
- Patient diary collection and registration of entered data;
- Handing over the Patient Diary.

Day 5 (96 hours after the start of therapy)

- 12-lead ECG;
- Urinalysis;

- Assessment of vital signs;
- Weighing;
- Dispensing questionnaires to the patient to record the following:
    - Pain intensity in the assessed joint according to VAS;
    - Patient global assessment of the efficacy using a categorical scale.
- Blood sampling for the following analyses:
    - Assessment of RPH-104 pharmacokinetics (only for patients randomized to the RPH-104 groups, central laboratory);
    - Complete blood count (local laboratory);
    - Blood creatinine level (local laboratory);
    - Calculation of creatinine clearance (automatically in CRF using the Cockcroft-Gault formula);
    - Blood chemistry with blood lipids (central laboratory);
    - Blood clotting tests (central laboratory);
    - hs-CRP (central laboratory);
    - Serum amyloid protein A (central laboratory);
    - Cytokines (central laboratory).
- Assessment of the degree of swelling, tenderness, erythema and movement restriction in the assessed joint;
- Evaluation of RPH-104 injection site reactions (only for patients who received RPH-104);
- Collecting information on concomitant therapy and adverse events;
- Patient diary collection and registration of entered data;
- Handing over the Patient Diary.

Day 6 (120 hours after the start of therapy)

- Assessment of vital signs;
- Dispensing questionnaires to the patient to record the following:
    - Pain intensity in the assessed joint according to VAS;
    - Patient global assessment of the efficacy using a categorical scale.
- Blood sampling for the following analyses:
    - Assessment of RPH-104 pharmacokinetics (only for patients randomized to the RPH-104 groups, central laboratory);
    - hs-CRP (central laboratory);
    - Serum amyloid protein A (central laboratory);
    - Cytokines (central laboratory);

- Assessment of the degree of swelling, tenderness, erythema and movement restriction in the assessed joint;
- Evaluation of RPH-104 injection site reactions (only for patients who received RPH-104);
- Collecting information on concomitant therapy and adverse events;
- Patient diary collection and registration of entered data;
- Handing over the Patient Diary.

Day 10 (216 hours after the start of therapy) and Day 18 (408 hours after the start of therapy)

- Blood sampling for the following analyses:
    - Assessment of RPH-104 pharmacokinetics (only for patients randomized to the RPH-104 groups, central laboratory);
- Dispensing questionnaires to the patient to record the following:
    - Pain intensity in the assessed joint according to VAS;
    - Patient global assessment of the efficacy using a categorical scale.
- Assessment of the degree of swelling, tenderness, erythema and movement restriction in the assessed joint;
- Evaluation of RPH-104 injection site reactions (only for patients who received RPH-104);
- Collecting information on concomitant therapy and adverse events;
- Patient diary collection and registration of entered data;
- Handing over the Patient Diary.

Day 15 (336 hours after the start of therapy)

- Urinalysis;
- Dispensing questionnaires to the patient to record the following:
    - Pain intensity in the assessed joint according to VAS;
    - Patient global assessment of the efficacy using a categorical scale.
    - Health assessment questionnaire completion;
- Blood sampling for the following analyses:
    - Assessment of RPH-104 pharmacokinetics (only for patients randomized to the RPH-104 groups, central laboratory);
    - A study of anti-RPH-104 antibodies (only for patients randomized to the RPH-104 groups, central laboratory);
    - Complete blood count (local laboratory);
    - Blood creatinine level (local laboratory);
    - Calculation of creatinine clearance (automatically in CRF using the Cockcroft-Gault formula);

  - Blood chemistry with blood lipids (central laboratory);
  - Blood clotting tests (central laboratory);
  - hs-CRP (central laboratory);
  - Serum amyloid protein A (central laboratory);
  - Cytokines (central laboratory);
- Assessment of the degree of swelling, tenderness, erythema and movement restriction in the assessed joint;
- Assessment of vital signs;
- Weighing;
- Physical examination;
- Evaluation of RPH-104 injection site reactions (only for patients who received RPH-104);
- Collecting information on concomitant therapy and adverse events;
- Patient diary collection and registration of entered data;
- Handing over the Patient Diary.

Day 22 (504 hours after the start of therapy)

- Assessment of vital signs;
- Dispensing questionnaires to the patient to record the following:
  - Pain intensity in the assessed joint according to VAS;
  - Patient global assessment of the efficacy using a categorical scale.
- Blood sampling for the following analyses:
  - Assessment of RPH-104 pharmacokinetics (only for patients randomized to the RPH-104 groups, central laboratory);
- Assessment of the degree of swelling, tenderness, erythema and movement restriction in the assessed joint;
- Evaluation of RPH-104 injection site reactions (only for patients who received RPH-104);
- Collecting information on concomitant therapy and adverse events;
- Patient diary collection and registration of entered data;
- Handing over the Patient Diary.

Day 29 (672 hours after the start of therapy)

- Dispensing questionnaires to the patient to record the following:
  - Pain intensity in the assessed joint according to VAS;
  - Patient global assessment of the efficacy using a categorical scale;
  - Health assessment questionnaire completion;

- Blood sampling for the following analyses:
    - Assessment of RPH-104 pharmacokinetics (only for patients randomized to the RPH-104 groups, central laboratory);
    - hs-CRP (central laboratory);
    - Serum amyloid protein A (central laboratory);
    - Cytokines (central laboratory);
- Assessment of the degree of swelling, tenderness, erythema and movement restriction in the assessed joint;
- Assessment of vital signs;
- Evaluation of RPH-104 injection site reactions (only for patients who received RPH-104);
- Collecting information on concomitant therapy and adverse events;
- Patient diary collection and registration of entered data;
- Handing over the Patient Diary.

Day 45 (1056 hours after the start of therapy)

- 12-lead ECG;
- Urinalysis;
- Dispensing questionnaires to the patient to record the following:
    - Pain intensity in the assessed joint according to VAS;
    - Patient global assessment of the efficacy using a categorical scale;
    - Health assessment questionnaire completion.
    - Blood sampling for the following analyses:
    - Assessment of RPH-104 pharmacokinetics (only for patients randomized to the RPH-104 groups, central laboratory);
    - A study of anti-RPH-104 antibodies (only for patients randomized to the RPH-104 groups, central laboratory);
    - Complete blood count (local laboratory);
    - Blood creatinine level (local laboratory);
    - Calculation of creatinine clearance (automatically in CRF using the Cockcroft-Gault formula);
    - Blood chemistry with blood lipids (central laboratory);
    - Blood clotting tests (central laboratory);
    - hs-CRP (central laboratory);
    - Serum amyloid protein A (central laboratory);
    - Cytokines (central laboratory);
    - Serum pregnancy test for women of childbearing potential;

- Assessment of the degree of swelling, tenderness, erythema and movement restriction in the assessed joint;
- Assessment of vital signs;
- Weighing;
- Physical examination;
- Evaluation of RPH-104 injection site reactions (only for patients who received RPH-104);
- Collecting information on concomitant therapy and adverse events;
- Patient diary collection and registration of entered data.

Day 60 (± 7 days)

On this day, the Investigator contacted the patient over the phone to collect information about adverse events, their characteristics (onset time, resolution time, severity, relationship to the investigational product, etc. as described in Section 12 of this protocol).

10.3 Follow-up visit for early patient withdrawal from the study

The follow-up visit for patients who withdraw from the study early is carried out for 7 days after the decision on early withdrawal. The minimum list of examinations at the Follow-up Visit is as follows:

- Adverse event recording
- Collection of information on concomitant therapy
- Assessment of vital functions
- Complete physical examination
- Weighing
- 12-lead ECG
- Urinalysis
- Blood sampling for the following analyses:
    - Complete blood count;
    - Blood chemistry with blood lipids (central laboratory); creatinine (local site laboratory);
    - Calculation of creatinine clearance (automatically in CRF using the Cockcroft-Gault formula);
    - Blood clotting tests (central laboratory);
    - Serum pregnancy test for women of childbearing potential;
- Blood samples to assess the pharmacokinetics of the investigational product and anti-drug antibodies (only for patients who received RPH-104, central laboratory).

10.4 Assessment of efficacy parameters before using the rescue medication

In this study, patients with unbearable pain are allowed to use the rescue medication no earlier than 2 hours after administration of the investigational drug. For such patients, it is necessary to carry out the following procedures:

- Before using the rescue medication, dispensing questionnaires to the patient to record the following:
    - Pain intensity in the assessed joint according to VAS;
    - Patient global assessment of the efficacy using a categorical scale;
- Registering the time of use of the rescue medication and enter the results in the source documentation and CRF.

10.5 Unscheduled visits

Patients can ask the investigator to appoint an unscheduled visit at any time if they have adverse events, or if their condition requires medical intervention. The investigator may schedule an unscheduled visit to the patient to assess the safety of the therapy.

To register an unscheduled visit, the Investigator shall enter obtained data in the source medical documents and the CRF ('Unscheduled Visit' page). The Investigator will have to make sure to record the following information: the date of the visit, the reasons for it, and the data obtained as a result of physical examination and additional tests conducted.

After an unscheduled visit, the next visit should be conducted as planned, in accordance with the Study Protocol.

11 DESCRIPTION OF THE VARIABLES AND ASSESSMENT METHODS

11.1 Baseline characteristics

11.1.1 Information on the primary disease

The CRF should contain the following characteristics of the underlying condition:

- The original diagnosis of the primary condition and the date of diagnosis;
- Date of diagnosis of acute gout attack;
- Count of joints affected by gout:
    - 1 joint affected (acute monoarticular gout)
    - 2 to 4 joints affected (acute oligoarticular gout)
    - 5 or more joints affected (polyarticular gout)
- Information on previous therapy (see Section 9.8) and its outcomes

11.1.2 Demographic data

The following demographic data will be registered at the study selection step:

- Date of birth
- Sex
- Race

11.1.3 Measurement of body weight and height

The patient's height (barefooted) will be measured at the screening visit, and the result recorded in the CRF (rounding to the nearest centimeter). Body weight measurements are taken at

screening visits, Days 5, 15 and 45, follow-up visits for early withdrawal of the patient from the study, and the result is reported to the nearest kilogram.

The body mass index is calculated automatically in the CRF after entering data on the patient's height and body weight.

11.1.4 Collection of medical history data and information on concomitant diseases

Detailed historical data will be collected during the screening period, including information on all current diseases and all significant (in the Investigator's opinion) past diseases, as well as information on tobacco smoking.

11.1.5 Evaluation of creatinine, complete blood count parameters, chest X-ray

At Screening, on Days 5, 15, and 45, the follow-up visit for early withdrawal from the study, the following tests are performed at the study site local laboratory:

- Measurement of creatinine level
- Complete blood count with an assessment of the following parameters:
  - Absolute neutrophil count
  - Total white blood cell count
  - Platelet count

Creatinine clearance is calculated automatically in CRF using the Cockcroft-Gault formula:

For men:

$$Creatinine\ clearance\ (mL/min) = \frac{(140 - age^{a}) \times (weight^{b}) \times 1.0}{0.81 \times \text{serum creatinine (μmol/L)}}$$

For women:

$$Creatinine\ clearance\ (mL/min) = \frac{(140 - age^{a}) \times (weight^{b}) \times 0.85}{0.81 \times \text{serum creatinine (μmol/L)}}$$

a. Age expressed in years.

b. Weight in kilograms.

Chest X-ray in 2 views is performed at screening if the patient does not have results of chest X-ray in 2 views or fluorography of the chest in 2 views or chest CT performed within 3 months before the expected date of the first injection of the investigational product.

11.1.6 Diagnosis of infections (HIV, hepatitis B, hepatitis C)

On Day 1, prior to patient randomization, the investigator will look for symptoms and signs of hepatitis B and C, including a medical history data. If a patient is suspected of having hepatitis B or C, the patient is not randomized.

To diagnose infections (HIV, HBsAg, HCV Ab) in patients, blood samples are taken on Day 1 prior to randomization for the following tests:

- Express tests for the diagnosis of HIV (OraQuick HIV ½), hepatitis B (SD BIOLINE HBsAg) and hepatitis C (OraQuick HCV Ab)
- Tests for HIV, HBsAg, HCV Ab performed at the central laboratory

Rapid tests for the study are provided by the sponsor. The Sponsor may provide analogs of the above rapid tests for the study. Details on how to perform rapid tests and how to handle blood samples to diagnose infections at the central laboratory are provided in the laboratory manual.

All rapid tests must be negative to randomize patients into the study.

Central laboratory testing for HIV, HBsAg, and HCV Ab is performed for all patients who signed the informed consent, regardless of rapid test results. The results of these tests will be known after administration of the investigational product to the patient(s) or a decision has been made to not to include the patient from the study. If the patient's test result at the central laboratory is positive for an infection, it will be communicated to the patient. Such patients will be referred to a specialist for further examination and treatment. For such patients, information about the identified concomitant infectious disease should be entered in the eCRF in the Concomitant Diseases section.

11.1.7 Diagnosis of tuberculosis

On Day 1, prior to the patient's randomization, the investigator will ask the patient all questions from the TB risk assessment questionnaire (Appendix 1). If the response to any of the questions in this questionnaire is yes, the patient will not be randomized.

The results of the chest x-ray in 2 views taken during the screening will be used to assess the patient's eligibility for participation in the study.

Blood sampling for a T-SPOT.TB test will be carried out either at screening, or during the time the patient is in the hospital.

This test will be carried out in a central laboratory. The results of these tests will be known after administration of the investigational product to the patient(s) or a decision has been made to not to include the patient from the study. If the patient's test result at the central laboratory is positive for an infection, it will be communicated to the patient. Such patients will be referred to a specialist (TB specialist) for further examination and treatment. For such patients, information about the identified concomitant infectious disease should be entered in the eCRF in the Concomitant Diseases section. A positive test result will be considered an AE.

11.1.8 Serum Pregnancy Test

Serum pregnancy test for women of childbearing potential will be performed at the study site. Serum pregnancy tests for women of childbearing potential should be performed at screening and at the Day 45 visit or follow-up visit if the patient withdraws from the study early. To enroll a patient in the study, a pregnancy test at screening must be performed after the patient has signed the informed consent from and the result of this test must be negative.

Women are considered postmenopausal and of non-childbearing potential if spontaneous (natural) amenorrhea has lasted at least 24 months with a respective clinical presentation (e.g. appropriate age, history of vasomotor symptoms), or if they underwent bilateral surgical removal of the ovaries (with or without hysterectomy) or tubal ligation at least 6 weeks before the proposed randomization date. In the case of removal of the ovaries only, a woman is of non-childbearing potential only after confirmation of the reproductive status by a hormone test.

11.2 Evaluation of pharmacokinetics and anti-drug antibodies

Evaluation of the RPH-104 pharmacokinetics and anti-drug antibodies is carried out only for patients treated with RPH-104.

The time of blood sampling for pharmacokinetics and anti-antibodies is presented in Table 3.1.

Acceptable time windows for blood sampling for pharmacokinetics and anti-antibodies are shown in Table 3.1.

It is essential to record in the CRF the real sampling time for each blood sample and to pay particular attention to labeling of the samples.

The methods used to collect blood samples, obtain plasma, and store samples are described in the guideline for laboratory tests.

Serum samples for the assessment of pharmacokinetics and anti-drug antibodies are sent to Covance Central Laboratories. The cargo handling procedure is described in the laboratory manual.

11.2.1 Analytical method

The assay of RPH-104 and anti-drug antibodies in blood serum will be carried out using a validated analytical procedure. The lower limit of quantification (LLoQ) of RPH-104 will not be higher than 5% of Cmax.

11.3 Assessment of pharmacodynamics

Serum levels of hs-CRP, amyloid protein, and cytokine levels (IL-1α, IL-1β, IL-1RA, IL-6, IL-8, TNF-α) are assessed in all randomized patients.

The time windows for blood sampling to assess levels of hs-CRP, serum amyloid A protein, and cytokine levels (IL-1α, IL-1β, IL-1RA, IL-6, IL-8, TNF-α) in serum is presented in Table 3.1.

The methods used to collect blood samples, obtain plasma, and store samples are described in the guideline for laboratory tests.

Serum samples to assess hs-CRP, serum amyloid protein A, and cytokine levels are sent to the Unimed central laboratory. The shipment handling procedure is described in the laboratory manual.

11.4 Efficacy assessment

11.4.1 Measurement of pain intensity in the assessed joint

To assess pain intensity, an affected joint with the maximum pain intensity on Day 1 is selected.

Pain intensity is assessed in all patients using a 100 mm VAS. Pain intensity assessments are carried out before the start of therapy with the investigational products, at 15, 30, 45 minutes, 1, 1.5, 2, 4, 8, 24, 48, 72 hours, 5, 6, 10, 15, 18, 22, 29 and 45 days after the start of the investigational product use. In case of the use of the rescue medication, pain intensity must be assessed before its administration.

For each assessment of pain intensity, the patient records the result of the assessment in the patient questionnaire.

Completed questionnaires should be dated with indication of time and signed by the patient.

When handing over the questionnaires to patients outside the study site, the investigator will instruct them on proper completion.

Patient questionnaires and instructions for completion are provided in a separate document.

11.4.2 Patient global assessment of efficacy

All randomized patients evaluate the efficacy of their prescribed therapy. The patients perform global assessment of efficacy at 15, 30, 45 minutes, 1, 1.5, 2, 4, 8, 24, 48, 72 hours, 5, 6, 10, 15, 18, 22, 29 and 45 days after the start of the investigational product use. In case of the use of the rescue medication, global assessment of efficacy must be carried out before its administration.

For global assessment of efficacy, patients use a categorical scale with 5 response options. For each assessment of response to therapy, the patient records the result of the assessment in the patient questionnaire.

Completed questionnaires should be dated with indication of time and signed by the patient.

When handing over the questionnaires to patients outside the study site, the investigator will instruct them on proper completion.

Patient questionnaires and instructions for completion are provided in a separate document.

11.4.3 Assessment of the degree of swelling, tenderness, and erythema in the assessed joint by physician

The severity of edema, tenderness, erythema in the assessed joint is assessed for all randomized patients at the time points indicated in Table 3.1. For assessment, categorical scales are used in accordance with the "Form for Assessment of the Degree of Swelling, Tenderness, Erythema and Movement Restriction in the Assessed Joint" (see Appendix 2) with the following response options:

Swelling assessment:

- "absence" – no swelling
- "mild" – palpable swelling
- "moderate" – visible swelling
- “severe" – bulging outside the joint

Tenderness assessment:

- "absence" – no tenderness
- “mild" – tenderness when touched
- "moderate" – pain and flinching
- "severe" – pain, flinching and withdrawal of the limb

Erythema assessment:

- absence
- presence
- unevaluable

The assessment results are recorded in the source documentation and eCRF.

11.4.4 Assessment of the degree of movement restriction in the assessed joint by physician

The investigator evaluates the range of motion in the assessed joint for all randomized patients at the time points indicated in Table 3.1. For assessment, a 5-point categorical scale is used in accordance with the "Form for Assessment of the Degree of Swelling, Tenderness, Erythema and Movement Restriction in the Assessed Joint" (see Appendix 2) with the following response options:

1. Normal range,
2. Slightly limited range,
3. Moderately limited range,
4. Significantly limited range,
5. Joint movement is impossible.

11.4.5 Assessment of the amount of the rescue medication used by the patient

All cases of the use of the rescue medication are recorded in the source documentation and CRF. The name, date, time and dose of the rescue medication used are recorded.

11.4.6 Health assessment questionnaire (HAQ) assessment

At visits on Day 1 (pre-randomization), Day 15, Day 29, and Day 45, patients are given the HAQ for self-completion.

The HAQ with instructions for completion is provided in a separate document.

11.5 Safety and tolerability assessment

11.5.1 Adverse event assessment

The assessment of adverse events is described in Section 12.

11.5.2 Assessment of injection site reactions

The presence of local reactions to the administration of the investigational product is assessed in patients who received RPH-104 at the time points indicated in Table 3.1. The Investigator assesses the presence of tenderness, redness, swelling, induration, hemorrhage and itching at the RPH-104 injection site. All cases of RPH-104 injection site must be followed-up until resolution.

11.5.3 Physical examination

Physical examination should be carried out in accordance with the study procedure schedule (see Section 3). Information about the completed physical examination and examined organ systems should be described in the source documents kept at the study site. Any abnormalities in physical examination findings obtained before the first self-administration of the investigational medicinal product should be recorded in the CRF, in the 'Concomitant diseases' section. Any abnormalities in physical examination findings obtained after the first self-administration of the investigational medicinal product and meeting the definition of an adverse event should be recorded in the CRF, in the 'Adverse events' section.

The CRF will have no section to record normal findings of periodic physical examinations; however, such results should be reflected in the source documents.

Complete physical examination includes: assessment of overall health, skin (presence of rash or lesions), head, mouth, eyes, ears, throat, nose, lungs (auscultation), heart (auscultation for murmurs, gallop rhythm, pericardial friction rubs), lower extremities (peripheral edema, presence of varicose veins), abdomen (palpation and auscultation), nervous system (mental status, gait, reflexes, motor and sensory functions, coordination) and lymph nodes.

11.5.4 Assessment of vital signs

Vital signs include: body temperature, pulse rate, respiratory rate, and sitting blood pressure measured after 5-minute rest. The Day 1 data obtained before the first dose of the investigational product are regarded as baseline vital signs. On subsequent days, vital signs should be evaluated and registered prior to the administration of Voltaren® (diclofenac) in patients treated with Voltaren® (diclofenac).

Clinically significant abnormalities in vital signs are to be recorded as adverse events.

11.5.5 Electrocardiography

A 12-lead electrocardiography should be carried out in accordance with the study flow chart.

Clinically significant ECG abnormalities detected at the screening visit should be recorded in the CRF as concomitant diseases. After that, all new, clinically significant ECG abnormalities should be registered as adverse events.

The ECG intervals (QT, RR, and QTcF) should be registered in the CRF for each ECG test.

11.5.6 Laboratory blood tests

Complete blood count

Complete blood count is carried out by the local laboratory of the study site in accordance with the procedure adopted by the site laboratory. A complete blood count involves assessment of the following peripheral blood parameters:

- Hemoglobin
- Hematocrit
- Erythrocytes
- Platelet count
- Total white blood cell count
- Absolute neutrophil count
- White blood cell differential in relative units:
  - Neutrophils (%)
  - Segmented neutrophils (%)
  - Stabs (%)
  - Eosinophils (%)
  - Basophils (%)
  - Monocytes (%)
  - Lymphocytes (%)

Blood chemistry, blood lipids, coagulation tests

Blood tests are carried out in the central laboratory, except for creatinine. Blood samples are collected under fasting conditions or before the patient receives the investigational product. Sample handling procedures for assessing blood chemistry, blood lipids, and coagulation are described in the laboratory manual.

The blood chemistry will include the following tests:

- Sodium
- Potassium
- Chloride
- Magnesium
- Calcium
- Phosphorus
- Bicarbonates
- Blood urea nitrogen (or urea)
- Uric acid
- Total protein
- Albumin
- Glucose
- Creatinine (local laboratory) with determination of creatinine clearance using the Cockcroft-Gault formula
- Total bilirubin

- Direct bilirubin
- AST
- ALT
- Alkaline phosphatase
- Lactate dehydrogenase
- Amylase
- Lipase
- GGT
- Creatine kinase
- MB-creatine kinase

Blood lipids include the following parameters:

- Low-density lipoprotein
- Triglycerides
- LDL
- HDL

Blood clotting tests includes the following parameters:

- Fibrinogen
- INR
- APTT

11.5.7 Urinalysis

Urinalysis is carried out by the local laboratory of the study site in accordance with the procedure adopted by the site laboratory.

The following urinalysis parameters will be assessed:

Physical parameters:

- Color
- Transparency
- Specific gravity
- pH value or reaction (acidic, alkaline, neutral)

Biochemical parameters:

- Glucose
- Protein
- Ketone bodies
- Bilirubin
- Urobilinogen
- Nitrites

In addition, information on the results of the analysis of sediment microscopy is recorded (leukocyte count, erythrocyte count, epithelial cell count with cell type, and bacterial count). Epithelial cell count with an indication of the cell type and bacterial count will be assessed as the presence or absence in the analysis.

12 ADVERSE EVENTS

In this study, an **adverse event** (AE) means any untoward medical event in a patient receiving the study drug that does not necessarily have a causal relationship with the drug. Thus, an adverse event can be any unintended and untoward symptom (for example, a laboratory abnormality), a symptom or a disease with temporal relationship with the use of the drug, regardless of whether they are considered to be related with the drug.

Clinical signs of treatment failure are not adverse events. For example, persistent pain or swelling in an affected joint should not be reported as an adverse event.

Symptoms, syndromes, and diseases noted prior to the study therapy, but after the patient signed the informed consent form, are recorded in the CRF as Concomitant Diseases.

Laboratory and investigation abnormalities should be registered as adverse events if these abnormalities are regarded by the investigator as clinically significant.

An **adverse drug reaction** is any adverse event with at least a possible (possible, probable, or certain) relationship with the use of the investigational medicinal product.

AE severity is graded according to the CTCAE classification v.5.0.

All adverse events should be monitored until resolution or stabilization (assessed by the investigator).

12.1 Adverse event recording

Adverse events are registered either on the basis of complaints spontaneously reported by the patient or by the Investigator interviewing the patient or using physical examination findings and results of laboratory and instrumental investigations. The investigator should formulate his / her questions to the patient so that they do not prompt the patient to report unreliable information.

Adverse events should be registered in respective sections of the CRF, as well as in the patient's source medical documents.

Serious AEs are recorded from the time of signing the informed consent to participate in the study. All other adverse events will be registered beginning from the first dose of the investigational medicinal product. Adverse events will be registered until the end of the follow-up period. Reporting of serious AEs is described in section 12.5.

The following information should be reported for a registered adverse event:

- Patient ID
- Diagnosis of the adverse event (a diagnosis should be preferred to listing symptoms)
- The onset and resolution dates for the adverse event (and the times if applicable)
- AE severity
- Study drug relationship
- The measures that have been taken due to the adverse manifestation
- Actions taken in relation to the investigational drug
- Whether the adverse event meets the serious adverse event criteria
- Adverse event outcome

12.2 Causality assessment between the adverse event and the use of the investigational product

To evaluate the causal relationship with the use of the investigational product, all available information should be taken into consideration if it can help characterize this relationship, in particular the mechanism of action of the investigational product, information about known adverse effects of the product from the Investigator's Brochure, characteristics of the adverse event, temporal relationship between the adverse event and the use of the study drug, time to resolution of the adverse event, and other possible causes of the adverse event, which may include the following:

- Use of other medications or exposure to chemical substances
- The natural course of the primary disease or other conditions
- Study procedures
- Other factors

The Investigator should determine the causal relationship for the adverse event using the definitions below:

- **Unlikely:** an adverse event is temporally related to the administration of the investigational product, but there are some other factors (such as a concomitant disease or an effect of other medications, chemical or physical factors) that appear to be more plausible causes of this adverse event;
- **Possible:** an adverse event is temporally related to the administration of the investigational product, but its development may also be explained by other factors (such as a concomitant disease or an effect of other medications, chemical or physical factors);
- **Probable:** an adverse event is temporally related to the administration of the investigational product. The causal relationship with other factors (such as a concomitant disease or an effect of other medications, chemical or physical factors) appears unlikely; The adverse event regresses after discontinuation of the investigational product;
- **Certain:** an adverse event is temporally related to the administration of the investigational product. The adverse event cannot be explained by other factors (such as a concomitant disease or an effect of other medications, chemical or physical factors); the adverse event regresses after discontinuation of the investigational product. The adverse event recurs after rechallenge;
- **Unrelated:** no relationship with the medicinal product: in the presence of an apparent alternative explanation and/or an unsubstantiated temporal relationship between the medicinal product and the event, and/or in the event when the relationship is biologically implausible.

If the assessed relationship changes over time as a result of new or changed information, it may be revised.

12.3 Adverse event severity

The investigator assesses the severity of all AEs reported during the study based on the following categories:

Mild:	The study participant tolerates the AE well, with minimal discomfort, does not interfere with normal daily activities.
Moderate:	The event causes significant discomfort and interferes with daily activities.
Severe:	The event does not allow carrying out daily activities.

In accordance with the standard healthcare practice in the Russian Federation, the following interpretation of AE severity by grade, used in the study, is considered correct:

Mild corresponds to CTCAE v 5.0 Grade 1,

Moderate corresponds to CTCAE v 5.0 Grade 2 and Grade 3,

Severe corresponds to CTCAE v 5.0 Grade 4 and Grade 5

A severe AE should not be confused with a serious AE. Severity is a category for assessing the intensity of an event, both non-serious AEs and serious AEs can be severe. A serious adverse event is an event that meets at least one of the criteria specified in the definition of a Serious Adverse Event (see 12.4).

12.4 Serious adverse events (SAEs)

A serious adverse event (SAE) is any adverse event that meets one or more of the criteria listed below:

1. Resulted in the patient's death
2. Is life-threatening
3. Requires hospitalization or prolongation of existing hospitalization
4. Resulted in persistent or significant disability or incapacity
5. Is a congenital anomaly or developmental defect occurring in children born to patients treated with the investigational drug.

In addition, serious adverse events may include other important medical manifestations if the investigator believes, on the basis of his/her medical experience, that this manifestation may result in one of the outcomes described above if no medical intervention is undertaken.

An adverse event is considered to be “life-threatening” if the patient is at an immediate risk of death at the time of the event. This category does not include adverse events, which hypothetically might have caused the patient's death if they were more severe.

12.5 SAE reporting procedure

To ensure safety for study subjects in case of any SAE developing after the patient signs the Informed Consent Form and before the end of the study, regardless of the suspected causes of the SAE or the relationship with the use of the investigational product, the SAE should be reported to the study Sponsor within 24 hours after the investigator becomes aware of the SAE.

If a study subject is found to develop a serious adverse event related to the use of the investigational product, it should be reported even if the study has already been completed.

Filling out the serious adverse event reporting form.

SAEs should be reported by sending a scanned copy of the completed Serious Adverse Event Reporting Form in paper format by e-mail to

Safety@Rpharm.ru.

or by fax:

+7 (495) 956-79-38

The primary contact for any issues related to the safety of the medicinal product is the Head of the Department of Drug Safety at R-Pharm JSC, Candidate of Medical Sciences, Sergey Alexandrovich Grishin.

Phone: +7 (495) 956-79-37 ext.1506

Mob. phone: +7 (963) 683-05-71

fax: +7 (495) 956-79-38

email:Safety@rpharm.ru; sa.grishin@rpharm.ru

The Investigator must notify the LEC about SAEs in accordance with the LEC standard operating procedures.

The Study Sponsor must notify the regulatory authorities of the Russian Federation of all suspected unexpected serious adverse reactions within the time frame specified by the Russian law. In the context of notifying regulatory authorities and investigators, suspected unexpected serious adverse reactions will be deemed to be unexpected serious adverse events assessed by the investigator and/or Sponsor to be doubtfully, possibly, probably, or certainly related to the investigational therapy.

12.6 Investigator's responsibilities related to reporting of serious adverse events

Reporting suspected unexpected serious adverse reactions (SUSAR).

The sponsor will inform investigators of all suspected unexpected serious adverse reactions recorded during the study. It is the investigator's responsibility to submit appropriate reports to the Local Ethics Committees of healthcare institution.

Submission of other safety reports.

The Investigators will report to the Local Ethics Committees of healthcare institutions on other treatment safety aspects subject to expedited reporting if they affect the benefit-risk ratio for the study therapy or might necessitate significant modification of the study therapy or study methods.

In addition to submitting expedited reports, the Sponsor will annually prepare development safety update reports for RPH-104, containing all new relevant safety information received during the reporting period. These reports will be forwarded to the investigator for submission to the Local Ethics Committees of healthcare institutions once a year.

12.7 Pregnancy

In the event of pregnancy in a female patient participating in the study, the investigational product will have to be immediately discontinued.

Pregnancy is not an adverse event as such, except where there is reason to believe that the use of the investigational product resulted in decreased effectiveness of the contraceptives used.

Information concerning pregnancies in female patients or sex partners of male patients participating in the study should be registered from the signing of the Informed Consent Form to the end of the study.

If a female patient or a female partner of a male patient participating in the study becomes pregnant, the study Sponsor should be notified by filling out the "Pregnancy reporting". A

pregnancy report should be filled out by an authorized employee of the study site within 24 hours after the pregnancy information is received. Pregnancy cases should be reported by sending a scanned copy of the filled pregnancy reporting form in paper format by e-mail to: Safety@Rpharm.ru.

Collection of pregnancy-related information should continue until the end of the pregnancy. After the end of the pregnancy, the study Sponsor should be informed about the outcome of the pregnancy (miscarriage, elective abortion, delivery of a healthy infant or infant with congenital anomalies or developmental defects). If possible, the newborn health should be monitored until 6 weeks, 6 months, and 12 months of age.

Any complications of pregnancy should be recorded as adverse events or serious adverse events depending on the seriousness criteria.

Congenital anomalies and developmental defects in subjects' children are serious adverse events. Miscarriages should be recorded as serious adverse events. Elective abortions carried out at the woman's discretion, without medical indications for abortion and not associated with complications, are not adverse events.

12.8 Actions in emergency situations

Medical equipment and pharmacological therapy.

The study site should have appropriate equipment and drugs necessary for emergency care. Their use (which may be necessary though unlikely) should be recorded in the CRF.

12.9 Follow-up of adverse events

All AEs are followed up until they resolve or stabilize.

13 DATA ANALYSIS AND STATISTICAL ANALYSES

13.1 General provisions

Standard statistical calculations for continuous data sets will be performed to indicate the number of cases (N), mean value, standard deviation, minimum, median, and maximum. Categorical data will be reflected by the N value and proportion (%). For all registered types of data, all individual patient values will be listed.

13.1.1 Analysis populations

Efficacy population

To assess the treatment efficacy, the population of all randomized patients who received at least one dose of the investigational product and who had at least one VAS measurement of the patient's pain intensity in the assessed joint after the start of the investigational product therapy will be used.

Safety population

The treatment safety population will include all subjects who have received at least one dose of the investigational medicinal product. This population will be used for all treatment safety assessments. The safety analysis of data will be performed based on the actual treatment received by the patients.

Pharmacokinetic population

The pharmacokinetic population will include all subjects who have received at least one dose of the investigational product and for whom sufficient data has been accumulated on the blood concentrations of the investigational product to allow pharmacokinetic calculations.

Pharmacokinetic data obtained for the investigational product will be analyzed in this patient population.

Pharmacodynamic population

The pharmacodynamic population will consist of all patients who received the investigational product, for whom sufficient data on levels of cytokines, hs-CRP and serum amyloid protein A have been obtained to assess the pharmacodynamic parameters of the investigational products.

13.1.2 Sample size

The study is planned to randomize 85 patients: 15 patients in the RPH-104 4 mg group, and 14 patients in the RPH-104 20 mg, 40 mg, 80 mg and 160 mg groups each, a total of 14 patients in the Voltaren® (diclofenac) group. This sample size will allow constructing 95% confidence intervals around the mean change in pain intensity at 72 hours after the start of the investigational product use in each group with an accuracy of 30 mm change in pain intensity.

In addition, this sample size will allow establishing statistically significant differences between the groups in pairwise comparisons, without control for type I error for multiple comparisons, taking into account the type I error $\alpha = 5\%$, if the difference between the compared groups is $\geq$ 20 mm. The sample size was calculated assuming a standard deviation of 26 mm for change in pain intensity at 72 hours [16].

13.1.3 Planned number of subjects in each site

It is planned to enroll approximately 7 to 12 patients at each study site.

13.1.4 Applicable level of significance

The observed differences will be considered statistically significant at the two-tailed 5% significance level. In view of the exploratory nature of the study, no corrections for multiple comparisons are planned.

13.1.5 Study termination criteria

Statistical criteria for early termination of the study are not provided for in the present study.

13.1.6 Missing data

Efficacy data

All efficacy data recorded for a patient after the use of the rescue medication or a prohibited drug with an analgesic effect by the patient will be considered missing.

The baseline observation carried forward method (BOCF) will be used to impute missing data for the main efficacy analysis. This method assumes that missing patient data will be replaced with a baseline value from the time patients withdraws from the study or the rescue medication use is started.

Other data

Details reflecting incomplete data for assessment of all other variables will be described in the statistical analysis plan compiled and approved before the data lock point for interim analysis.

13.1.7 Deviations from the statistical analysis plan

The main provisions of the statistical analysis are described in this Study Protocol. More details on the statistical analysis plan will be presented in a separate document compiled and approved before the data lock point for an interim analysis. All deviations from the statistical analysis plan will be described in the Report for this clinical study.

13.1.8 Demographics, information concerning the primary disease, and other baseline parameters

The body weight index will be calculated for the patient based on the height and weight before the start of the investigational product use.

Demographic and underlying disease information will be presented using descriptive statistics by treatment group for all patients in the safety population.

Baseline parameters will include all measurements related to the efficacy and pharmacodynamics, performed on Day 1 prior to the first investigational product administration.

Baseline parameters related to the pharmacodynamic assessment will be presented using descriptive statistics by treatment group for all patients in the pharmacodynamic population.

Baseline parameters related to the efficacy assessment will be presented using descriptive statistics by treatment group for all patients in the efficacy population.

13.1.9 Concomitant therapy

Concomitant drugs will be coded according to their international nonproprietary names, using the WHO drug terminology. Standard frequency tables and a list of data for all patients in the safety population will be presented.

13.2 Pharmacokinetic analysis

All types of pharmacokinetic analysis will be conducted for the pharmacokinetic population.

The following parameters will be assessed to analyze the pharmacokinetic properties of the investigational product after single dose administration using a non-compartmental approach:

- AUC0-t
- AUC0-∞
- Cmax
- tmax
- t1/2
- Kel

13.3 Analysis of anti-drug antibody levels

An analysis of anti-drug antibody levels will be carried out in all patients who have received RPH-104. Information on anti-drug antibody levels will be presented by end point, treatment group, and for all patients regardless of treatment group, using descriptive statistics.

A list of all measured anti-drug antibody levels will be compiled.

13.4 Pharmacodynamic analysis

Pharmacodynamic variables

- Change in serum hs-CRP levels at 24, 72 hours, 5, 6, 15, 29 and 45 days after start of the investigational product therapy compared to baseline.
- Changes in the level of amyloid A protein in the blood serum at 24, 72 hours, days 5, 6, 15, 29 and 45 after start of the investigational product therapy compared to baseline.
- Change in serum cytokine (IL-1α, IL-1β, IL-1RA, IL-6, IL-8, TNF-α) levels at 24, 72 hours, 5, 6, 15, 29 and 45 days after start of the investigational product therapy compared to baseline.

Analysis of pharmacodynamic data

The levels of hs-CRP, serum amyloid protein A and cytokines will be presented by measured parameters, measurement points and treatment groups using descriptive statistics.

For hs-CRP, serum amyloid protein A, and cytokines, graphs of changes in the concentration of these substances versus time for the treatment groups will be plotted.

Model mean changes (least squares means) in hs-CRP, serum amyloid protein and cytokine levels from baseline and confidence intervals for pairwise differences between each RPH-104 group and Voltaren® (diclofenac) group will be presented for each parameter and measurement point using ANCOVA with the baseline value of the parameter as a covariate.

All measured hs-CRP, serum amyloid protein A and cytokine levels will be presented as lists.

13.5 Efficacy analysis

13.5.1 Efficacy endpoints

Primary efficacy endpoint

Change in pain intensity in the assessed joint at 72 hours after start of the investigational product therapy compared to baseline, as measured on the visual analogue scale (VAS).

Secondary efficacy endpoints

- Change in pain intensity in the assessed joint at 15, 30, 45 minutes, 1, 1.5, 2, 4, 8, 24, 48, 72 hours, on days 5, 6, 10, 15, 18, 22, 29 and 45 after start of the investigational product therapy compared to baseline (as measured on VAS).
- Proportion of patients who rated the response to the investigational product therapy as "Excellent" or "Good" at 15, 30, 45 minutes, 1, 1.5 hours, 2, 4, 8, 24, 48, 72 hours, on days 5, 6, 10 15, 18, 22, 29, and 45 after initiation of the investigational product therapy;
- Change in the degree of swelling, tenderness, erythema in the assessed joint at 24, 48, 72 hours, on days 5, 6, 10, 15, 18, 22, 29 and 45 after start of the investigational product therapy compared to baseline;

- Change in movement restriction in the assessed joint at 24, 48, 72 hours, on days 5, 6, 10, 15, 18, 22, 29 and 45 after start of the investigational product therapy compared to baseline;
- Time to 50% reduction in pain intensity in the assessed joint relative to the baseline level according to the VAS;
- Time to use of the rescue medication
- The proportion of patients who received the rescue medication within 72 hours of starting the investigational product therapy and over the entire treatment period;
- Changes in the health assessment questionnaire scores 2, 4, and 6 weeks after start of the investigational product therapy compared to baseline.

13.5.2 Analysis of the primary efficacy endpoint

The results of the primary endpoint assessment will be presented using descriptive statistics.

The confidence intervals for the change in pain intensity on VAS in each treatment group will be calculated by ANCOVA using the baseline values and treatment group as covariates.

As supplemental analyses for the primary endpoint, model mean values (least squares means) of changes in pain intensity and confidence intervals for pairwise differences between each RPH-104 therapy group and Voltaren® (diclofenac) group will be presented using ANCOVA model with factors of the baseline pain intensity score and baseline body mass index (BMI) as covariates.

13.5.3 Analysis of other efficacy endpoints

All results of patient assessment of pain intensity in the assessed joint on VAS will be presented by measurement points and treatment groups using descriptive statistics.

For all patient assessments of pain intensity in the assessed joint on VAS, pain intensity versus time by the treatment groups will be plotted.

Model means of changes from baseline in pain intensity in the assessed joint on VAS and confidence intervals for pairwise differences between each RPH-104 treatment group and the Voltaren® (diclofenac) group will be presented for each measurement point using repeated measures ANOVA. A model for assessing differences between groups will be selected after assessment of the primary endpoint.

The patient's response to therapy will be presented as frequency tables by assessment point and therapy group.

The results of assessing the degree of swelling, tenderness, erythema and movement restriction in the assessed joint will be presented as frequency tables by points of assessment and treatment groups.

Changes in the degree of swelling, tenderness, erythema and movement restriction in the assessed joint from baseline will also be presented as continuous variables using descriptive statistics by measurement points and treatment groups.

Graphs of changes in the parameters versus time by the treatment groups will be plotted for changes in the degree of swelling, tenderness, erythema and movement restriction in the assessed joint from baseline.

The analysis of time to 50% reduction in pain intensity in the assessed joint will be carried out using the Kaplan-Meier method. Comparison between groups will be carried out using a log-rank test.

More details on the efficacy endpoint analysis methods will be described in the statistical analysis plan, which will be developed and approved prior to the data lock point for interim analysis.

13.6 Safety data analysis

Safety parameters include the frequency and severity of adverse events, the frequency of serious adverse events, vital signs, 12-lead ECG findings, echocardiography findings, physical examination findings, complete blood count, blood chemistry tests, and urinalysis results. The safety population will be used to present the safety data for the study therapy.

13.6.1 Adverse events

Adverse events occurring starting from the time of investigational product administration (start of use) until 45 days after the investigational product administration will be considered treatment-emergent adverse events.

Serious adverse events developing between the signing by the patient of the Informed Consent Form for participation in this study and the administration of the investigational medicinal product will be regarded as pre-treatment SAEs.

Adverse event data will be coded using the last version of the MedDRA medical terminology. Frequency rates of adverse events during the study therapy will be calculated for each organ system, by primary diagnosis, investigational product dose, and absolute and relative amounts of patients developing adverse events. Summary data reflecting the severity of adverse events will be presented by organ system and primary disease. Adverse events related to the investigational product (‘possibly related,’ ‘probably related,’ and ‘definitely related’) will be presented separately.

Summary data reflecting withdrawals from the study due to adverse events will be presented by organ system and primary disease.

Serious adverse event data will be presented as listings and summary data by organ system and primary disease.

13.6.2 Vital signs

Results obtained for vital sings and changes from baseline in these parameters (body temperature, respiratory rate, systolic blood pressure, diastolic blood pressure, and pulse rate) will be presented as listings and as summary data for each measurement point.

13.6.3 Electrocardiography

Electrocardiography findings will be presented as listings and as summary data for each measurement point. ECG intervals (QT interval, RR and QTcF) will be presented as absolute values for each measurement point and changes from baseline for each measurement point.

13.6.4 Laboratory tests

Laboratory results (complete blood count, blood chemistry, blood lipids, coagulation tests, and urinalysis) will be tabulated by treatment group using descriptive statistics for each measurement point and for changes from baseline.

All laboratory results will be presented as lists with values for each teste and changes from baseline. Laboratory findings that are outside of the reference interval will be marked in the listings.

13.6.5 Concomitant therapy

Data on concomitant therapy will be presented as a patient-specific listing and summary data.

13.7 Interim data analysis

Due to the low patient recruitment rate in the study and the adverse impact of the COVID-19 pandemic on the recruitment, at the decision of the sponsor, an interim analysis of the data of 47 patients included in the study as of November 2020 will be carried out in order to assess the feasibility of continuing recruitment and further conducting the study. All patients whose data will be included in the interim analysis completed their participation in the study; follow-up is not required in the study. The interim analysis will include the efficacy, safety, pharmacokinetics and pharmacodynamics data available and verified at the time of analysis. No changes in the declared statistical methods in connection with the interim analysis are planned. The dose dependence of the pharmacokinetics and pharmacodynamics of the investigational product, as well as the main efficacy measures (reduction in pain intensity) will be studied using descriptive statistics, a confidence interval approach, and graphical methods. The safety analysis will be carried out using descriptive statistics methods. Formal testing of hypotheses is not planned in the study. In view of the exploratory nature of the study, no corrections for multiple comparisons are planned.

14 DATA HANDLING, DOCUMENTATION MANAGEMENT AND STORAGE

14.1 Source documents

All obtained data should be first recorded in the source documentation on paper or electronic media, and only after that recorded in the CRF. It is prohibited in this study to record data directly in the CRF without first recording them in source documents, with the exception of creatinine clearance, which is calculated automatically in the CRF.

Source documents may include out-patient charts, in-patient medical records, office visit logs, patient questionnaires, laboratory and investigation reports.

The Investigator and the healthcare institution conducting the study must ensure access to the source documentation for study monitors, auditors, and inspectors, as well as representatives of the Local Ethics Committee / Institutional Review Board and inspectors of the regulatory authorities.

14.2 Archiving of study documentation at the study site

After completion of the study, the Investigator must continue to keep all study-related documentation (except documents that should be kept by other persons in accordance with local regulations) in a safe, secure place. This documentation should be stored so as to allow simple access if necessary for audit or inspection, and should be available for verification, along with assessment of the study conditions, auxiliary systems, and study site personnel.

Documentation may be stored only on paper, using media that can ensure long-term storage of recorded information. In this regard, source medical documents available on thermal printer paper (ECG recording or facsimile copy of a laboratory test report) should be copied to regular paper by means of photocopying. Any copy should be dated and authenticated by the study site personnel; the original thermal printer paper recording should be stored with the copy even if the original becomes illegible.

The Investigator will be notified by the sponsor of the document retention period. The minimal shelf-life is 15 years after completion of the study; it may be prolonged if permitted by the Sponsor or allowed by legislation.

The Investigator should notify the sponsor about all changes in the archiving procedure, including, but not limited to, storage of the archives outside of the healthcare institution or

transfer of the property rights to the documentation in case the Investigator changes the place of employment.

15 STUDY MONITORING AND QUALITY ASSURANCE

15.1 Study monitoring

Monitoring is carried out by R-Pharm JSC on behalf of the sponsor R-PHARM INTERNATIONAL LLC. Monitors and other authorized representatives of the Sponsor may contact the Investigator and visit the study site. At request, they should be allowed direct access to all study documents (CRFs of study subjects and other documents related to the study), provided that the confidentiality requirements are observed in relation to personal patient data and the inspection is conducted in accordance with applicable local regulatory requirements.

Responsibilities of the study site monitor include regular verification of the CRFs throughout the study to ensure that they meet the requirements of the Study Protocol, control of the completeness, accuracy, and consistency of the study data, as well as the compliance with the regulatory requirements and the ICH GCP guidelines.

The Investigator should assist the Monitor as much as possible and cooperate with the Monitor with the aim to resolve any problems identified during monitoring visits.

The Monitors will be provided with a separate guideline on the control of the study conduct that will contain additional instructions concerning the monitoring procedures.

15.2 Study quality assurance

Quality of this study will be ensured through audits conducted by representatives of the sponsor or authorized representatives. They should be allowed direct access to all study documents (CRFs of study subjects and other documents related to the study), provided that the confidentiality requirements are observed in relation to patients' personal data and the inspection is conducted in accordance with applicable local regulatory requirements.

16 ETHICAL ASPECTS OF THE STUDY

16.1 General provisions

This study is conducted in accordance with this protocol, the ethical principles set forth in the Declaration of Helsinki of the World Medical Association (last revision), and the current edition of Good Clinical Practice (ICH GCP E6), the legislation and standards of the Russian Federation: the Constitution of the Russian Federation; the current edition of Federal Law No. 61-FZ of the Russian Federation of April 12, 2010 *On the circulation of medicinal products*; the current edition of Federal Law No. 323-FZ of the Russian Federation of November 21, 2011 *On the basics of protecting the health of citizens in the Russian Federation*; Decree No. 714 of the Government of the Russian Federation of September 13, 2010 *On Approval of Model Rules for Compulsory Life and Health Insurance of a Patient Participating in Clinical Trials of a Medicinal Product*" (as amended on September 4, 2012); Decree No. 393 of the Government of the Russian Federation of May 18, 2011 *On Amendments to the Model Rules for Compulsory Life and Health Insurance of a Patient Participating in Clinical Trials of a Medicinal Product*; Order No. 703n of the Ministry of Health and Social Development of Russia of August 23, 2010 *On Approval of the Notification Form for the Completion, Suspension or Termination of a Clinical Trial of a Medicinal Product for Medical Use*; Order No. 774n of the Ministry of Health and Social Development of Russia of August 31, 2010 *On the Ethics Council*, Order No. 200n of the Ministry of Health of Russia of April 1, 2016 *On Approval of Good Clinical Practice Guidelines*, GOST R52379-2005 *Good Clinical Practice* and other applicable legislative acts.

16.2 Informed Consent Form for participation in the study, consent to transfer and management of personal data, and consent to disclosure of confidential health information

Informed consent to participation in the clinical study

The Investigator is responsible for obtaining the patient's written informed consent to participation in the study. A patient's consent should be obtained prior to the commencement of any study procedures and after providing the patient with adequate information concerning the objectives and methods of the study, expected benefits and potential risks associated with participation in the study. The subject should be given one copy of the Patient Information Sheet with Informed Consent Form for participation in the study prepared in the subject's native language. The signed and dated Informed Consent Form for participation in the study should be stored in the archives of the study site, and may be requested by employees of the sponsoring company or representatives of the regulatory authorities during audits and inspections.

16.3 Confidentiality and identification of study subjects

The Investigator should ensure preservation of the confidentiality of the patient's identity. Only the patient identification number should be used for identification purposes in the CRF and other documents forwarded to the contract research organization / sponsor, the central laboratory and safety and efficacy committees. Documents that are not forwarded to the contract research organization / sponsor (such as signed Informed Consent Forms for participation in the study) must be kept confidential by the investigator.

The Investigator must ensure access to CRFs and source documentation for authorized representatives of the sponsor, regulatory authorities, and the Local Ethics Committee / Institutional Review Boards for verification during monitoring visits, audits, and inspections.

16.4 Ethics Committee / Local Ethics Committee

Prior to the start of the study, the Protocol, any amendments, and the Informed Consent Form with Patient Information Sheet, as well as any information that is given to the patient (for example, a patient diary) should be approved by the health care authorities (as required by current legislation) and the Local Ethics Committee.

17 FUNDING AND INSURANCE

This study is sponsored by the study sponsor.

Subjects participating in this study are insured in accordance with the requirements of the legislation of the Russian Federation (Federal Law No. 61-ФЗ *On the circulation of medicinal products* and Resolution No. 714 of the Government of the Russian Federation *On Approval of Model Rules for Compulsory Life and Health Insurance of a Patient Participating in Clinical Trials of a Medicinal Product* of September 13, 2010).

18 PUBLICATION

It is expected that the results of this study will be published as a summary after all patients have completed their participation in the study and the data obtained in the course of the study have been analyzed. The Investigator may not publish results obtained at the study site until a publication is prepared covering the results of the study as a whole.

Before publishing results of the study or reporting these results, the Investigator undertakes to submit the manuscript and draft report to the Sponsor for review at least 30 days in advance.

The Investigator may not publish results obtained in the study without the prior consent of the sponsoring company.

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APPENDIX 1. Tuberculosis risk assessment questionnaire

The following questions should be asked of each patient at the screening visit to identify complaints and symptoms consistent with TB. Responses to each question must be entered in this document, which is the source document.

Question	Response	
1) Does the patient has current or a history of active TB infection?	☐ Yes	☐ No
2) Has the patient had close contact (i.e. cohabitation or other closed environment) with a person with active TB in the last 1.5 years?	☐ Yes	☐ No
3) Does the patient work at a healthcare facility treating patients with suspected TB, a medical examiner's office or a mortuary?	☐ Yes	☐ No
4) Does the patient work in or has visited long-stay facilities (e.g., nursing home or residential care home, prison, homeless shelter or long-term care facility, etc.)?	☐ Yes	☐ No
5) Has the patient had close contact with underprivileged people (homeless or other people in need of social assistance)?	☐ Yes	☐ No
6) Has the patient developed a cough lasting more than 14 days or there has been a change in chronic cough?	☐ Yes	☐ No
7) Has the patient experienced night sweats?	☐ Yes	☐ No
8) Has the patient had persistent fever?	☐ Yes	☐ No
9) Has the patient experienced an unintentional weight loss (greater than 10%) in the past 3 months?	☐ Yes	☐ No
10) Does the patient look emaciated?	☐ Yes	☐ No
11) Has the patient had abnormal chest x-rays since the previous assessment?	☐ Yes	☐ No

Physician’s signature _____

APPENDIX 2. Assessment of the degree of swelling, tenderness, erythema and movement restriction in the assessed joint

CL04018054		Assessment of the degree of swelling, tenderness, erythema and movement restriction in the assessed joint
Patient ID	☐☐☐☐☐	Day ☐☐ (Scheduled visit day: 01, 02, 03, 04, 05, 06, 10, 15, 18, 22, 29 or 45)

Assess the severity of SWELLING of the patient's assessed joint:

"absence" ☐ no swelling

"mild" ☐ palpable swelling

"moderate" ☐ visible swelling

“severe" ☐ bulging outside the joint

Assess the severity of TENDERNESS of the patient's assessed joint:

"absence" ☐ no tenderness

“mild" ☐ tenderness when touched

"moderate" ☐ pain and flinching

"severe" ☐ pain, flinching and withdrawal of the limb

Assess the severity of ERYTHEMA of the patient's assessed joint:

☐ “absence”

☐ “presence”

☐ “unevaluable”

Assess the RANGE OF MOTION in the assessed joint:

☐ Normal range

☐ Slightly limited range

☐ Moderately limited range

☐ Severely limited range

☐ Joint movement is impossible