# CLINICAL STUDY PROTOCOL

**International, double blind, randomized, placebo-controlled study to evaluate the effect on parameters of systemic inflammation and disease outcomes and safety of RPH-104 in subjects with acute ST-elevation myocardial infarction.**

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| Study ID | CL04018075 |
| Protocol version | 4.0 final |
| Protocol date | **October 02, 2021** |
| Test product: | RPH-104<br>solution for subcutaneous injections<br>40 mg/mL |
| Study phase | 2a |
| Study sponsor | **R-Pharm International, LLC in the Russian Federation**<br>Address: Berzarina St., 19, bldg 1, floor 1, room V, office 9, Moscow, 123154<br>Phone: ++7 (495) 956-79-37<br><br>**R-Pharm Overseas, Inc. in the USA**<br>Address: 505 Coast Blvd, South Suite 102.<br>La Jolla, CA 92037<br>Telephone: (858) 900-2656 |
| Person authorized by Sponsor to sign Protocol and Protocol amendments | **Samsonov Mikhail Yuryevich, candidate of medical sciences**<br>Medical Department Director, R-Pharm, JSC<br>Address: Leninskiy pr., 111, bldg. 1, Moscow<br>Telephone: +7 (495) 956-79-37 |

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# Sponsor's signature

**Protocol CL04018075**

**version 4.0 dated October 02, 2021.**

**International, double blind, randomized, placebo-controlled study to evaluate the effect on parameters of systemic inflammation and disease outcomes and safety of RPH-104 in subjects with acute ST-elevation myocardial infarction.**

This clinical study Protocol version 4.0 dated October 02, 2021 has been critically reviewed and approved by the Sponsor's relevant Protocol Review Committee. The information contained in this Protocol is consistent with the current assessment of the risk and benefit of the test product. The clinical study will be conducted in accordance with the moral, ethical and scientific principles set forth in the Declaration of Helsinki, the Guideline of the International Conference on Harmonization (ICH GCP E6, current edition), the requirements set forth in the Code of Federal Regulations section 21 (21 CFR) parts 50, 54, 56 and 312, and in accordance with the applicable local regulatory requirements of the Russian Federation (RF), Eurasian Economic Union (EAEU) and the United States of America (USA). The investigator will receive detailed information about any significant or new data, including adverse effects, associated with the use of the test product.

I approve this Protocol, including its appendices.

| Name and position | Signature | Date |
|---|---|---|
| | | |

# Signature of Principal Investigator

**Protocol CL04018075**

**version 4.0 dated October 02, 2021.**

**International, double blind, randomized, placebo-controlled study to evaluate the effect on parameters of systemic inflammation and disease outcomes and safety of RPH-104 in subjects with acute ST-elevation myocardial infarction.**

I have been warned that the information contained in this Protocol and all other information related to RPH-104, is the Sponsor's confidential and private information, and, except when required by federal, state or local laws or regulations, cannot be disclosed to third parties without the prior written permission of the Sponsor.

I have read the Protocol, including all appendices, and agree that it contains all the necessary information for me and my staff to conduct this study as described. I will conduct the study as described in this document, in accordance with the moral, ethical and scientific principles described in the Declaration of Helsinki, the rules set forth in the International Conference on Harmonization Good Clinical Practice Guideline (ICH GCP E6, current edition), the requirements set forth in the Code of Federal Regulations section 21 (21 CFR) parts 50, 54, 56 and 312, and in accordance with the applicable local regulations of the RF, EAEU and the USA, and I will make reasonable efforts to complete the study at the scheduled time. I will provide all study staff under my control with copies of the Protocol and copies of any amendments, and I will provide access to all information provided by the Sponsor or designated authorized person. I will discuss the materials with the study team members to make sure they are fully informed about RPH-104 and the study.

**Signature of Principal Investigator:**

Full name in printed letters

Name of facility

Signature

Date

## Document history

| Protocol version and date | List of changes |
|---|---|
| Protocol version 1.0 dated December 26, 2019 | Not applicable – original version |
| Protocol version 2.0 dated June 18, 020 with incorporated Amendment 1 | **Sponsor's signature** page: text changed.<br>**Signature of Principal Investigator** page: text changed<br>**Inclusion criteria:**<br>3. STEMI diagnosis defined as chest pain or its equivalent with debut no more than 12 hours before randomization (*instead of 24 hours*).<br>4. PCI with stenting was performed within no more than 12 hours after onset of chest pain or its equivalent before randomization (*instead of 24 hours*).<br>**Exclusion criteria:**<br>6. the phrase *"and/or unstable hemodynamics"* was added<br>Complications of acute myocardial infarction in the form of acute left ventricular failure and cardiogenic shock defined as stable blood pressure decrease (SBP<90 mm Hg) associated with signs of hypoperfusion as well as cases when inotropic and/or mechanical support is required to maintain SBP; and/or unstable hemodynamics.<br>8. the phrase *"IL-1 and other biological drugs"* was added<br>Recent (less than 5 half-life periods) or current administration of agents with an immunosuppressant mechanism of action, including, but not limited to, high doses of glucocorticoids (> 1 mg/kg of methylprednisolone equivalent), TNFα blockers, IL-1 and other biological drugs, cyclosporine and other immunosuppressants. NSAIDs are allowed.<br>9. – *a new criterion was added*<br>Immunization with live vaccines within 90 days prior to the study product administration.<br>**Sections 4.5.1 and 4.6** were supplemented with clarifying information about the screening and randomization numbers.<br>**Section 8.2.1 General provisions**<br>The following text was added: "The unblinded medical monitor will receive and evaluate all adverse event reports on a regular basis during the study."<br>Section 10.5. Protocol deviations |

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| | *The following text was added:* "For the USA only. By signing a copy of the FDA 1572 form or other country-specific regulatory forms, the Principal Investigator confirms that he/she has received a copy of the Investigator's Brochure for RPH-104 and assures the Sponsor that he/she will comply with the Protocol and provisions included in the FDA 1572 form or other country-specific regulatory forms. No changes to this Protocol may be made without the written consent of the Sponsor."<br><br>The following **sections** were added:<br><br>**11.1** Ethics aspects of the study<br><br>**11.2** Local Ethics Committee / Institutional Review Board<br><br>**14.** Protocol amendments<br><br>**15**. Study report and publications<br><br>Clarifying information was added to **Sections 11.3 "Confidentiality of the study subjects" and 12.5 "Document archiving."** |
| Protocol version 3.0 dated October 29, 2020, with incorporated Amendment 2 | **Table 1. Schedule of visits and procedures**<br><br>Added visit interval of ± 3 days for Day 14 and Day 28. *Hereinafter, where applicable.*<br><br>The name of the "measurement of height" procedure was changed to "Height registration" - in the table and further in the text, where applicable.<br><br>Added blood sampling procedure for clinical and biochemical blood tests on Day 14. *Hereinafter, where applicable.*<br><br>The footnotes regarding the following were added: conducting the Day 3 visit procedures ahead of schedule (on Day 2) for patients discharged on Day 2, performing the administration of the study product within 3 hours of randomization, possible performing of Echo-CG within 24 hours of randomization on Day1, height measurement at Visit 3: "It is permissible to record any value obtained during the hospitalization, when it was possible to measure the patient's height". *Hereinafter, where applicable.*<br><br>ESR was removed from the complete blood count parameters. *Hereinafter, where applicable.*<br><br>LDH "isoforms" were removed from the blood chemistry parameters.<br><br>**Section 2.1. Introduction**<br><br>The description of anakinra studies has been supplemented with a reference to a literature source describing the current study, Abbate A. et al., 2020. |

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| | **Section 2.2. Cumulative presentation of the results of nonclinical and clinical studies relevant for this study**<br><br>Information on current and planned clinical trials of RPH-104 was updated, currently available data on the safety and efficacy of the drug were added.<br><br>**Section 2.3. Brief summary of known and potential risks and benefits for study subjects**<br><br>The list of expected adverse events was adjusted based on the known safety profile of drugs belonging to the IL-1 inhibitor class.<br><br>**Section 2.4. Description and justification of method of administration, dose, dosing regimen and therapy duration**<br><br>Information from dose-ranging studies of rilonacept (a drug with a similar mechanism of action) was added.<br><br>**Section 3.2. Study objectives**<br><br>Objective 5 was corrected: “including but not limited to” was added to the determined echocardiographic parameters, “and the right ventricle” was removed - in this section and further in the text, where applicable.<br><br>**Section 4.2.1. Discussion of study design**<br><br>A clarification was added: "During the first 10 weeks, not more than 3 patients per week will be included in the study".<br><br>**Section 4.3.3. Follow-up periods**<br><br>*The text was added:* “If the patient's visit to the study site is administratively limited due to the current epidemiological situation associated with the SARS-CoV-2 coronavirus, the procedures of Visit 3 (Day 14±3) and Visit 4 (Day 28±3) can be carried out at the patient's home, if the patient agrees, by authorized employees of the study site team. At the same time, if possible, all efficacy and safety assessment procedures planned for a particular visit are carried out. The conduct of visits outside the study site must be agreed with the Sponsor in each case".<br><br>**Section 4.3.4.1. Visit 1 (Day 1)**<br><br>“If available” was added for weight measurement on a hospital bed.<br><br>**Section 5.1. Inclusion criteria**<br><br>Criterion # 3 was adjusted:removed "starting no more than 12 hours before randomization".<br><br>Criterion # 4 has been revised to add "randomization within 12 hours after PCI (ie, no more than 24 hours from the onset of chest pain to randomization)". |

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| | **Section 5.2. Exclusion criteria:**<br><br>Criterion # 3 has been adjusted: AHA/ACC class C-D, NYHA FC III-IV have been clarified, removed "due to heart defects".<br><br>Criterion # 4 has been adjusted: "decompensated" is replaced by "heavy valvular", added "according to the investigator's assessment".<br><br>Added criterion # 5: "Pre–existance of left ventricular dysfunction (ejection fraction <40%)".<br><br>Criterion # 8 (7) regarding the use of immunosuppressive drugs was adjusted.<br><br>**Section 6.1.1.2. Placebo**<br><br>Added information about additional manufacturer and release form.<br><br>**Section 6.2.1. Allowed concomitant therapy**<br><br>Clarification was made on the collection of concomitant therapy data: "within 5 half-lives of the drug or 30 days (whichever is longer)".<br><br>**Section 6.2.2. Forbidden concomitant therapy**: The list of prohibited drugs was adjusted.<br><br>**Section 6.3. Study drugs accounting**<br><br>Added information on the storage of placebo (manufactured by the Hospira incorporated, USA) at a temperature of +20 - + 25 °C.<br><br>**Section 7.1. List of efficacy endpoints**<br><br>Secondary Endpoint 5: "including but not limited to" was added to the determined echocardiographic parameters, "and the right ventricle" was removed - *in this section and hereinafter where applicable.*<br><br>**Section 7.2. Methods and terms of evaluation, reporting and analysis of efficacy parameters**<br><br>It was clarified that echocardiography measurements would be carried out in accordance with the internal document on the interpretation of echocardiography findings. The echocardiography parameters were specified.<br><br>**Section 8.2.1.2. Laboratory examination**<br><br>Clarification was made: "At Visit 1 determination of the absolute neutrophil count is performed in the local laboratory of the site to assess the inclusion/exclusion criteria."<br><br>The blood chemistry parameters were adjusted: "LDH" was added.<br><br>**Section 8.2.3. Adverse events of interest:** updated. |

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| | **Section 8.2.10. AE outcome:** the definition of the "Aggravation" outcome was removed.<br><br>**Section 10.7. Study monitoring**<br><br>*Text was added:* “Remote monitoring may be used for these purposes, if necessary (for example, if administrative or sanitary and epidemiological restrictions are imposed in connection with the current epidemic situation associated with the SARS-CoV-2 coronavirus)”; “Remote monitoring, if necessary, will be carried out using the appropriate module of the electronic data acquisition system. The investigator will upload anonymized copies of the source documents of patients to this module for verification of the source data, as well as copies of other documents required for remote verification by the monitor. These documents will be temporarily stored in the data collection system, in the remote monitoring section. Upon completion of the scheduled check and resolution of all issues, copies of all documents will be removed from the system by the responsible data manager. "<br><br>**Section 12.3. Data confidentiality**<br><br>*Text was added:* “In case of remote monitoring, the investigator will provide the monitor with anonymized copies of the source documents of patients for verification of the source data. These source documents will be temporarily stored in the data collection system, in the remote data verification section. Upon completion of data verification and resolution of all issues regarding this data, the uploaded copies of source documents will be deleted from the system by the responsible data manager. Data circulation during remote monitoring will be carried out in accordance with the regulatory requirements of the country participating in the study."<br><br>**Section Appendix 1**: Definition of “stroke and transient ischemic attack” and Definition of “interventional cardiology procedures” were added. |
| Protocol version 4.0 of October 02, 2021 with an incorporated amendment 3 | **Section 2.2 Cumulative presentation of the results of nonclinical and clinical studies relevant for this study**<br><br>Information about ongoing and planned clinical studies or RPH-104 has been updated; new available safety and efficacys data have been added.<br><br>**Section 2.3 Brief summary of known and potential risks and benefits for the study subjects and section 2.4 Description and justification of method of administration, dose, dosing regimen and therapy duration**<br><br>Information regarding risk assessment for the study participants and justification of the selected dose based on the |

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| | currently available safety and effectiveness data has been clarified.<br><br>**Section 3.2 Study objectives**<br><br>The wording of the objective No.5 has been adjusted: a clarification "including, but not limited to, left ventricular (LV) dimensions, LVMMI, systolic and diastolic function" has been deleted.<br><br>**Section 4.1 Principal and additional study parameters (Table 2. Study endpoints)**<br><br>The wording "including, but not limited to, left ventricular (LV) dimensions, LVMMI, systolic and diastolic function" has been deleted from the description of the respective objective and the study endpoint.<br><br>The endpoint: "Rate of fatal outcomes (cardiac and non-cardiac), hospitalizations (due to HF and other cardiac reasons not associated with HF or due to non-cardiac reasons) during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365]"<br><br>has been changed to:<br><br>"Incidence of fatal outcomes (cardiac and non-cardiac) during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365]";<br><br>"Incidence of hospitalizations due to HF or other cardiac reasons not associated with HF, or due to non-cardiac reasons during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365]".<br><br>The endpoint: "Frequency of new cases of HF (defined as hospitalization due to HF or necessity in a new loop diuretic administration intravenously or oral dose doubling in the relevant clinical facilities) during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365]"<br><br>has been changed to:<br><br>"Incidence of new cases of HF (defined as hospitalization due to HF or new onset of HF) during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365]."<br><br>Two additional secondary effectiveness endpoints have been introduced:<br><br>Incidence of "fatal outcome (due to any reason) or hospitalization due to HF or new onset of HF" during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365];<br><br>Incidence of "fatal outcome (due to any reason) or hospitalization due to HF" during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365]. |

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| | Similar changes have been introduced into section 7.1 List of efficacy parameters, section 9.3.3.2 Analysis of secondary endpoints.<br><br>**Section 4.4.3 Information on the underlying disease**<br><br>Data that should be recorded at the screening have been clarified.<br><br>**Section 5.2 Exclusion criteria**<br><br>A clarification has been added to the criterion No.17: "If, in the Investigator's opinion, administration of a non-live COVID-19 (SARS-CoV-2) vaccine increases the risk for the patient related to his/her participation in the study, the Investigator can make a decision not to include this patient into the study."<br><br>**Section 6.2.2 Forbidden concomitant therapy**<br><br>The list of prohibited immunosuppressive agents has been clarified.<br><br>**Section 7.2 Methods and terms of evaluation, reporting and analysis of efficacy parameters**<br><br>A clarification has been added regarding the recording hospitalization as an outcome: "Hospitalization due to HF will also include cases of prolongation of current hospitalization for the treatment of ST segment elevation MI if HF has developed within 24 hours following hospital admission".<br><br>**Sections 9.3.3.2 Analysis of secondary endpoints and 9.3.3.3 Analysis of exploratory endpoints** have been corrected<br><br>**Section 9.4 Sample size rationale**<br><br>The description of the planned number of included participants has been corrected.<br><br>**Section 9.7 Interim analysis**<br><br>The procedure of the interim statistical analysis has been corrected.<br><br>**The Protocol Summary has been updated in accordance with the changes introduced in mentioned sections.**<br><br>Other changes have been introduced to avoid contradictions in the Protocol, namely:<br><br>**Section 4.2.1 Discussion of study design** – the missing procedures have been added to the description of the screening period;<br><br>**Section 4.3.1 Screening** – the text related to the diagnosis required for the inclusion in the study has been corrected; |

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| | **Section 4.4.2 Past medical history** – a clarification has been added regarding the period of menopause – "if applicable";<br><br>**Section 6.1.3 Administration of the study product** – a clarification has been added that the study product administration will be performed by "unblinded" qualified study site personnel;<br><br>**Section 8.1 List of safety parameters** – a phrase "during the study" has been added to the safety endpoints;<br><br>**Section 9 Statistics** – the section has been corrected.<br><br>**Section 11.4 Informed consent** – a phrase has been added: "If a patient agrees to participate in the study, he/she has to sign and date the Informed Consent Form for participation in the study in two copies".<br><br>**The rest of the changes have been introduced in order to avoid technical errors in the Protocol.** |

## Ethical approval

Prior to the implementation of this version of the Protocol with the incorporated Amendment 3, it must be reviewed and approved by the regulatory healthcare authorities and the Independent Ethics Committee (IEC). Signed and dated evidence that the Protocol and other necessary documents have been approved by the IEC must be provided to the Sponsor or its representative before these documents become effective.

# Contact information

**Names and addresses of clinical and other medical and/or technical services and/or institutions involved in the study:**

| Name of organization | Study role | Organization address |
|---|---|---|
| R-Pharm, JSC | Study facility in the RF | Legal address: Berzarina St., 19/1, Moscow, 123154<br>Postal address: Leninskiy pr., 111/1, Moscow, 119421, Russia |
| K-Research, LLC | Study facility in the RF | Marshala Koneva prospekt, 29, office 43, Smolensk, 214019, Russia |
| Cromos Pharma LLC | Study facility in the USA | 148 Canyonview Dr, Longview, WA 98632, USA |
| DM 365, LLC | Access to database, its setting, adaptation, modification, validation, testing, maintenance | Vsevoloda Vishnevskogo St., 12, lit. A, Saint-Petersburg, 197022, Russia |
| Keystat, LLC | Statistical analysis of data | 20-ya Liniya Krasnoarmeyskoy Slobody, 3, Smolensk, 214000, Russia.<br>Tel.: +7 (915) 644-47-13 |

**Contact information of investigators responsible for performance of the study and study sites:**

The list of the study sites involved in this clinical study (name, address and phone of each study site) and contact information of principal investigators responsible for the study performance are presented in an individual List of study sites and principal investigators.

**CONTACT INFORMATION FOR EMERGENCY CASES**

To obtain medical consultation in emergency cases, contact the Study Medical Monitor – a scientific adviser of R-Pharm, JSC, Daria Bukhanova

**Phone number for emergency cases:**

**+7 (495) 956-79-37**

**E-mail:** bukhanova@rpharm.ru

When reporting serious adverse events the procedures described in section 8.2.6 should be followed.

## Abbreviations

| | |
|---|---|
| **AE** | Adverse event |
| **AHA/ACC** | The American Heart Association / The American College of Cardiology |
| **ALT** | Alanine aminotransferase |
| **ANOVA** | Analysis of variance |
| **AP** | Alkaline phosphatase |
| **AST** | Aspartate aminotransferase |
| **AUC** | Area under curve |
| **BNP** | Brain natriuretic peptide |
| **BP** | Blood pressure |
| **BUN** | Blood urea nitrogen |
| **CAG** | Coronary angiography |
| **$C_{max}$** | Peak blood product concentration |
| **CFR** | Code of Federal Regulations |
| **CHD** | Coronary heart disease |
| **CI** | Confidence interval |
| **CPK** | Creatinine phosphokinase |
| **CPK-MB** | Creatine phosphokinase cardiac specific isoenzyme |
| **(e)CRF** | (electronic) Case Report Form |
| **CRO** | Contract research organization |
| **(hs)CRP** | (high-sensitive) C-reactive protein |
| **CTCAE** | Common Terminology Criteria for Adverse Events |
| **CVD** | Cardiovascular diseases |
| **CYP** | Cytochrome P450 |
| **DBP** | Diastolic blood pressure |
| **DNA** | Deoxyribonucleic acid |
| **EAEU** | Eurasian Economic Union |
| **ECG** | Electrocardiogram |
| **Echo-CG** | Echocardiography |
| **EF** | Ejection fraction |
| **EU** | European Union |
| **FAS** | Full Analysis Set |
| **Fc** | Fragment crystallizable |
| **FC** | Functional class |
| **FL** | Federal law |
| **GCP** | Good Clinical Practice |
| **GDP** | Gross domestic product |
| **GGT** | Gamma-glutamyltranspeptidase |
| **HF** | Heart failure |
| **HR** | Heart rate |
| **$IC_{50}$** | 50% inhibitory concentration |
| **ICF** | Informed Consent Form |
| **ICH** | The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| **IEC** | Independent Ethics Committee |

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|---|---|
| **IgG1** | Immunoglobulin type G1 |
| **IL-1** | Interleukin-1 |
| **IL-1R(1)** | Interleukin-1 receptor |
| **IL-1RA** | Interleukin-1 receptor antagonist |
| **IL-1RAcP** | Interleukin-1 receptor accessory protein |
| **IRB** | Institutional Review Board |
| **ISF** | Investigator Site File |
| **ISOAC** | Independent study outcome assessment committee |
| **IV** | Intravenous |
| **IWRS** | Interactive Web Response System |
| **kDa** | Kilo Dalton |
| **LBBB** | Left bundle branch block |
| **LDH** | Lactate dehydrogenase |
| **LEC** | Local ethics committee |
| **LV** | Left ventricle |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **MI** | Myocardial infarction |
| **MMRM** | Mixed effect Model Repeat Measurement |
| **MRC5** | Non-transformed human lung fibroblast cell line |
| **NOAEL** | No observed adverse effect level |
| **NSAID** | Nonsteroidal anti-inflammatory drugs |
| **NT-pro-BNP** | N-terminal (NT)-pro hormone brain natriuretic peptide |
| **NYHA** | New York Heart Association |
| **OATP1B1** | Organic-anion-transporting polypeptide 1B1 |
| **PCI** | Percutaneous coronary intervention |
| **PEG** | polyethylene glycol |
| **PK** | Pharmacokinetics |
| **PPS** | Per Protocol Set |
| **RF** | Russian Federation |
| **RR** | Respiration rate |
| **SAA** | Serum amyloid A |
| **SAE** | Serious adverse event |
| **SAP** | Statistical analysis plan |
| **SBP** | Systolic blood pressure |
| **SC** | subcutaneously |
| **SOP** | Standard Operating Procedure |
| **STEMI** | Acute ST-segment elevation MI |
| **SUSAR** | Suspected Unexpected Serious Adverse Drug Reaction |
| **$T_{max}$** | Time to peak blood product concentration |
| **TMF** | Trial Master File |
| **TNF** | Tumour necrosis factor |
| **USA** | United States of America |
| **WHO** | World Health Organization |

# 1. Protocol summary

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| **Clinical study title** | International, double blind, randomized, placebo-controlled study to evaluate the effect on parameters of systemic inflammation and disease outcomes and safety of RPH-104 in subjects with acute ST-elevation myocardial infarction. |
| **Study ID** | CL04018075 |
| **Clinical study phase** | 2a |
| **Protocol date and version** | 4.0. dated October 02, 2021 final |
| **Study type** | interventional |
| **Test product** | RPH-104, solution for subcutaneous injections, 40 mg/mL. |
| **Reference product** | placebo |
| **Study purpose** | Evaluate the effect of single administration of RPH-104 at 80 mg and 160 mg on parameters of systemic inflammation and outcomes of the disease in subjects with ST-segment elevation myocardial infarction (STEMI). |
| **Study objectives** | 1. Evaluate the effect of single administration of RPH-104 at 80 mg and 160 mg compared to placebo on hsCRP level reduction within 14 days in subjects with STEMI.<br>2. Evaluate the effect of single administration of RPH-104 at 80 mg and 160 mg compared to placebo on hsCRP level reduction within 28 days in subjects with STEMI.<br>3. Evaluate the effect of single administration of RPH-104 at 80 mg and 160 mg compared to placebo on cardiovascular and other clinical outcomes within 12 months in subjects with STEMI.<br>4. Evaluate the effect of single administration of RPH-104 at 80 mg and 160 mg compared to placebo on changes in levels of HF biomarkers (BNP and NT-pro-BNP) within 12 months in subjects with STEMI.<br>5. Evaluate the effect of single administration of RPH-104 at 80 mg and 160 mg compared to placebo on parameters of cardiac remodeling (changes in structural and functional echocardiographic parameters) within 12 months in subjects with STEMI.<br>6. Evaluate safety and tolerability of single administration of RPH-104 at 80 mg and 160 mg compared to placebo in subjects with STEMI during the study.<br>**Exploratory objective:**<br>Evaluate interaction between STEMI outcomes and peculiarities of coronary bed lesion based on baseline CAG results. |

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| **Study design** | International, multicenter, phase 2a, double-blind, randomized, placebo-controlled clinical study comparing single administration of RPH-104 80 mg, RPH-104 160 mg and placebo (1:1:1)<br><br>After signing the informed consent form, the investigator will assess the subject's eligibility for the study. The following procedures will be performed during the screening: collection of medical history, recording previous and concomitant therapy, demographic data, recording 12-lead ECG findings on which STEMI diagnosis was based, recording date and time of STEMI symptom development, recording date, time and results of CAG at admission to the study site, measurement of blood neutrophil count, vital signs, physical examination including measurement of body weight (if hospital bed is available), blood sampling for hematology, biochemistry, determination of concentration of hsCRP and brain natriuretic peptide (BNP; NT-pro-BNP), for females with retained reproductive potential – pregnancy test (test strips).<br><br>The subjects meeting selection criteria will be randomized to one of the three groups for single subcutaneous administration of RPH-104 80 mg, RPH-104 160 mg or placebo.<br><br>Therefore, screening, randomization and administration of the study products will be made on the same (first) study day.<br><br>Further 4-week (28-day) clinical follow-up and additional 6- and 12-month clinical follow-up period will be performed.<br><br>The end of clinical part of the study will be the date of the last visit of the last subject within additional 12-month clinical follow-up.<br><br>An overview of the study design is provided in Figure 1. |
| **Scheduled number of subjects** | The maximum number of screened patients will be 146 subjects, 102 subjects will be randomized, 34 subjects per group. |
| **Study population** | Male and female subjects aged from 18 years old (inclusive) hospitalized with STEMI to the study sites of the RF and the USA. |
| **Inclusion criteria** | The subjects eligible for the study should meet all of the following criteria:<br><br>1. Subjects of either gender aged from 18 years old inclusive.<br><br>2. Subjects who gave voluntary written informed consent to participate in the study and to follow all Protocol procedures.<br><br>3. STEMI diagnosis defined as chest pain or its equivalent with ECG findings evidencing ST elevation (>1 mm) in two or more consecutive leads or acute left bunch branch block according the investigator's judgement.<br><br>4. PCI with stenting was performed within no more than 12 hours after onset of chest pain or its equivalent and randomization was performed in no more than 12 hours after PCI (overall within 24 hours of onset of chest pain or equivalent).<br><br>5. Consent of female subjects with childbearing potential defined as all female subjects with physiological potential to conceive, to use |

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| | highly effective contraceptive methods throughout the study starting from screening (signing Informed Consent Form) and negative pregnancy test.<br>Highly effective contraceptive methods include combination of two of the following methods (a+b or a+c or b+c):<br>a) oral, injection or implanted hormonal contraceptives; in case of oral contraceptives, the female subjects should administer the same product for at least 3 months prior to the study therapy;<br>b) intrauterine device or contraceptive system;<br>c) barrier methods: condom or occlusive cap (diaphragm or cervical cap/vaginal fornix cap) with spermicidal foam/gel/film/cream/vaginal suppository<br>6. Ability and willingness of the subject, according to the reasonable investigator's judgment, to attend the study site at all scheduled visits, undergo the study procedures and follow the Protocol requirements including subcutaneous injections by qualified site personnel. |
| **Non-inclusion criteria** | The subjects meeting any of exclusion criteria should not be enrolled:<br>1. Hypersensitivity to test product (RPH-104) and/or its ingredients/excipients.<br>2. Pregnancy and breastfeeding.<br>3. Verified chronic HF (AHA/ACC C-D class, NYHA FC III-IV).<br>4. Pre-existing severe valvular heart disease according to the investigator's assessment.<br>5. Pre-existing LV dysfunction (EF<40%).<br>6. History of STEMI.<br>7. Complications of acute MI in the form of acute left ventricular failure and cardiogenic shock defined as stable blood pressure decrease (SBP<90 mm Hg) associated with signs of hypoperfusion as well as cases when inotropic and/or mechanical support is required to maintain SBP; and/or unstable hemodynamics.<br>8. Active infections (acute or chronic); active tuberculosis.<br>9. Recent (less than 5 half-life periods) or current administration of colchicine, as well as agents with an immunosuppressant mechanism of action, including, but not limited to: glucocorticoids at doses of > 1 mg/kg of methylprednisolone equivalent, TNFα blockers, IL-1 and other biological drugs, cyclosporine and other immunosuppressants. NSAIDs are allowed.<br>10. Immunization with live vaccines within 90 days prior to the study product administration. |

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| | 11. Chronic systemic autoimmune or autoinflammatory diseases.<br>12. Suspected necessity in cardiosurgery.<br>13. Oncology (or diagnosis of oncology within the last 5 years).<br>14. History of organ transplantation or necessity in transplantation at the screening initiation or scheduled transplantation during the study.<br>15. Neutropenia (absolute neutrophil count <1800/mm$^3$).<br>16. Participation in another clinical study within the previous 3 months prior to Screening visit.<br>17. Other medical (including mental) conditions or abnormal laboratory findings which may increase the risk for the subject associated with the study participation or administration of the study products or which may affect interpretation of the study results and, according to the investigator, render the subject ineligible for the study.*<br>18. The subjects working at the study site or subjects working for Sponsor directly involved in this clinical study.<br>* *If, in the Investigator's opinion, administration of a non-live COVID-19 (SARS-CoV-2) vaccine increases the risk for the patient related to his/her participation in the study, the Investigator can make a decision not to include this patient into the study*. |
| **Test product. Posology and method of administration** | ***Trade name:*** not assigned.<br>***International nonproprietary name:*** goflikicept<br>***Product in-house code:*** RPH-104<br>***Dosage form:*** solution for subcutaneous injections<br>***Strength:*** 40 mg/mL<br>***Doses:*** 80 mg and 160 mg<br>***Dosing frequency:*** single<br>***Route of administration:*** subcutaneous<br>***Duration of treatment:*** single dose |
| **Reference product.**<br>**Posology and method of administration** | ***Placebo***<br>***Trade name:*** not applicable<br>***International nonproprietary name:*** not applicable<br>***Dosage form:*** solution for subcutaneous injections<br>***Strength:*** not applicable<br>***Dosing frequency:*** single<br>***Route of administration:*** subcutaneous<br>***Duration of treatment:*** single dose |

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| **Study product dosing scheme in treatment groups** | To provide double blind design the study, the study products will be administered as follows:<br>– in RPH-104 80 mg group, the subjects will receive 2 mL (80 mg) of RPH-104 and 2 mL of placebo on different administration sites;<br>– in RPH-104 160 mg group, the subjects will receive 2 mL (80 mg) of RPH-104 and 2 mL of (80 mg) of RPH-104 on different administration sites;<br>– in placebo group, the subjects will receive 2 mL of placebo and 2 mL of placebo on different administration sites. |
| **Concomitant therapy** | During the study, the following medicinal products will be forbidden in the terms specified:<br>– biological medicinal drugs (except for RPH-104) including but not limited to: tocilizumab, rituximab, TNFα inhibitors [Visit 1 Day 1 - Visit 4 Day 28].<br>– immunosuppressants [Visit 1 Day 1 – Visit 4 Day 28] including but not limited to:<br>o corticosteroids at doses of >1 mg/kg of methylprednisolone equivalent orally as well as systemic, except for IV ones for acute allergic reactions;<br>o cyclosporine A, methotrexate, etc.<br>– colchicine [Visit 1 Day 1 – Visit 4 Day 28];<br>– anakinra, canakinumab, rilonacept [Visit 1 Day 1 – Visit 6 Month 12].<br>– immunization with live vaccines within 90 days prior to or after the study product administration.<br>– any experimental products.<br>NSAIDs are not forbidden. |
| **Study duration** | The study will consist of 1 day of the study product administration, 4-week follow-up period and 6- and 12-month clinical follow-up periods.<br>Scheduled recruitment duration: 9 months.<br>Scheduled clinical part duration: 1 year 10 months.<br>Scheduled period for study result report preparation: 3 months. |
| **Efficacy evaluation** | **Primary endpoint**:<br>1. hsCRP area under curve (AUC) from Day 1 (baseline) until Day 14 [Visit 1 Day 1 – Visit 3 Day 14].<br>**Secondary endpoints**:<br>1. hsCRP area under curve (AUC) from Day 1 (baseline) until Day 28 [Visit 1 Day 1 – Visit 4 Day 28]. |

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| | 2. BNP area under curve (AUC) from Day 1 (baseline) until Day 28 [Visit 1 Day 1 – Visit 4 Day 28].<br>3. NT-pro-BNP area under curve (AUC) from Day 1 (baseline) until Day 28 [Visit 1 Day 1 – Visit 4 Day 28].<br>4. Incidence of fatal outcomes (cardiac and non-cardiac) during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].<br>5. Incidence of hospitalizations due to HF or other cardiac reasons not associated with HF, or due to non-cardiac reasons during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].<br>6. Incidence of new cases of HF (defined as hospitalization due to HF or new onset of HF) during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].<br>7. Incidence of "fatal outcome (due to any reason) or hospitalization due to HF or new onset of HF" during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].<br>8. Incidence of "fatal outcome (due to any reason) or hospitalization due to HF" during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].<br>9. Changes in levels of BNP andNT-pro-BNP during 12-month follow-up period compared to baseline [Visit 1 Day 1 – Visit 6 Day 365].<br>10. Changes in structural and functional echocardiographic parameters after 12 months compared to baseline [Visit 1 Day 1 – Visit 6 Day 365].<br>**Exploratory endpoints:**<br>1. Changes in concomitant therapy [Visit 1 Day 1 – Visit 6 Day 365].<br>2. Interaction between STEMI outcomes and peculiarities of coronary bed lesion based on baseline CAG results [Visit 1 Day 1 – Visit 6 Day 365]. |
| **Safety evaluation** | **Safety endpoints:**<br>1. Frequency of AE/SAE during the study.<br>2. Changes in physical examination (including body weight), vital signs during the study. |
| **Statistical analysis** | Statistical analysis will be performed in the following populations.<br>*Full Analysis Set (FAS):*<br>Full analysis set for efficacy analysis will include all randomized subjects, who received the study products and underwent at least one CRP measurement after administration of the study products. This set is the main population for efficacy analysis.<br>*Per Protocol Set (PPS):*<br>All FAS subjects without relevant Protocol deviations affecting assessment of the primary efficacy parameter. Such major Protocol deviations will be defined before database lock in a blinded data |

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| | review. This set is supplementary population for efficacy assessment.<br><br>*Safety Population*:<br><br>All randomized subjects, who received the study products.<br><br>**General considerations:**<br><br>Detailed description of statistical data analysis including last observation carried forward will be presented in statistical analysis plan (SAP). SAP development will be finalized until the study database lock. Any deviations from analysis planned in SAP should be justified in the report on study results.<br><br>Any data will be generalized using descriptive statistics: number of the subjects, mean value, minimum and maximum, median and quartiles for continuous variables, frequency of observations with percentages - for qualitative variables.<br><br>After the last subject completes 28-day follow-up period, an analysis of hsCRP, BNP and NT-pro-BNP will be performed for 14 and 28 days of the study. The analysis results may be used to define the strategy for further RPH-104 development.<br><br>At this stage the primary efficacy analysis will be performed. This analysis will be performed only once and will not be repeated during the final analysis stage. Sensitivity analysis cannot be done during the interim stage and will be performed during the final analysis stage.<br><br>Secondary efficacy variables (AUC from day 1 to day 28) will be derived and analysed for parameters hsCRP, BNP and NT-pro-BNP at the interim analysis stage. This analysis will be performed only once and will not be repeated during the final analysis stage.<br><br>After the completion of the study, a final statistical data analysis will be conducted, and the final study report will be prepared. |

**Table 1. Schedule of visits and procedures**

| Time point/Study procedures | Day 1 | Day 3[1] | Day 14±3 | Day 28±3 /Early withdrawal visit (from Day 1 till Day 28) | Month 6[2] ±2 weeks | Month 12 ±2 weeks /Early withdrawal visit (from Day 29 till Day 365) |
|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** |
| Informed consent | X | | | | | |
| Evaluation of inclusion/exclusion criteria | X | | | | | |
| Medical history | X | | | | | |
| Recording previous therapy | X | | | | | |
| Demographic data | X | | | | | |
| Recording 12-lead ECG results[3] | X | | | | | |
| Recording CAG findings[4] | X | | | | | |
| Randomization | X | | | | | |
| Administration of the study product[5] | X | | | | | |
| Urine pregnancy test for females with childbearing potential (test strips) | X | | | | | |
| Hematology[6] | X | | | | | |
| **Efficacy evaluation** | | | | | | |
| Blood sampling for measuring hsCRP, BNP, NT-pro-BNP | X | X | X | X | | X[7] |
| Outcome registration | | X | X | X | X | X |
| Echo-CG | X[8] | | | X | | X |
| **Safety evaluation** | | | | | | |
| Vital signs (BP, HR, RR, body temperature) | X | X | X | X | | X |
| Physical examination | X | X | X | X | | X |
| Body weight measurement | X[9] | X[10] | X | X | | X |
| Height registration | | | X[11] | | | |
| Blood sampling for hematology and[12] biochemistry[13] | X | | X | X | | |
| AE/SAE recording | X | X | X | X | X | X |
| Recording concomitant therapy | X | X | X | X | X | X |

[1]For patients discharged on Day 2, the procedures of the Day 3 visit can be carried out ahead of schedule (on Day 2).
[2]The visit might be conducted in the form of a telephone conversation with the patient.
[3]Recording 12-lead ECG results on which STEMI diagnosis was based.
[4]Recording CAG results performed at admission to the study.
[5]Must be performed within 3 hours of randomization.
[6]Hematology: determination of absolute neutrophil count in local laboratory of the site.
[7]BNP and NT-pro-BNP will be determined.
[8]On Day 1, Echo-CG can be performed within 24 hours of randomization.
[9]Body weight is measured using hospital bed on Day 1; if not available, on Day 3.
[10]Body weight measurement (for subjects who did not undergo measurement on Day 1).
[11]It is permissible to record any value obtained during the hospitalization, when it was possible to measure the patient's height.
[12]Hematology: hemoglobin, erythrocyte count, leukocyte count, leukogram with obligatory measurement of absolute neutrophil count, platelet count.
[13]Biochemistry: hepatic chemistry values (AST, ALT, GGT, AP, LDH, total bilirubin, direct bilirubin, indirect bilirubin), renal chemistry values (serum creatinine, serum urea / urea nitrogen [BUN]), serum electrolytes (sodium, potassium, chlorides), CPK, CPK-MB.

# 2. Study rationale

## 2.1. Introduction

The term "myocardial infarction" (MI) is used when there is verified myocardial lesion (defined as increased cardiac troponin level by at least one value exceeding 99$^{th}$ percentile of normal reference value) and myocardial necrosis in clinical situations suggesting myocardial ischemia. To ensure urgent selection of treatment approach including reperfusion therapy, MI is diagnosed in cases of anginal pain or its equivalents with ST elevation in at least 2 or more consequent leads or acute left bundle branch block (LBBB) and defined as ST-segment elevation MI (STEMI) (Ibanez B. et al, 2017).

Coronary heart disease (CHD) is the leading cause of mortality globally (1.8 million deaths annually) and is 20% of all fatal outcomes in Europe despite relevant variations between the countries (Ibanez B. et al, 2017).

Epidemiological data in the RF are disparate. According to the available assessments, in Russia economic losses from all cardiovascular diseases (CVD) in 2016 was 2.7 trillion rubles being equivalent to 3.2% of GDP. In the structure of losses among all circulatory diseases, CHD rates the first, financial burden in Russia is more than 1 trillion rubles (Kontsevaya A.V. et al, 2018).

One of the most relevant forms of CHD characterized by high mortality is MI. Globally more than 15 million of new onset MI cases are reported annually (Garganeyeva A.A. et al, 2015; WHO, 2017). MI aggravates prognosis significantly: according to European register, mortality among the subjects with STEMI during hospitalization varies from 4% to 12%, 6-month mortality may exceed 12%, 12-month mortality is approximately 10% and may reach 20% within 5 years (Ibanez B. et al, 2017). At that, unfavourable prognosis is still relevant for surviving post-MI subjects (Berger C.J., 1992; VNOK Work Group, 2007; Minzdrav, 2016).

According to some authors, the urgency of MI epidemiological situation is determined by its frequency among the population aged > 60 years old both by morbidity and mortality parameters and by hospital and pre-hospital lethality (Okrugin S.A., 2018).

The main therapeutic measures are directed at myocardial reperfusion as soon as possible with recanalization by percutaneous coronary intervention (PCI) (Ibanez B. et al, 2017).

Despite significant progress in MI therapy, more than 20% surviving subjects develop HF (HF) within 90 days (Gjesing A. et al., 2014).

According to Russian epidemiological studies (EPOHA-CHF, EPOHA-Hospital-CHF and EPOHA-Decompensation-CHF), prevalence of chronic HF in the RF increased from 4.9% (1998) to 10.2% (2014) within 16 years. At that, the number of subjects with chronic HF functional class (FC) II-IV increased significantly due to increased age of the subjects as well as increased weight of etiological CHD causes (69.7% in 2014) and previous MI (15.3% in 2014). Overall mortality is 6% annually (Fomin I.V., 2016).

STEMI is associated with intensive inflammatory response promoting further lesion and predicting increased mortality or HF risk (Frangogiannis N.G., 2008; Velagaleti R.S. et al., 2008; Vanhaverbeke M. et al., 2018).

Interleukin-1 (IL-1) is the key mediator of local and systemic inflammatory response to injury. Nonclinical studies demonstrated that IL-1 inhibition improves infarction healing and prevents the development of HF (Abbate A. et al., 2006).

The studies indicated that concentration of high-sensitive C-reactive protein (hsCRP), the marker of inflammatory response and surrogate marker of IL-1 activity, in subjects with acute coronary

syndrome/MI, independently correlated with the risk of unfavourable cardiovascular outcomes (including HF) (Ridker P. et al., 2005; Scirica B.M., 2009; Vanhaverbeke M. et al., 2018). Individual studies also demonstrated that, where the signs of persistent inflammation (increased hsCRP level) and hemodynamic stress (an increase in a proBNP level) are observed, the subjects are under the highest risk of HF (Scirica B.M., 2009; Vanhaverbeke M. et al., 2018).

Currently evaluation of medicinal products blocking activity of IL-1 (anakinra, rilonacept, canakinumab) is performed to improve outcomes in subjects with acute coronary syndrome/MI (Buckley L.F. and Abbate A., 2018).

Randomized double-blind placebo-controlled study of canakinumab (CANTOS) enrolled 10061 subjects with MI and hsCRP level of ≥ 2 mg/L. The subjects received 50 mg, 150 mg or 300 mg of canakinumab or placebo subcutaneously every 3 months. It was demonstrated that,after a single administration of the product, the subjects reaching reduced hsCRP below 2 mg/L showed reduced frequency of major adverse cardiovascular events by 25% and mortality by 31% compared to the subjects not reaching hsCRP reduction. Similar results were demonstrated for other outcomes (including hospitalization due to unstable angina requiring unscheduled revascularization (Ridker P.M. et al., 2017; Ridker P.M. et al., 2018).

Three pilot clinical studies of anakinra for STEMI were carried out: VCU-ART, VCU – ART2 and VCU-ART3 (Abbate A. et al., 2010; Abbate A., 2013, Abbate A. et al., 2020; Van Tassell B.W. et al., 2018). In total, these pilot studies enrolled 140 subjects with STEMI receiving reperfusion therapy who were randomized (within 12 hours post coronary angiography) for daily anakinra therapy for 14 days. Anakinra, a recombinant human IL-1 receptor antagonist (IL-1RA), was tolerated well and reduced serum hsCRP level. Anakinra-treated subjects showed tendency for more favourable left ventricular (LV) remodelling and lower frequency of HF in the mid-term and long run.

RPH-104 belongs to the class of target agents affecting IL-1. It is a hybrid protein selectively binding and inactivating IL-1β. Nonclinical studies show that RPH-104 is being developed for the treatment of human subjects with diseases associated with increased activity of IL-1β.

To date, the clinical study of drug use in treatment of acute gout attacks has been completed, and the studies of potential benefits of the drug for the treatment of Familial Mediterranean fever, idiopathic recurrent pericarditis are ongoing.

Given similar mechanism of action of RPH-104 and anakinra, RPH-104 is expected to reduce intensity of inflammatory response at myocardial lesion in subjects with STEMI and, therefore, to reduce hsCRP level and improve short-term and long-term outcomes.

## 2.2. Cumulative presentation of the results of nonclinical and clinical studies relevant for this study

RPH-104 is a hybrid protein with a molecular weight of the non-glycosylated form of 126.8 kilodalton (kDA) selectively binding and inactivating IL-1β. Two active parts of the molecule are responsible for RPH-104 binding with IL-1β: an extracellular portion of human IL-1 receptor type 1 (IL-1R1), type 1 and a portion of human IL-1 receptor accessory protein (IL-1RAcP) that is an IL-1 co-receptor.

Structurally, RPH-104 molecule contains two polypeptide chains: the first one consists of extracellular part of IL-1 receptor (amino acids from 18 to 333 of human IL-1R1) and mutant Fc-fragment of human immunoglobulin G1 (IgG1); the second one consists of the part of IL-1RAcP (amino acids from 21 to 358 of human IL-1RAcP) and mutant Fc-fragment of human IgG1. Each of the extracellular parts of the molecule also contains 7 covalently bound glycans, and each of Fc-

fragments carries one glycan.

RPH-104 is a highly active inhibitor of IL-1β-mediated signal pathway.

Investigation of inhibitory effect of RPH-104 on IL-1β-mediated secretion of IL-6 cell line of non-transformed human lung fibroblasts (MRC5) demonstrated that 50% inhibitory concentration of RPH-104 ($IC_{50}$) is about 0.4 ng/mL (2.0 pmol/L).

The amino acid sequence of the extracellular domain of IL-1 receptor in the RPH-104 molecule subunit is 94.7% identical to the amino acid sequence of IL-1 receptor of cynomolgus monkeys and only 64% identical to the IL-1R1 sequence of rodents. In addition, RPH-104 has comparable cross-reactivity in tissues of humans and cynomolgus monkeys. Therefore, cynomolgus monkeys are a suitable biological species for nonclinical studies of RPH-104 *in vivo*.

RPH-104 shows linear pharmacokinetics (PK) in animals and humans. After a single subcutaneous administration to cynomolgus monkeys, RPH-104 bioavailability is 52-85% without signs of accumulation. After repeated administration to cynomolgus monkeys, plasma concentration and half-life tended to decrease by 20-80% compared to single dose values due to production of anti-product antibodies. Apparent gender-related differences in the product PK are lacking.

RPH-104 toxicity has been studied in mice and monkeys. Clinical symptoms and abnormal laboratory values during 4-week study of the product were mild and reversible in most animals by the end of recovery period. No cases of product-related animal mortality were reported in this study. In a 26-week RPH-104 repeated dose nonclinical study on cynomolgus monkeys, cases of serious toxicity requiring early euthanasia were reported. The cases recorded were considered as related to immunosuppressive mechanism of action of RPH-104 as an IL-1β antagonist. Immunosuppression on the background of long-term administration of high doses of RPH-104 is due to inhibition of IL-1β and meets the purpose of RPH-104 administration for the treatment of autoinflammatory diseases.

The medicinal product has immunogenic properties in monkeys.

The results of repeated dose toxicity studies with weekly subcutaneous 4-week administration suggest that RPH-104 no adverse effect level (NOAEL) in mice and monkeys was 100 mg/kg.

Mathematic modeling studies demonstrated that the minimum effective dose of RPH-104 required to achieve the desired plasma level of free IL-1β was 1 mg upon once weekly dosing. Maximum tolerated dose (MTD) for humans is 6.4 mg/kg which is equivalent to 384 mg based on a 60 kg body weight.

Nonclinical studies on the model of acute MI were not performed.

Given its mechanism of action, RPH-104 is designed for investigation and use in humans for the treatment of autoinflammatory diseases associated with increased activity of IL-1β.

In 2018, the first clinical study (phase 1) of RPH-104 was completed. The study aimed at evaluating the tolerability, safety, pharmacokinetics, pharmacodynamics and immunogenicity of the drug (RPH104FIH01/CL04018045) in healthy volunteers. The study results demonstrated that RPH-104 at doses from 4 to 160 mg inclusive with a single subcutaneous injection are tolerated well by the volunteers of either gender. No serious adverse events (SAEs) or any other adverse events (AEs) resulting in early withdrawal have been reported. All adverse events (70 in total) in all dose groups were mild and resolved completely without any complications. Headache was the only AE with tendency for higher frequency in RPH-104 group compared to placebo.

The results of investigation of RPH-104 PK after a single administration presented in analysis of this clinical study demonstrated linear and dose-dependent increase in $C_{max}$ and $AUC_{(0-t)}$ values. In general, median $T_{max}$ was 96 hours (4 days), however the median was 120 hours (5 days) in 40 and 160 mg groups. Half-life was similar in all dose groups and was equivalent to 235-249 hours (10

days).

The results of pharmacodynamic (PD) study presented in the RPH104FIH01/CL04018045 study report demonstrated that administration of the product at 4 to 160 mg did not cause any significant changes in IL-1α or IL-1β levels in healthy volunteers. The changes in the level of CRP were regarded as normal fluctuations. Volunteers receiving RPH-104 showed increased IL-1RA levels due to the time post dosing starting from 20 mg dose which was not observed in placebo group. This trend towards an increase in the IL-1RA levels over time after the product administration was noted at all dose levels. Such increase in IL-1RA level is considered as an additional benefit, potentially capable of increasing RPH-104 efficacy without increasing the drug-related safety risks. Nevertheless, this requires confirmation in further studies. The volunteers in the study did not show any relevant product-related changes in IL-6 levels associated. During the study, there were no signs of the effect of RPH-104 on S100 A8 levels.

No antibodies to RPH-104 were detected in the blood samples of healthy volunteers collected during the study.

In 2020, an international multicenter randomized double-blind adaptive placebo-controlled single-dose study to evaluate the efficacy and safety of olokizumab (IL-6 inhibitor) and RPH-104 in patients with severe COVID-19 (SARS-CoV-2) infection conducted in RF was completed (CL04041078). The analysis of primary efficacy endpoint (response to treatment) showed no significant differences between the treatment groups.

During the study of RPH-104 administration, 128 AEs were reported in 61 (49.6%) patients in the RPH-104 group and 111 AEs in 48 (38.7%) patients in the placebo group. The most common AEs belonged to the systemic organ class of “Investigations” (ALT increased, AST increased, GGT increased): 29 (23.6%) patients in the RH-104 group and 23 (18.5%) patients in the placebo group. Less common AEs belonged to the SOC of “Infections and infestations” (e.g. acute sinusitis, bacterial bronchitis, COVID-19, *C.difficile*-induced pseudomembranous colitis, otitis media, otosalpingitis, pneumonia, pseudomembranous colitis, sepsis, septic shock, urinary tract infection, fungal urinary tract infection, viral sepsis – none of events were reported in more than 5% in each treatment group).

At least one SAE was reported in 12.2% of patients in the RPH-104 group and 6.5% of patients in the placebo group. The majority of SAEs belonged to the SOC “Infections and infestations” (i.e. sepsis, septic shock, COVID-19, viral sepsis). SAEs that led to death were reported in 11.4% and 4.8% of patients in the RPH-104 and placebo groups, respectively. Only one SAE that resulted in death in the RPH-104 group was considered related to the study drug (i.e. a case of septic shock). RPH-104 was generally well-tolerated by patients. No new safety signals related to the use of RPH-104 were identified. It should be noted that no cases of death have been reported in any other ongoing studies of RPH-104 so far.

In 2021, an open-label randomized phase 2a clinical study assessing the safety, tolerability, pharmacokinetics and pharmacodynamics of RPH-104 at various doses in subjects with an acute gout episode in the RF (CL04018054) was completed. In this study, the subjects received RPH-104 at single subcutaneous doses of 4 mg, 20 mg, 40 mg, 80 mg, or 160 mg, control subjects received diclofenac orally for 12 days.

The most pronounced decrease in the joint pain severity 72 hours after the start of the study treatment (primary endpoint) was observed in the RPH-104 20 mg, 80 mg and 160 mg dose groups, as well as the diclofenac group. In all groups, the use of the study treatment resulted in decreased severity of swelling and pain in the affected joint, elimination of erythema and improvement of the patients’ performance status. The results of analysis of changes in the health assessment parameters (using the HAQ) indicated clinically significant improvement of the patients’ performance status while on

the study treatment in the 20 mg, 40 mg, 160 mg dose groups, and the diclofenac group.

The analysis of PK parameters in this study demonstrated a tendency to increased $C_{max}$ and AUC with the drug dose increased, except for the 20 mg dose group, which demonstrated higher mean values of these parameters, similar to those observed in the 80 mg dose group. High interindividual variability of $T_{max}$ was observed. The half-life in the dose groups was about 10 days.

RPH-104 dosing in patients with acute gout attacks resulted in decreased concentrations of the main inflammatory markers – hsCRP and serum amyloid A (SAA). hsCRP and SAA levels tended to show more significant decrease in the RPH-104 80 mg and 160 mg dose groups; the 80 mg dose group also demonstrated a statistically significant superiority in respect of hsCRP level increase compared to the diclofenac group.

The study demonstrated a favorable safety profile of the drug. AEs related to the use of RPH-104 included: in the 40 mg dose group – injection site hemorrhage, gouty arthritis; in the 80 mg group – drug-induced liver injury; in the 160 mg group - leukocytosis, sinus tachycardia, injection site erythema, injection site itching, cholesterol level increased, creatinine level increased, triglyceride level increased, blood urea level increased, lymphocyte count increased, creatinine clearance decreased, neutrophil count and percentage decreased, arthralgia, joint swelling, pain in extremities, allergic dermatitis. Injection site reactions were observed only in three patients treated with RPH-104: two patients in the 4 mg dose group (swelling, hemorrhage) and one patient in the 160 mg dose group (injection site erythema and itching).

Two serious adverse events (SAEs) were reported in patients receiving the test product and one SAE in the active control group; there were no deaths.

A 47-year-old male patient with acute gouty arthritis treated with RPH-104 SC 80 mg developed highly active drug-induced hepatitis on a background of fatty liver (Medical Dictionary for Regulatory Activities [MedDRA] preferred term: drug-induced liver injury). The investigator regarded this event as probably related to the study drug and acknowledged the possible role of existing liver disease. However, taking into account the normalization of liver enzyme levels within a few days after the onset of symptoms, along with a persisting noticeable increase in pancreatic enzyme levels (which is typical for pancreatitis of biliary origin), the patient's history of chronic pancreatitis, chronic cholecystitis, deformity of the duodenum (which could predispose to the development of acute pancreatitis or exacerbation of chronic pancreatitis), the Sponsor classified this event as unrelated to the study drug and regarded the detected disorders as more typical for pancreatitis than hepatitis.

Another patient (male, 66 years old), who received once subcutaneous injection of RPH-104 80 mg for an acute attack of gout, had a positive test for *Mycobacterium tuberculosis complex* and was diagnosed with pulmonary fibrosis. According to the Investigator’s assessment, the study drug was not related to these events. The Sponsor assessed both events as unrelated to the use of RPH-104: a blood sample was taken 4 days after the RPH-104 administration, which makes the relationship of a positive result of the test for tuberculosis and the administration of the study drug biologically and chronologically implausible; the connection of pulmonary fibrosis with the use of PH-104 is chronologically impossible, since pulmonary fibrosis could not develop in such a short period.

In general, the available data on the safety of RPH-104 do not indicate that there is a significant risk to the safety of the study participants.

Based on the results of the efficacy assessment in the CL04041078 study, it was concluded that RPH-104 does not contribute to improving the clinical status (with respect to respiratory system function) or mortality rates in patients with severe COVID-19, however, the potential benefit in relation to other clinical outcomes requires study in further clinical studies. The results of the CL04018054 study indicate the potential efficacy of RPH-104 in the dose range from 20 mg to

160 mg for the treatment of acute gout attack, and are also promising with regard to the doses of 80-160 mg in terms of treatment of diseases associated with increased IL-1 activity. To date, no data are available on the efficacy of RPH-104 in humans with other disorders.

The efficacy and safety of the use of RPH-104 is also being studied in an ongoing double-blind randomized placebo-controlled phase 2/3 clinical trial in patients with idiopathic recurrent pericarditis (CL04018068) in the RF, during which patients receive the investigational product according to the following regimen: the first injection at a "loading" dose of 160 mg, then – at a dose of 80 mg – at Week 1 and 2 after the first injection, and then at a dose of 80 mg once every 2 weeks. Three SAEs have been reported in this study: community-acquired pneumonia associated with coronavirus infection (RPH-104/placebo), exacerbation of idiopathic recurrent pericarditis (RPH-104), and bacterial community-acquired pneumonia (RPH-104). The case of bacterial community-acquired pneumonia was regarded by both the Investigator and the Sponsor as associated with RPH-104 due to the known effect of IL-1 inhibitors on the risk of infections' development. These events were not included in the current safety analysis. In addition, patients are being recruited to an international multicenter double-blind placebo-controlled randomized clinical trial of the efficacy and safety of RPH-104 used to prevent recurrent seizures in adult patients with Familial Mediterranean fever with colchicine resistance or colchicine intolerance (CL04018065), for which a subsequent long-term open-label extension study is planned (CL04018071).

A Phase 2, double-blind, placebo-controlled, randomized trial evaluating the efficacy and safety of RPH-104 in patients with Schnitzler syndrome is also planned to be conducted (CL04018066), and so is a double-blind randomized placebo-controlled phase 3 study to evaluate efficacy and safety of RPH-104 in adult-onset Still's disease (CL04018093).

In view of the mechanism of action, RPH-104 is expected to be a highly effective, safe drug for reducing the inflammatory response to myocardial injury in STEMI patients and for improving short- and long-term outcomes.

Detailed data on the results of nonclinical and clinical studies of RPH-104 are provided in the Investigator's Brochure.

## 2.3. Brief summary of known and potential risks and benefits for the study subjects

RPH-104 study program currently includes the data from nonclinical studies and phase 1 clinical study on healthy volunteers, as well as a randomized double-blind placebo-controlled study of the use of RPH-104 in patients with severe COVID-19 (SARS-CoV-2 infection), and an open-label randomized phase 2a clinical study in patients with gout. Phase 1 study showed that RPH-104 administration to healthy volunteers at doses from 4 mg to 160 mg inclusive were tolerated well by male and female volunteers after a single subcutaneous administration. There were no SAEs or AEs leading to withdrawal from the study. The only AE with a tendency towards a higher incidence in the RPH-104 group versus placebo group was headache. No antibodies to RPH-104 were detected in blood samples of healthy volunteers during the study. No new safety signals have been identified during the studies of RPH-104 in patients with COVID-19 or gout.

Based on the known safety profile of drugs in this class (IL-1 inhibitors), the following adverse reactions should be carefully monitored during their use:

- Any infections (including serious infections), including but not limited to: upper respiratory tract infections, pneumonia, urinary tract infection, gastroenteritis, tuberculosis, opportunistic infections, sepsis;
- Decreased neutrophil count;

- Decreased platelet count;
- Drug-induced liver injury, any liver enzyme increase;
- Elevation of blood lipid;
- Development of malignant neoplasms;
- Ineffective vaccination or generalized vaccine-associated infection;
- Macrophage activation syndrome;
- Development of anaphylactic and anaphylactoid reactions. These reactions can manifest as acute infusion reactions, allergic reactions, or delayed-type hypersensitivity reactions.

To detect AEs and take timely medical measures, all subjects will undergo regular examinations including vital signs, physical examination, laboratory tests and evaluation of the product administration site.

In addition, to assure safety of the subjects involved in the study, selection criteria stipulate ineligibility of the subjects in which the study product may increase the risk of AEs such as infections or reduced blood neutrophil count.

Since the RPH-104 is a protein product, it may cause anaphylactic and anaphylactoid reactions when administered. These reactions may manifest as acute infusion reactions, allergic reactions or delayed-type hypersensitivity reactions. Therefore, administration of RPH-104 will be performed at the study sites provided with medicinal products and equipment designed for the treatment of anaphylactic and anaphylactoid reactions.

Based on the information available from the results of nonclinical studies and from RPH-104 administration to healthy volunteers, patients with COVID-19 and gout, single subcutaneous administration to the subjects with acute STEMI at 80 mg or 160 mg is not expected to cause severe or serious AEs.

Placebo administration is not associated with additional risks for the study subjects with STEMI as the Protocol does not define any additional or treatment-limiting conditions. The subjects who, based on their status, will await for cardiosurgery will not be enrolled in this study.

Physical methods of examination to be performed in this study are routine methods (weight and height measurement, evaluation of vital signs – blood pressure [BP], heart rate [HR], respiratory rate [RR], body temperature], physical examination) and do not pose any additional risk for the subjects during their participation in the study.

Echocardiography (Echo-CG) is a routine examination method for the subjects with STEMI and does not pose additional burden and/or risks for the subjects participating in the study.

According to the Protocol, laboratory examination requires blood sampling, therefore there is low risk of infection which may be ruled out by qualified performance of the procedure by experienced personnel of the study sites involved in this study.

By means of examination and monitoring, the subjects will obtain reliable information on their health status within the examinations.

In addition, based on the results of the studies of the products with similar mechanism of action in the same population, improved STEMI outcome may be expected: more favourable LV remodeling and lower rate of HF in the mid-term and long run.

Therefore, benefit from the study for the patients is expected to outweigh the risk and overall risk-benefit ratio is favorable.

## 2.4. Description and justification of method of administration, dose, dosing regimen and therapy duration

The study product will be administered as a single subcutaneous dose of 80 mg (2 mL) or 160 mg (overall volume 4 mL: 2 mL in different administration sites).

Placebo will be used as a single subcutaneous injection at 2 mL or 4 mL (2 mL in different administration sites).

Nonclinical dose-ranging studies were not performed on relevant animal models.

In the studies of anakinra, an agent with similar mechanism of action, the product was administered once daily for 14 days in subjects with STEMI. Given that RPH-104 half-life is 250 hours, single administration is supposed to provide inhibition of IL-1 with reduced hsCRP level.

According to study data for rilonacept, a drug with a similar mechanism of action, a single dose of 320 mg of rilonacept is well tolerated, and a dose of 160 mg weekly has proven its therapeutic efficacy in patients with diseases in which IL-1 plays a leading pathogenic role (Hashkes P.J. et al., 2012; Hoffman H.M. et al., 2008; Krause K. et al., 2012). RPH-104 contains active fragments similar to rilonacept, while the molecular weight of the former is 2 times less, therefore the same dose of RPH-104 can provide a molar ratio 2 times higher than that of rilonacept. In addition, according to the results of phase 1 study (RPH104FIH01/CL04018045) in healthy volunteers doses of 80 and 160 mg provide higher blood concentrations of the drug with a similar safety profile compared to lower doses.

In addition, in an open-label phase 2a study in patients with gout, there was a tendency to a more pronounced decrease in hsCRP in the dose groups RPH-104 80 mg and 160 mg. A comparative intergroup analysis (RPH-104 at doses of 4 mg, 20 mg, 40 mg, 80 mg and 160 mg versus diclofenac) revealed a statistically significant superiority compared to the diclofenac group in reducing the hsCRP from the baseline level for the 80 mg dose group at certain time points after administration of the study drug.

Dose selection (80 mg or 160 mg) for further phases of clinical studies will be based on the results of analysis of data from this study in terms of risk-benefit ratio for two doses of RPH-104.

The results of phase 1 study demonstrated that single subcutaneous administration of RPH-104 at doses from 4 mg to 160 mg was tolerated well by healthy volunteers. These results, as well as the results of the use of RPH-104 in patients with COVID-19 or gout (during which no new safety signals were identified) suggest that in the present clinical study RPH-104 at 80 mg or 160 mg will be tolerated well by the subjects with acute STEMI.

## 2.5. Legal framework

This clinical study will be carried out in accordance with the present Protocol, Good Clinical Practice guidelines adopted at the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP E6 in the current version), ethical principles outlined in Helsinki Declaration of World Medical Association (Fortaleza, 2013), European Union Directive 2001/20/EC and requirements of laws of the RF, EAEU and USA:

- Federal Law dated 21.11.2011 No. 323-FL (current version) "On fundamental healthcare principles in the RF";
- Good Clinical Practice. GOST R 52397-2005 (app. by Decree of Federal Agency on Technical Regulation and Metrology dated 27.09.2005 No. 232-st);

- Federal Law dated April 12, 2010 No. 61-FL (current version) "On medicinal products circulation";
- Decree of the RF Government dated 13.09.2010 No. 714 “On approval of standard regulations for obligatory insurance of life and health of the subject involved in clinical studies of medicinal product” (according to amendments made by Decree of the RF Government dated May 18, 2011 No. 393);
- Decree of the RF Ministry of Health dated April 01, 2016 No. 200n "On approval of Good Clinical Practice";
- Resolution of the Council of the Eurasian Economic Commission dated November 3, 2016 No. 79 "Regulations of Good Clinical Practice of Eurasian Economic Union";
- Title 21 of the Code of Federal Regulations;
- other applicable regulations.

## 2.6. Description of study population

The study is supposed to enroll male and female subjects aged from 18 years old (inclusive) hospitalized with STEMI to the study sites of the RF and USA. Given that STEMI is a common condition and is a critical issue among the subjects of higher age groups, the study did not determine upper age limit.

Selection criteria for this study were carefully developed to assure safety of the subjects and authenticity of the study results.

# 3. Study purpose and objectives

## 3.1. Study purpose

Evaluate the effect of single administration of RPH-104 at 80 mg and 160 mg on parameters of systemic inflammation and outcomes of the disease in subjects with STEMI.

## 3.2. Study objectives

1. Evaluate the effect of single administration of RPH-104 at 80 mg and 160 mg compared to placebo on hsCRP level reduction within 14 days in subjects with STEMI.

2. Evaluate the effect of single administration of RPH-104 at 80 mg and 160 mg compared to placebo on hsCRP level reduction within 28 days in subjects with STEMI.

3. Evaluate the effect of single administration of RPH-104 at 80 mg and 160 mg compared to placebo on cardiovascular and other clinical outcomes within 12 months in subjects with STEMI.

4. Evaluate the effect of single administration of RPH-104 at 80 mg and 160 mg compared to placebo on changes in levels of HF biomarkers (BNP and NT-pro-BNP) within 12 months in subjects with STEMI.

5. Evaluate the effect of single administration of RPH-104 at 80 mg and 160 mg compared to placebo on parameters of cardiac remodeling (changes in structural and functional echocardiographic parameters) within 12 months in subjects with STEMI.

6. Evaluate safety and tolerability of single administration of RPH-104 at 80 mg and 160 mg compared to placebo in subjects with STEMI during the study.

**Exploratory objective:**

Evaluate interaction between STEMI outcomes and peculiarities of coronary bed lesion based on baseline coronary angiography (CAG) results.

# 4. Study design

## 4.1. Principal and additional study parameters

**Table 2. Study endpoints**

| Objectives | Endpoints |
|---|---|
| Evaluate the effect of single administration of RPH-104 at 80 mg and 160 mg compared to placebo on hsCRP level reduction within 14 days in subjects with STEMI. | hsCRP area under curve (AUC) from Day 1 (baseline) until Day 14 [Visit 1 Day 1 – Visit 3 Day 14]. |
| Evaluate the effect of single administration of RPH-104 at 80 mg and 160 mg compared to placebo on hsCRP level reduction within 28 days in subjects with STEMI. | hsCRP area under curve (AUC) from Day 1 (baseline) until Day 28 [Visit 1 Day 1 – Visit 4 Day 28]. |
| Evaluate the effect of single administration of RPH-104 at 80 mg and 160 mg compared to placebo on cardiovascular and other clinical outcomes within 12 months in subjects with STEMI. | Incidence of fatal outcomes (cardiac and non-cardiac) during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].<br>Incidence of hospitalizations due to HF or other cardiac reasons not associated with HF, or due to non-cardiac reasonsduring 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].<br>Incidence of new cases of HF (defined as hospitalization due to HF or new onset of HF) during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].<br>Incidence of “fatal outcome (due to any reason) or hospitalization due to HF or new onset of HF” during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].<br>Incidence of “fatal outcome (due to any reason) or hospitalization due to HF” during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].<br>***Exploratory endpoint***:<br>Changes in concomitant therapy [Visit 1 Day 1 – Visit 6 Day 365]. |
| Evaluate the effect of single administration of RPH-104 at 80 mg and 160 mg compared to placebo on changes in levels of HF biomarkers (BNP and NT-pro-BNP) within 12 months in subjects with STEMI. | BNP area under curve (AUC) from Day 1 (baseline) until Day 28 [Visit 1 Day 1 – Visit 4 Day 28].<br>NT-pro-BNP area under curve (AUC) from Day 1 (baseline) until Day 28 [Visit 1 Day 1 – Visit 4 Day 28].<br>Changes in levels of BNP and NT-pro-BNP during 12-month follow-up period compared to baseline [Visit 1 Day 1 – Visit 6 Day 365]. |

| | |
|---|---|
| Evaluate the effect of single administration of RPH-104 at 80 mg and 160 mg compared to placebo on parameters of cardiac remodeling (changes in structural and functional echocardiographic parameters) and others within 12 months in subjects with STEMI. | Changes in structural and functional echocardiographic parameters after 12 months compared to baseline [Visit 1 Day 1 – Visit 6 Day 365]. |
| Evaluate safety and tolerability of single administration of RPH-104 at 80 mg and 160 mg compared to placebo in subjects with STEMI during the study. | Frequency of AE/SAE during the study.<br>Changes in physical examination (including body weight), vital signs during the study. |
| ***Exploratory objective:***<br>Evaluate interaction between STEMI outcomes and peculiarities of coronary bed lesion based on baseline CAG results. | ***Exploratory endpoint:***<br>Interaction between STEMI outcomes and peculiarities of coronary bed lesion based on baseline CAG results [Visit 1 Day 1 – Visit 6 Day 365]. |

See detailed description in Section 7 and Section 8.

## 4.2. Description of the study design, design flow chart, description of the study procedures and stages

### 4.2.1. Description of the study design

International, multicenter, phase 2a, double-blind, randomized, placebo-controlled clinical study comparing single administration of RPH-104 80 mg, RPH-104 160 mg and placebo (1:1:1) in subjects with STEMI at the study sites of the RF and USA.

After the signing informed consent form (ICF), the investigator will assess the subject's eligibility for the study. The following procedures will be performed during the screening: collection of medical history, recording previous and concomitant therapy, demographic data, recording 12-lead electrocardiography (ECG) findings on which STEMI diagnosis was based, recording date and time of STEMI symptom development, recording date, time and results of CAG at admission to the study site, measurement of blood neutrophil count, vital signs assessment, physical examination (including weight measurement if a functional bed is available), blood collection for hematology, biochemistry, determination of concentration of hsCRP and brain natriuretic peptide (BNP; NT-pro-BNP), for females with retained reproductive potential – pregnancy test (test strips).

During the first 10 weeks, not more than 3 patients per week will be included in the study.

The subjects meeting selection will be randomized to one of the three groups for single subcutaneous administration of RPH-104 80 mg, RPH-104 160 mg or placebo.

Therefore, screening, randomization and administration of the study products will be made on the same (first) study day.

Further 4-week (28-day) clinical follow-up and additional 6- and 12-month clinical follow-up period will be performed.

The end of clinical part of the study will be the date of the last visit of the last subject within additional 12-month clinical follow-up.

An overview of the study design is provided in Figure 1.

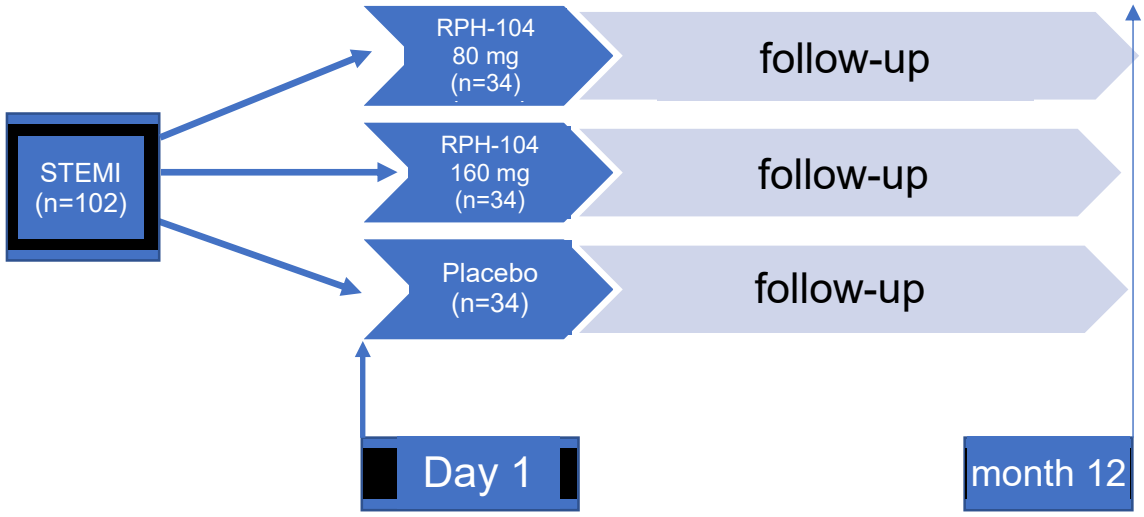


**Figure 1. Study design flow chart**

### 4.2.2. Discussion of the study design including selection of control groups

The design chosen was multicenter, double blind, randomized, placebo-controlled clinical study comparing single administration of RPH-104 80 mg, RPH-104 160 mg and placebo (1:1:1) in subjects with acute STEMI.

Randomized, double-blind, controlled studies are currently a golden standard of the clinical study design as they minimize risk of bias upon distribution to treatment groups and outcome evaluation.

Selection of two doses of test product and placebo as a reference product will allow to obtain reliable data concerning safety and efficacy of lower and higher doses of the product compared to placebo.

Selection of a surrogate endpoint - area under concentration - time curve (AUC) for hsCRP from Day 1 (baseline) till Day 14 – as a primary efficacy criterion is determined by necessity to confirm the study concept that administration of RPH-104 reduces concentration of hsCRP, a surrogate marker of IL-1 activity and predictor of adverse cardiovascular outcomes (Ridker P. et al., 2005; Scirica B.M., 2009; Abbate A. et al., 2010; Abbate A., 2013; Ridker P.M. et al., 2017; Vanhaverbeke M. et al., 2018; Ridker P.M. et al., 2018; Van Tassell B.W. et al., 2018).

At that, direct cardiovascular and other clinical outcomes were chosen as secondary endpoints in accordance with international definitions of cardiovascular outcomes for clinical studies (Hicks K.A.et al., 2018) allowing to evaluate direct product effects on the disease outcomes.

In addition, structural and functional cardiac parameters (based on the Echo-CG findings) allowing to consider remodelling and concentration of brain natriuretic peptide (BNP, NT-pro-BNP), a surrogate marker of HF will be evaluated.

Therefore the selected study design and endpoints will suggest reasonability of RPH-104 administration in subjects with acute STEMI and further development of the product for this indication based on the study results.

## 4.3. The scheduled duration of participation in the study, description of sequence and duration of all study stages including follow-up period

Study duration shall be determined for each subject by duration of each study period. Scheduled study duration for each subject will be no more than 12 months.

### 4.3.1. Screening

The screening will be made on Day 1. The screening is intended to obtain written informed consent of the subject to participate in the study and examine the subject's eligibility for the study. Informed consent will only be obtained after full explanation of the study essence and procedures to each subject and before any of the procedures or assessments are performed. Obtaining informed consent is detailed in Section 11.4.

The subjects should have diagnosis of acute STEMI defined as chest pain or its equivalent with ECG findings evidencing ST elevation (>1 mm) in two or more consecutive leads or acute LBBB according the investigator's judgement. At that, the time from the symptom debut until PCI with stenting should be no more than 12 hours after debut of chest pain or its equivalent, and randomization should be conducted within 12 hours after the PCI (i.e. the period of time from the onset of chest pain to the randomization should be not more than 24 hours).

### 4.3.2. Treatment period

The day of treatment initiation will coincide with the day of screening, treatment period will include single administration of the study products.

### 4.3.3. Follow-up periods

Follow-up period after administration of the study products will last for 4 weeks and will include follow-up after administration of the study product (Day 1), Visit 2 (Day 3), Visit 3 (Day 14±3) and Visit 4 (Day 28±3). The following will be performed during this period: the subject's condition monitoring, laboratory and instrumental examination.

Additional clinical follow-up will last for 12 months after the study product administration and will include Visit 5 (Month 6±2 weeks) and Visit 6 (Month 12±2 weeks). During this period, the subject's condition will be monitored and laboratory and instrumental examination will be performed.

If the patient's visit to the study site is administratively limited due to the current epidemiological situation associated with the SARS-CoV-2 coronavirus, the procedures of Visit 3 (Day 14±3) and Visit 4 (Day 28±3) can be carried out at the patient's home, if the patient agrees, by authorized employees of the study site team. At the same time, if possible, all efficacy and safety assessment procedures planned for a particular visit are carried out. The conduct of visits outside the study site must be agreed with the Sponsor and the patient in each case, which must be documented.

### 4.3.4. Description of visits

Periodicity of the procedures and assessments is also provided in Schedule of visits and procedures (see Table 1).

#### *4.3.4.1. Visit 1 (Day 1)*

Visit 1 (Day 1) includes screening, randomization and administration of the study products.

Before any study-related procedures are performed, the study nature and study-related potential risks should be explained to all study subjects and they should provide their informed consent. After informed consent is obtained, the following procedures will be carried out:

- collection of medical history;
- recording previous and concomitant therapy;
- collection of demographic data;
- recording 12-lead ECG results on which STEMI diagnosis was based

- recording CAG results;
- evaluation of vital signs (BP, HR, RR, body temperature);
- physical examination;
- body weight measurement (using hospital bed, if available);
- determination of absolute neutrophil count (in local laboratory);
- urine pregnancy test for females with childbearing potential (test strips);
- blood collection for hematology and blood chemistry, determination of hsCRP, BNP and NT-pro-BNP;
- Echo-CG (this procedure is permitted to be done within 24 hours from the moment of randomization);
- evaluation of inclusion/exclusion criteria.

After the above-mentioned procedures if the subject meets selection criteria, the following procedures will be carried out:

- randomization;
- administration of the study product (must be done within 3 hours after the randomization);
- recording AE and SAE;
- recording concomitant therapy.

#### *4.3.4.2. Visit 2 (Day 3)*

The following procedures will be carried out at the visit:

- blood sampling for measuring hsCRP, BNP and NT-pro-BNP;
- outcome registration;
- evaluation of vital signs (BP, HR, RR, body temperature);
- body weight measurement (for subjects who did not undergo measurement on Day 1);
- physical examination;
- recording AE and SAE;
- recording concomitant therapy.

For patients discharged on Day 2, the procedures of the Day 3 visit can be carried out ahead of schedule (on Day 2).

#### *4.3.4.3. Visit 3 (Day 14±3)*

The following procedures will be carried out at the visit:

- blood sampling for hematology and biochemistry, for measuring hsCRP, BNP and NT-pro-BNP;
- outcome registration;
- evaluation of vital signs (BP, HR, RR, body temperature);
- body weight measurement;
- height registration (it is permissible to record any value obtained during the hospitalization, when it was possible to measure the patient's height);
- physical examination;
- recording AE and SAE;
- recording concomitant therapy.

#### *4.3.4.4. Visit 4 (Day 28±3)*

The following procedures will be carried out at the visit:

- blood collection for hematology and biochemistry, determination of hsCRP, BNP and NT-pro-BNP;
- outcome registration;
- evaluation of vital signs (BP, HR, RR, body temperature);
- physical examination;
- body weight measurement;
- Echo-CG;
- recording AE and SAE;
- recording concomitant therapy.

#### *4.3.4.5. Visit 5 (Month 6±2 weeks)*

The visit may be made by phone. The following procedures will be performed at the visit:

- outcome registration;
- recording AE and SAE;
- recording concomitant therapy.

#### *4.3.4.6. Visit 6 (Month 12±2 weeks)*

The following procedures will be performed at the visit:

- blood sampling for measuring BNP and NT-pro-BNP;
- outcome registration;
- evaluation of vital signs (BP, HR, RR, body temperature);
- physical examination;
- body weight measurement;
- Echo-CG;
- recording AE and SAE;
- recording concomitant therapy.

By the end of all visit procedures, the study will be considered as completed for the subject.

#### *4.3.4.7. Unscheduled visits*

The subjects may consult Investigator and make an unscheduled visit at any time in case they have adverse events or if, according to investigators, their condition requires medical intervention.

Investigator shall record the data into source medical documentation and the electronic Case Report Form (eCRF) (Unscheduled visit page). The following information should be added on an obligatory basis: visit date, visit reason, examination findings and data of additional investigations. If an AE was the reason of the visit or if an AE was revealed at unscheduled visit, recording of such AE shall be made using regular scheme (see Section 8).

After an unscheduled visit, the next visit shall be made according to the pre-established plan per Protocol.

#### *4.3.4.8. Early withdrawal visits*

In case of early withdrawal at the follow-up period post dosing (Visit 1 Day 1 – Visit 4 Day 28), an early withdrawal visit is advised including Visit 4 (Day 28±3) procedures:

- blood collection for hematology and biochemistry, determination of hsCRP, BNP and NT-pro-BNP;
- outcome registration;

- evaluation of vital signs (BP, HR, RR, body temperature);
- physical examination;
- body weight measurement;
- Echo-CG;
- recording AE and SAE;
- recording concomitant therapy.

In case of early withdrawal during additional clinical follow-up period (Day 29 – Visit 6 Month 12), an early withdrawal visit is advised including Visit 6 (Month 12±2 weeks) procedures:

- blood sampling for measuring BNP and NT-pro-BNP;
- outcome registration;
- evaluation of vital signs (BP, HR, RR, body temperature);
- physical examination;
- body weight measurement;
- Echo-CG;
- recording AE and SAE;
- recording concomitant therapy.

## 4.4. Description of procedures and assessments

Periodicity of the procedures and assessments is also provided in Schedule of visits and procedures (see Table 1).

### 4.4.1. Demographic and other baseline assessments

At the screening (Day 1, baseline), the following data will be recorded:

- date of birth;
- sex;
- race.

### 4.4.2. Past medical history

At the screening (Day 1, baseline), the data on previous and concomitant diseases, surgeries and injuries will be collected. The following data will be recorded for female subjects: contraception method, menopause terms (if applicable) or causes for which she is considered infertile (see also Section 6.2.1.2.). The resulting data will be recorded in source medical documentation and in eCRF in section "Previous Diseases" and "Comorbidities".

### 4.4.3. Information on the underlying disease

At the screening (Day 1, baseline), the following data will be recorded:

- date and time of manifestations of ST-segment elevation myocardial infarction with which the patient is included in the study;
- results of 12-lead ECG based on which STEMI diagnosis was made (specifying the leads with elevated ST and extent of elevation in mm);
- date and time of CAG (specifying relevant findings based on its results), the fact of performing a PCI with stenting;
- history of MI (specifying the date) if any;
- diagnosis of chronic HF (specifying the date of diagnosis) if any.

The data obtained will be recorded in source medical documentation and eCRF.

### 4.4.4. Pregnancy test

Urine pregnancy test will be performed by female subjects with retained childbearing potential at the screening (Day 1, baseline) using test strips. The data obtained will be recorded in source medical documentation and eCRF.

### 4.4.5. Efficacy assessment procedures

Efficacy assessment procedures will include:

- determination of hsCRP concentration;
- determination of concentration of HF biomarkers (BNP and NT-pro-BNP);
- echo-CG;
- outcome registration.

Description of procedures is provided in Section 7.2.

### 4.4.6. Safety cohort

Safety assessment procedures will include:

- evaluation of vital signs (BP, HR, RR and body temperature),
- physical examination (with obligatory assessment of injection site);
- hematology;
- biochemistry;
- AE/SAE recording.

Description of procedures is provided in Section 8.2.1.

## 4.5. Subjectivity minimization measures

### 4.5.1. Randomization

The subjects will be randomized in 1:1:1 ratio without stratification into one of treatment groups - RPH-104 80 mg, RPH-104 160 mg or placebo based on randomization scheme prepared using the relevant software by the responsible study statistician. Distribution will be made using block, non-adaptive, centralized randomization using Interactive Web Response System (IWRS).

At Visit 1 after eligibility of the patient is confirmed by the authorized blinded investigator, the unblinded investigator will perform randomization using the IWRS and obtain information about the patient's randomization number and assigned therapy group.

Detailed information on IWRS system will be presented in an individual IWRS manual kept in Trial Master File (TMF) and in each Investigator Site File (ISF).

The unblinded researcher will keep a register linking the screening and randomization numbers of study participants and therapy groups. Access to these registers for blinded employees will be limited.

Study participant randomization number may not be changed during the study. Distribution of the subject to a treatment group may not be changed during the study.

If the subject decides to refuse to participate or withdraw from the study for any reason, his/her randomization number may not be re-used.

Randomization scheme and identification of each subject will be added to the study report.

### 4.5.2. Blinding

The study will be double-blind, i.e. neither the physician (investigator) performing examination and follow-up, nor the subject will be aware of the treatment group to which the subject has been assigned and of the product administered. To assure double blind design, unblinded investigator's team and unblinded monitor will be involved. Detailed description of operational peculiarities will be presented in an individual Guidelines on medicinal product handling.

Given that administration of RPH-104 at 160 mg is only possible by two 80 mg injections (2 mL) at different sites and appearance of the finished forms of test product and placebo may differ, the following dosing regimen will be used to assure double blind design:

- in RPH-104 80 mg group, the subjects will receive 2 mL (80 mg) of RPH-104 and 2 mL of placebo on different administration sites;
- in RPH-104 160 mg group, the subjects will receive 2 mL (80 mg) of RPH-104 and 2 mL of (80 mg) of RPH-104 on different administration sites;
- in placebo group, the subjects will receive 2 mL of placebo and 2 mL of placebo on different administration sites.

Unblinded investigators will be aware of the treatment group from IWRS and perform administration of the study products.

Additional conditions limiting the subject's visual control will be enforced upon the study product administration.

Monitoring of this process on Sponsor's behalf will be made by unblinded monitor.

## 4.6. Storage of randomization/identification codes and their unblinding

The investigator should ensure confidentiality of the subjects. CRFs and other documents should only identify the subjects by their identification codes rather than by their names or surnames. In this study, the screening number is the patient’s identification code. The screening number is assigned by the IWRS system after the patient has signed the ICF.

The blinded investigator must enter the patient’s screening number in the source documentation and keep a separate screening and randomization log. The patient’s screening number cannot be changed during the study.

The investigator should keep a special identification log/list of numbers, surnames, addresses and phones and numbers of medical documentation (if available).

Unblinding of the identification code of the subject is only possible with his consent verified in writing and/or for the sake of his life and health.

Until the end of the study, randomization plan will be kept by the responsible study statistician. Unblinded staff of the center should ensure that a clinical study participant receives the therapy matching the therapy group assigned by the IWRS system.

Unblinding randomization codes and treatment groups may be performed as agreed with Sponsor in case of urgency and/or SAEs. Treatment group unblinding will be performed by the unblinded investigator using the IWRS and the subject’s identification number, according to the procedure described in an individual IWRS guideline.

## 4.7. List of data recorded directly in CRF

Electronic case report form (eCRF) shall be filled for each subject participating in the study including basic study-related data.

All the information added to eCRF should comply with the one in source documents (medical treatment record, clinical record, laboratory test reports, Protocols and extracts from other examinations).

No data to be entered in eCRF without reflecting the same information in source documentation will be stipulated by the current study. All study-related data will be first recorded in source documentation and then in eCRF.

# 5. Selection and exclusion of the study subjects

## 5.1. Inclusion criteria

The subjects eligible for the study should meet all of the following criteria:

1. Subjects of either gender aged from 18 years old inclusive.
2. Subjects who gave voluntary written informed consent to participate in the study and to follow all Protocol procedures.
3. STEMI diagnosis defined as chest pain or its equivalent with ECG findings evidencing ST elevation (>1 mm) in two or more consecutive leads or LBBB according the investigator's judgement.
4. PCI with stenting was performed within no more than 12 hours after onset of chest pain or its equivalent and randomization was performed in no more than 12 hours after PCI (overall within 24 hours of onset of chest pain or equivalent).
5. Consent of female subjects with childbearing potential defined as all female subjects with physiological potential to conceive, to use highly effective contraceptive methods throughout the study starting from screening (signing informed consent) and negative pregnancy test.

   Highly effective contraceptive methods include combination of two of the following methods (a+b or a+c or b+c):

   a) oral, injection or implanted hormonal contraceptives; in case of oral contraceptives, the female subjects should administer the same product for at least 3 months prior to the study therapy;
   b) intrauterine device or contraceptive system;
   c) barrier methods: condom or occlusive cap (diaphragm or cervical cap/vaginal fornix cap) with spermicidal foam/gel/film/cream/vaginal suppository.

6. Ability and willingness of the subject, according to the reasonable investigator's judgment, to attend the study site at all scheduled visits, undergo the study procedures and follow the Protocol requirements including subcutaneous injections by qualified site personnel.

## 5.2. Non-inclusion criteria

The subjects meeting any of exclusion criteria should not be enrolled:

1. Hypersensitivity to test product (RPH-104) and/or its ingredients/excipients.
2. Pregnancy and breastfeeding.
3. Verified chronic HF (AHA/ACC C-D class, NYHA FC III-IV).
4. Pre-existing severe valvular heart disease according to the investigator’s assessment.
5. Pre-existing LV dysfunction (EF<40%).
6. History of STEMI.

7. Complications of acute MI in the form of acute left ventricular failure and cardiogenic shock defined as stable blood pressure decrease (SBP<90 mm Hg) associated with signs of hypoperfusion as well as cases when inotropic and/or mechanical support is required to maintain SBP; and/or unstable hemodynamics.
8. Active infections (acute or chronic); active tuberculosis.
9. Recent (less than 5 half-life periods) or current administration of colchicine, as well as agents with an immunosuppressant mechanism of action, including, but not limited to: glucocorticoids at doses of > 1 mg/kg of methylprednisolone equivalent, tumor necrosis factor-alfa (TNFα) blockers, IL-1 and other biological drugs, cyclosporine and other immunosuppressants. The use of non-steroidal anti-inflammatory drugs (NSAIDs) are allowed.
10. Immunization with live vaccines within 90 days prior to the study product administration.
11. Chronic systemic autoimmune or autoinflammatory diseases.
12. Suspected necessity in cardiosurgery.
13. Oncology (or diagnosis of oncology within the last 5 years).
14. History of organ transplantation or necessity in transplantation at the screening initiation or scheduled transplantation during the study.
15. Neutropenia (absolute neutrophil count <1800/mm$^3$).
16. Participation in another clinical study within the previous 3 months prior to Screening visit.
17. Other medical (including mental) conditions or abnormal laboratory findings which may increase the risk for the subject associated with the study participation or administration of the study products or which may affect interpretation of the study results and, according to the investigator, render the subject ineligible for the study. *
18. The subjects working at the study site or subjects working for Sponsor directly involved in this clinical study.

**If, in the Investigator's opinion, administration of a non-live COVID-19 (SARS-CoV-2) vaccine increases the risk for the patient related to his/her participation in the study, the Investigator can make a decision not to include this patient into the study.*

Presence of neutropenia for evaluation of exclusion criteria will be performed based on hematology performed at the study site local laboratory.

## 5.3. Deviations from inclusion/exclusion criteria

No deviations from the inclusion/exclusion criteria are permitted. The investigator can call the study's medical monitor to discuss eligibility for any study participant.

## 5.4. Study termination or suspension, early withdrawal criteria

### 5.4.1. Study termination criteria.

Sponsor and principal investigator will have the right to terminate or suspend the study at any time for the reasons including (but not limited to) safety issues, ethical issues or major Protocol violations, lack of achievement of the study purposes or for other reasons.

Particularly, the study will be terminated early or suspended in the following cases:

- at Sponsor's initiative;
    a) upon receipt of new toxicological or pharmacological data or data concerning SAEs requiring revision of earlier evaluation of risk-benefit ratio for participation in the study;

b) frequency of AEs and/or their severity do not allow to continue the study;
c) other reasons including administrative ones;

- at investigator's initiative: frequency of AEs and/or their severity unacceptably increases the risk for the study subjects.
- at the decision of regulatory authorities.

At that, Sponsor shall notify Investigator or management of medical facility on early discontinuation/suspension of the study in writing.

If the study will be terminated/suspended for safety reasons, Sponsor shall immediately report this to the investigators as well as to regulatory authorities and ethics committees.

Where the investigator terminates the study before its termination at the study site, he/she should notify Sponsor immediately and provide the reasons.

Regulatory authorities or ethics committees will be entitled to terminate the study for the reasons including (but not limited to) safety issues according to the current local regulatory requirements.

### 5.4.2. Early withdrawal criteria

The subject may withdraw the study at any time before its termination (Visit 6). The investigator may also decide to withdraw a subject at his/her own discretion.

The reasons for study withdrawal will be reflected in source medical documents and eCRF and may include the following:

1. Recall of informed consent to participate in the study.
2. Serious or intolerable AE requiring withdrawal from the study at the investigator's discretion.
3. Investigator's decision that continuation of the study participation contradicts the subject's interests.
4. Investigator's decision if the subject does not follow the study procedures and/or Protocol.
5. Protocol deviation which, according to the investigator, requires early subject withdrawal from the study (e.g. necessity or performance of additional therapy forbidden by the Protocol). In this case, decision on the subject withdrawal will be agreed with Sponsor.
6. Study termination by Sponsor.
7. Study termination by regulatory authorities.
8. Pregnancy of the subject.
9. Death of the subject.

### 5.4.3. The list of data by early withdrawn subjects and terms of their collection

In case of early withdrawal, justification of such decision and its reason should be specified in source medical documents and eCRF.

Where a subject recalls his/her informed consent, the investigator should try to learn the cause of such a decision.

In case of early withdrawal at the follow-up period post dosing (Visit 1 Day 1 – Visit 4 Day 28) an early withdrawal visit is advised including Visit 4 procedures.

In case of early withdrawal during additional clinical follow-up period (Day 29 – Visit 6 Month 12) an early withdrawal visit is advised including Visit 6 procedures.

### 5.4.4. Replacement of withdrawn subjects and accounting of their data

The subjects withdrawn will not be replaced.

The data of the subjects withdrawn before randomization will be taken into account in the study report in subject disposition analysis only. The data from the subjects withdrawn post randomization will be taken into account in the final analysis in the relevant set (see Section 9).

#### 5.4.5. Follow-up of withdrawn subjects

Follow-up of the subjects withdrawn due to a SAE will be performed until its resolution or stabilization.

The subjects withdrawn for other reasons will not be followed.

# 6. Treatment of the study subjects

## 6.1. Study products

### 6.1.1. Description of the study products

*6.1.1.1. Test product*

***Trade name:*** not assigned

***International nonproprietary name:*** goflikicept

***Product in-house code:*** RPH-104

***Dosage form:*** solution for subcutaneous injections

***Strength:*** 40 mg/mL

***Doses:*** 80 mg and 160 mg

***Dosing frequency:*** single

***Route of administration:*** subcutaneous

***Duration of treatment:*** single dose

Composition:

| **Component** | **Content in 1 mL** | **Relative content** |
|---|---|---|
| *Active ingredient* | | |
| RPH-104 | 40 (± 4) mg | - |
| *Composition of buffer solution* | | |
| sucrose | 60 mg | 6% |
| polyethylene glycol (PEG) 3350 | 30 mg | 3% |
| sodium chloride | 2.92 mg | 50 mmol/L |
| L-histidine | 3.1 mg | 20 mmol/L |
| pH 6.5 | | |

Presentation: 4 mL transparent glass vials with rubber stopper, aluminum crimp cap and red lid. 1 vial contains 2 mL of study product solution 40 mg/mL.

Shelf life: 24 months. The expected maximum shelf life of the medicinal product is 3 years on the basis of the existing stability program.

Storage conditions: Protected from light at +2 to +8ºC.

Manufacturer: Branch of R-Pharm, JSC "Yaroslavl Plant of Finished Dosage Forms", Gromova St., 15, Yaroslavl, 150061

*6.1.1.2. Placebo*

***Trade name:*** not applicable

***International nonproprietary name:*** not applicable

***Dosage form:*** solution for subcutaneous injections

***Strength:*** not applicable

***Dosing frequency:*** single

***Route of administration:*** subcutaneous

***Duration of treatment:*** single dose

Composition:

| Component | Content in 1 mL | Relative content |
|---|---|---|
| Sodium chloride | 9 mg | 0.9% |
| water for injection | up to 1 mL | 99.1% |

Presentation: 4 mL transparent glass vials with a rubber stopper, aluminum crimp cap and red lid. 1 vial contains 2 mL of 0.9% sodium chloride solution (manufactured by JSC "R-Pharm", Russia) / plastic ampoules, 10 ml, 1 ampoule contains 10 ml of sodium chloride solution 10 ml (manufactured by the Hospira inc., USA).

Shelf life: 3 years.

Storage conditions: Protected from light at +2 to +8ºC (manufactured by JSC R-Farm Russia) / at temperatures from +20 to + 25 ° C (manufactured by Hospira inc., USA).

Manufacturer: Branch of R-Pharm, JSC "Yaroslavl Plant of Finished Dosage Forms", Gromova St., 15, Yaroslavl, 150061 / Hospira incorparated, Lake Forest, USA.

*6.1.1.3. Packing and labelling*

Test product and placebo will be prepared and provided by Sponsor. Sponsor will provide the study sites with test product and placebo. Sponsor will be responsible for manufacturing, package and labelling of the products for the clinical study in accordance with the applicable local regulatory requirements.

### 6.1.2. Study product dosing scheme in treatment groups

To provide double blind study design, the study products will be administered as follows:

- in RPH-104 80 mg group, the subjects will receive 2 mL (80 mg) of RPH-104 and 2 mL of placebo on different administration sites;
- in RPH-104 160 mg group, the subjects will receive 2 mL (80 mg) of RPH-104 and 2 mL of (80 mg) of RPH-104 on different administration sites;
- in placebo group, the subjects will receive 2 mL of placebo and 2 mL of placebo on different administration sites.

### 6.1.3. Administration of the study product

Preparation of the study products will be made by unblinded study site personnel.

The study products will be administered by unblinded qualified study site personnel.

RPH-104/placebo will be administered subcutaneously at anterior abdominal wall at one of the areas shown in Figure 2. Each injection will be made to different sites with relevant records in eCRF.

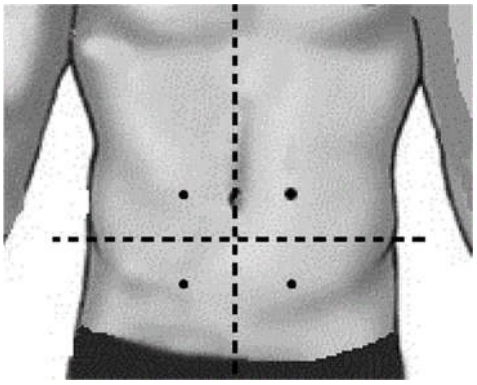

**Figure 2. Anterior abdominal wall sites for the study product administration**

### 6.1.4. Treatment compliance

Given that administration of the study products will be performed by the study site personnel, evaluation of dosing regimen compliance is not planned.

### 6.1.5. Overdose management

No cases of RPH-104 overdose have been reported. The treatment of overdose cases is symptomatic.

## 6.2. Allowed and forbidden concomitant therapy

### 6.2.1. Allowed concomitant therapy.

#### *6.2.1.1. General provisions*

If concomitant pathology is not an exclusion criterion, the treatment of concomitant pathology during the study should be carried out according to the regular scheme. At that, concomitant therapy should not be forbidden by the Protocol (see section 6.2.2).

Concurrent/ongoing treatment with any cytochrome P450 substrate (see Table 3) with a narrow therapeutic index should be clinically monitored to ensure therapeutic effect is maintained; doses of the cytochrome P450 substrate may need to be adjusted as the enzyme may be normalized with co-administration with RPH-104.

**Table 3. Examples of drugs that are P450 substrates**

| | **Highly sensitive substrates** | **Moderately sensitive substrates** |
|---|---|---|
| CYP1A2 | alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, tizanidine | clozapine, pirfenidone, ramosetron, theophylline |
| CYP2B6 | bupropion[1] | efavirenz [1] |
| CYP2C8 | repaglinide[2] | montelukast, pioglitazone, rosiglitazone |

| | **Highly sensitive substrates** | **Moderately sensitive substrates** |
|---|---|---|
| CYP2C9 | celecoxib[3] | glimepiride, phenytoin, tolbutamide, warfarin |
| CYP2C19 | S-mephenytoin, omeprazole | diazepam, lansoprazole[4], rabeprazole, voriconazole |
| CYP2D6 | atomoxetine, desipramine, dextromethorphan, eliglustat[5], nebivolol, nortriptyline, perphenazine, tolterodine, R-venlafaxine | encainide, imipramine, metoprolol, propafenone, propranolol, tramadol, trimipramine, S-venlafaxine |
| CYP3A | alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir[6], ebastine, everolimus, ibrutinib, lomitapide, lovastatin[7], midazolam, naloxegol, nisoldipine, saquinavir[6], simvastatin[7], sirolimus, tacrolimus, tipranavir[6], triazolam, vardenafil | alprazolam, aprepitant, atorvastatin[3], colchicine, eliglustat[5], pimozide, rilpivirin, rivaroxaban, tadalafil |
| | budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir[6], lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan | |

1 Listed based on an in vivo induction study and the observed effect might be partly attributable to induction of other pathway(s).
2 OATP1B1 substrate.
3 Listed based on pharmacogenetic studies.
4 S-lansoprazole is a sensitive substrate in CYP2C19 extensive metabolizer subjects.
5 Sensitive substrate of CYP2D6 and moderate sensitive substrate of CYP3A.
6 Usually administered to patients in combination with ritonavir, a strong CYP3A inhibitor.
7 Acid form is an OATP1B1 substrate.
Abbreviations: CYP: cytochrome P450;OATP1B1: organic anion transporting polypeptide 1B1.
Source: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-1; accessed 30 Dec 2019.

Information on concomitant medicinal products (trade name, composition, dose or dose adjustment, indications, dosing frequency, method of administration, treatment initiation, treatment discontinuation) taken by the subject for 5 half-lives of the drug or 30 days (whichever is longer) prior to enrollment and during the study should be recorded in the relevant section of eCRF including screening visit. All subsequent changes in concomitant therapy during the study should also be reflected in eCRF.

#### *6.2.1.2. Contraception*

Throughout the clinical study female subjects with childbearing potential should use highly effective contraceptive methods including combination of two of the following methods (a+b or a+c or b+c):

a) oral, injection or implanted hormonal contraceptives; in case of oral contraceptives, the female subjects should administer the same product for at least 3 months prior to the study therapy;
b) intrauterine device or contraceptive system;

c) barrier methods: condom or occlusive cap (diaphragm or cervical cap/vaginal fornix cap) with spermicidal foam/gel/film/cream/vaginal suppository

The study may enroll females not using highly effective methods of contraception if they are diagnosed as sterile for the following reasons:

- history of hysterectomy, bilateral ovariectomy, bilateral tubal ligation;
- menopause (physiological amenorrhea with lack of menses within at least 2 years);

Prior to the study, female subjects of childbearing potential should be informed on the importance of contraception during the study and potential risk factors in case of unwanted pregnancy.

Subjects should sign ICF specifying this information. Pregnancy test will be performed by female subjects with childbearing potential.

### 6.2.2. Forbidden concomitant therapy

During the study, the following medicinal products will be forbidden in the terms specified:

- biological (except for RPH-104) including but not limited to: tocilizumab, rituximab, TNFα inhibitors [Visit 1 Day 1 - Visit 4 Day 28];
- immunosuppressants [Visit 1 Day 1 – Visit 4 Day 28] including but not limited to:
  - corticosteroids at doses of >1 mg/kg of methylprednisolone equivalent orally as well as systemic, except for intravenous (i.v.) ones for acute allergic reactions;
  - cyclosporine A, methotrexate etc.;
- colchicine [Visit 1 Day 1 – Visit 4 Day 28];
- anakinra, canakinumab, rilonacept [Visit 1 Day 1 – Visit 6 Month 12];
- immunization with live vaccines within 90 days prior to or after the study product administration;
- any experimental products.

NSAIDs are not forbidden.

### 6.2.3. Use of the medicinal products not allowed or not provided for by the Protocol

If a life- or health-threatening situation took place during the study and the subject required additional therapy with forbidden medicinal products or the medicinal products not specified in the Protocol, such medicinal products may be prescribed in this case. However, Study Sponsor should be notified on the Protocol deviation within 24 hours. In this case, the subject who received forbidden medicinal products or medicinal products not specified in the Protocol may be excluded from the study.

## 6.3. Accounting of the study products

The products for the study will be provided by Sponsor to the study initiator with Acceptance act and certificate of analysis. The product delivery from Sponsor should be accepted and processed by a responsible person (Investigator or authorized person). All study product accounting and storage procedures will be made using specially appointed unblinded members of the investigator's team. The products will be stored until their dispensing in a dry, protected from light place: in the fridge (suitable for medicinal product storage) at temperature from +2 to +8°C for RPH-104 and placebo manufactured by JSC R-Pharm, and at a temperature from +20 to + 25 ° C - for placebo produced by Hospira inc., USA. The products will be stored in specially equipped limited access premises.

The study organizer will provide the study products to the study site in the amount sufficient for the study.

Control, accounting and storage of the products in clinical center shall be made by the qualified person authorized by the principal investigator according to the internal regulations of the clinical center and Sponsor's instructions.

Unblinded investigators should assure the product storage in safe conditions preventing from loss, theft and impaired environmental conditions (temperature) outlined in Guidelines on medicinal product handling and Investigator's Brochure.

Administration of the study products will always be made at the study site by the appointed unblinded study team member.

More detailed information on acceptance, storage, accounting and administration to the study subjects is provided in Guidelines on medicinal product handling for investigators.

Study product accounting, storage and issue will also be monitored by unblinded monitor on behalf of Sponsor.

## 6.4. Control of compliance

Monitoring of compliance with all the study procedures will be made by the Principal Investigator.

# 7. Efficacy evaluation

## 7.1. List of efficacy parameters

**Primary endpoint**

1. hsCRP area under curve (AUC) from Day 1 (baseline) until Day 14 [Visit 1 Day 1 – Visit 3 Day 14].

**Secondary endpoints**

1. hsCRP area under curve (AUC) from Day 1 baseline) until Day 28 [Visit 1 Day 1 – Visit 4 Day 28].
2. BNP area under curve (AUC) from Day 1 (baseline) until Day 28 [Visit 1 Day 1 – Visit 4 Day 28].
3. NT-pro-BNP area under curve (AUC) from Day 1 (baseline) until Day 28 [Visit 1 Day 1 – Visit 4 Day 28].
4. Incidence of fatal outcomes (cardiac and non-cardiac) during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].
5. Incidence of hospitalizations due to HF or other cardiac reasons not associated with HF, or due to non-cardiac reasons during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].
6. Incidence of new cases of HF (defined as hospitalization due to HF or new onset of HF) during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].
7. Incidence of “fatal outcome (due to any reason) or hospitalization due to HF or new onset of HF” Frequency of fatal outcomes for any cause OR hospitalization for HF OR the development of HF in the outpatient settingsduring 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].
8. Incidence of “fatal outcome (due to any reason) or hospitalization due to HF” during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].

9. 9. Changes in levels of BNP and NT-pro-BNP during 12-month follow-up period compared to baseline [Visit 1 Day 1 – Visit 6 Day 365].
10. Changes in structural and functional echocardiographic parameters after 12 months compared to baseline [Visit 1 Day 1 – Visit 6 Day 365].

**Exploratory endpoints**

1. Changes in concomitant therapy [Visit 1 Day 1 – Visit 6 Day 365].
2. Interaction between STEMI outcomes and peculiarities of coronary bed lesion based on baseline CAG results [Visit 1 Day 1 – Visit 6 Day 365].

## 7.2. Methods and terms of evaluation, reporting and analysis of efficacy parameters

Periodicity of the procedures and assessments is also provided in Schedule of visits and procedures (see Table 1).

Blood sampling to determine concentration of hsCRP and level of brain natriuretic peptide (BNP, NT-pro-BNP) will be made at Visit 1 Day 1 (at baseline), Visit 2 (Day 3), Visit 3 (Day 14±3) and Visit 4 (Day 28±3) of the study. In addition, blood sampling to determine level of brain natriuretic peptide (BNP, NT-pro-BNP) will be made at Visit 6 (Month 12±2 weeks) of the study. Concentration of hsCRP and level of brain natriuretic peptide (BNP, NT-pro-BNP) will be determined in central laboratory.

Throughout the clinical study, the investigator will follow the subjects to evaluate and record cardiovascular and other outcomes (fatal outcomes, hospitalizations[1], new HF) based on the current clinical recommendations and terminological criteria "2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials" (Hicks K.A.et al., 2018) (see Attachment 1).

Echo-CG will be carried out at Visit 1 (Day 1) (this procedure is permitted to be done within 24 hours from the moment of randomization), Visit 4 (Day 28±3) and Visit 6 (Month 12±2 weeks) by qualified personnel of the study site using relevant diagnostic equipment. Measurements will be carried out in accordance with the internal document on the interpretation of echo-CG findings. Echo-CG parameters assessed during the study are described in detail in the Statistical Analysis Plan. Given than Echo-CG is an operator-dependent technique, assessment and recording echo-CG results will be centralized.

The following information will be collected upon dose change, dosing scheme modification or product discontinuation in concomitant therapy: date of change, description of change (discontinuation, dose escalation, dose reduction, switch to another product of another group), cause of changes (improved condition, aggravated condition, adverse events/adverse reactions associated with the study product).

# 8. Safety evaluation

## 8.1. List of safety parameters

**Safety endpoints:**

1. Incidence of AE/SAE during the study.
2. Changes in physical examination (including body weight), vital signs during the study.

[1]Hospitalization due to HF will also include cases of prolongation of current hospitalization for the treatment of ST segment elevation MI if HF has developed within 24 hours following hospital admission

## 8.2. Methods and terms of evaluation, registration and analysis of safety parameters

### 8.2.1. General provisions

Safety assessment will include monitoring all recording all AEs and SAEs according to MedDRA and Common Terminology Criteria for Adverse Events (CTCAE v.5.0.).

The unblinded medical monitor will receive and evaluate all AE reports on a regular basis during the study.

Monitoring will include physical examination including vital signs, hematology, serum chemistry as outlined in Schedule of visits and procedures (see Table 1).

#### *8.2.1.1. Physical examination*

Physical examination will be carried out at Visit 1 (Day 1), Visit 2 (Day 3), Visit 3 (Day 14±3), Visit 4 (Day 28±3) and Visit 6 (Month 12± 2 weeks) and will include the assessment of the following: general condition, injection site, condition of skin, musculoskeletal system, lymph nodes, thyroid gland, upper and lower respiratory tract, heart, vessels, abdominal organs, kidneys, psychoneurological status. Abnormal values reported at the screening visit will be recorded in eCRF section "Co-morbidities". At the following visits, "Adverse Events" section of eCRF will include only abnormal values/changes relative to screening physical examination values meeting AE definition.

Weight measurement will be carried out at Visit 1 (Day 1) or Visit 2 (Day 3), Visit 3 (Day 14± 3), Visit 4 (Day 28±3) and Visit 6 (Month 12±2 weeks). Based on severity of the subject's condition, body weight will be measured in recumbent condition at Visit 1 Day 1 using hospital bed or, if not available, at Visit 2 (Day 3) in standing position using the relevant balance. At the remaining visits, measurement will be done in standing position using the relevant balance.

Height measurement will be done in a standing position at Visit 3 (Day 14±3) or at any time during the hospitalization (it is permissible to record any value obtained during the hospitalization, when it is possible to measure the patient's height).

Vital signs will be measured at Visit 1 (Day 1) or Visit 2 (Day 3), Visit 3 (Day 14±3), Visit 4 (Day 28±3), Visit 6 (Month 12±2 weeks). Based on severity of the subject's condition, vital signs will be measured in recumbent position or sitting position after a 5-min rest. Systolic and diastolic BP will be measured on the same arm using the same device. HR will be measured on the apex of heart using phonendoscope. HR and RR will be measured for 1 min. Body temperature will be taken by the axillary route.

#### *8.2.1.2. Laboratory examination*

Hematology and biochemistry will be made at Visit 1 (Day 1) (baseline), at Visit 3 (Day 14±3) and Visit 4 (Day 28±3) in central laboratory. At Visit 1 determination of the absolute neutrophil count is performed in the local laboratory of the site to assess the inclusion/exclusion criteria.

Hematology will include the following parameters: hemoglobin, erythrocyte count, leukocyte count, leukogram with obligatory measurement of absolute neutrophil count, platelet count.

Biochemistry will include the following parameters: hepatic chemistry values (AST, ALT, GGT, AP, LDH, total bilirubin, direct bilirubin, indirect bilirubin), renal chemistry values (serum creatinine, serum urea/urea nitrogen [BUN]), serum electrolytes (sodium, potassium, chlorides), CPK, CPK-MB.

Results of laboratory tests performed within 12 hours before randomization may be used for the study eligibility assessment.

### 8.2.2. Adverse event determination

An adverse event - AE - is any untoward medical event arising after administration of the study product regardless of causality. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs include (but not limited to) the following:

- Laboratory values outside normal range having clinical relevance.
- Pre-existing findings at physical examination which aggravated compared to baseline and are considered clinically relevant.
- Physical examination findings (including vital signs) considered clinically relevant.

### 8.2.3. Adverse events of interest

The following safety concerns have been identified as Adverse Events of Special Interest (AESIs) based on the safety data currently available for RPH-104 and IL-1 inhibitor biologics:

- Infections (including serious infections), including tuberculosis and opportunistic infections
  - Confirmed cases of active tuberculosis should also be documented as SAEs;
- Malignant neoplasms
  - The investigator will be asked to provide relevant medical information/documentation (i.e. the results of pathological/histological examination) for all cases of malignant neoplasms, regardless of their seriousness, as these cases are subject to entry into the safety database;
- Increased blood lipids (i. e., hypercholesterolemia, increased blood cholesterol, increased blood triglycerides, hypertriglyceridemia, and increased LDL cholesterol);
- Systemic reactions to drug administration and hypersensitivity reactions;
- Neutropenia, thrombocytopenia, leukopenia;
- Drug-induced liver injury, any liver enzyme increase;
- Injection site reactions.

All of the above events are subject to recording and analysis as AESIs.

#### *8.2.3.1. Emergency*

Given that in rare cases anaphylactic and anaphylactoid reactions are possible during the product administration, the study site should dispose of the relevant medicines and equipment for urgent medical assistance including antishock therapy. Development of such urgency and measures taken should be recorded on the relevant pages of eCRF.

### 8.2.4. Reporting about adverse events

The investigator and study site personnel will be responsible for detection, relevant medical assistance, documentation and reporting of cases meeting AE and SAE definition.

Information on AEs will be collected since signing ICF and until the study completion by the subject. SAEs will be recorded since signing ICF and for up to 30 days after the study product treatment discontinuation or until the last visit whichever is the latter. AEs recorded prior to the study product administration will be added to eCRF section "Medical history".

The investigator should document all the AEs during the study in case histories and eCRFs.

Adverse events will be recorded based on complaints reported by the subjects themselves, results of interviews between investigator and subject, results of physical examination and laboratory tests. The investigator should formulate his questions to the subject in the manner not provoking the subject to report unreliable information.

AEs will be recorded in the relevant eCRF sections as well as in source medical documents of the subject.

The following information should be specified when recording adverse events:

- Subject identification number;
- Nature of AE (preferably diagnosis rather than the list of symptoms);
- Date of AE onset and resolution (and time if applicable);
- Measures related to AE;
- AE meeting SAE criteria;
- AE severity;
- AE meeting unexpected AE criteria;
- Relationship between the AE and study product administration (according to the investigator);
- Outcome of AE.

### 8.2.5. Definition of a serious adverse event

A serious adverse event - SAE - is defined as any untoward medical occurrence that:

- Resulted in death;
- Was life-threatening;
- Resulted in permanent or pronounced incapacity or disability;
- Required hospitalization or its prolongation;
- Resulted in a birth defect/congenital abnormality in children of patients who had been treated with the drug.
- Furthermore, serious adverse events include any event not meeting the criteria above though being a relevant medical event according to the investigator.

Any other AEs not meeting these criteria will be rated as non-serious.

### 8.2.6. Serious adverse event reporting

To assure safety of the subjects in case of any SAE development after signing ICF and until the end of the study, regardless of suspected causes of SAE or association with the study product, SAE should be reported to Sponsor within 24 hours after the investigator became aware of the SAE.

If a subject has a SAE considered to be related to the study product, a report thereof should be submitted even in case the study has been terminated already.

**Filling serious adverse event report form**

SAEs should be reported by filling out the SAE page in the eCRF within 24 hours from the time the investigator finds out about the SAE. In the event that access to the eCRF is temporarily impossible, the center has the opportunity to report the SAE by sending a scan of the hard copy of the serious adverse event report by email to

Safety@Rpharm.ru

or by fax:

+7 (495) 956-79-38

The investigator must notify the Local Ethics Committee (LEC)/Institutional Review Board (IRB) on the SAE according to LEC/IRB standard operation procedures.

### 8.2.7. Definition of unexpected adverse events

An unexpected AE in its nature or severity is inconsistent with the ones outlined in the current Investigator's Brochure.

Any other AEs are considered to be expected.

### 8.2.8. Submission of reports on suspected unexpected adverse reactions (SUSAR)

The study sponsor should notify regulatory authorities on all suspected unexpected serious adverse reactions (SUSARs)within the terms specified by laws. In context of notification of regulatory authorities and investigators, the SUSARs will mean unexpected SAEs considered by the investigator and/or Sponsor as related to the study product.

### 8.2.9. Adverse event severity assessment

AE severity will be evaluated according to CTCAE v5.0 classification. If an AE is lacking in CTCAE classification, it will be classified based on the following grading:

| | |
|---|---|
| Grade 0: | No AE |
| Grade 1: | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| Grade 2: | Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living.[2] |

[2] Limitation of age-appropriate self-care includes cooking, purchasing goods and clothes, using phone, money management, etc.

| | |
|---|---|
| Grade 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.[3] |
| Grade 4 | Life-threatening consequences; urgent intervention indicated. |
| Grade 5 | Death related to AE. |

Severe AE is not necessarily serious by nature and SAE is not necessarily severe by definition.

### 8.2.10. Adverse event outcome evaluation

AE outcome will be determined as follows:

| | |
|---|---|
| Fatal: | The subject died due to AE (death is an outcome, not an AE) |
| Recovering/Resolving | Reduced intensity of AE |
| Not Recovered/ Not Resolved (Continuing) | AE did not resolve, intensity unchanged |
| Recovered/Resolved with Sequelae | AE resolved but with a permanent defect. |
| Recovered/Resolved | AE resolved completely without sequelae |
| Unknown: | AE outcome is unknown as the subject did not attend the follow-up visit and attempts to obtain the follow-up information were useless (loss to follow-up) |

### 8.2.11. Relationship between an adverse event and study drugs

The investigator will be responsible to assess causality between the AE and study product administration (related/unrelated). The investigator should use his knowledge on the subject, circumstances of the event and evaluation of any potential alternative causes to determine whether the AE is related to the study product or not. One of the following options should be chosen for relationship between AE and the study product: "related" or "unrelated". The following recommendations should be taken into account:

- relationship between AE development and initiation of the study product administration;
- AE changes over time after discontinuation of the study product;
- known relationship between the study product or similar treatments;
- risk factors increasing the risk of AE;
- any non-treatment-related factors associated with the event frequency.

The investigator should report relationship of every event with the study product based on the most probable relationship assessment, at that the study site personnel will be responsible to obtain any lacking data.

[3]Limitation of self-care includes bathing, dressing and undressing, using the toilet, taking medications, but not bedridden.

If relationship assessment changes over time due to new or modified information, it may be revised.

### 8.2.12. Follow-up of adverse events

All AEs should be monitored until their resolution or stabilization.

### 8.2.13. Pregnancy

Pregnancy per se is not an AE except for the cases when it is reasonable to suppose that administration of the study product reduced efficacy of contraceptive methods. Congenital abnormalities or birth defects in children of study subjects are considered to be SAEs. Elective abortions, abortions for medical reasons, with sequelae as well as any serious pregnancy complications (including spontaneous abortions) should be recorded as SAEs. Planned abortions without sequelae are not AEs.

All pregnancy cases reported during the study (including pregnancies of female partners of the study subjects) should be duly recorded. Where pregnancy is confirmed, the investigator should notify Sponsor pharmacovigilance officer by submitting a pregnancy report. Pregnancy report should be filled by authorized employee of the study site within 24 hours after obtaining pregnancy information. A pregnancy should be reported by filling out the “Pregnancy” page in the eCRF within 24 hours by an authorized study site employee from the time the information about pregnancy becomes available. If access to the eCRF is temporarily impossible, the center has the opportunity to report the pregnancy by sending a scan of the hard copy of the Pregnancy Report Form by email to:

Safety@Rpharm.ru

or by fax:

+7 (495) 956-79-38

Further Sponsor should be provided with the information on the pregnancy outcome. Pregnancy of the study subjects and partners of male study subjects will be recorded since the study product administration until the last study-related procedure.

Outcome of each pregnancy (spontaneous abortion, elective abortion or for medical reasons, normal delivery or delivery of a child with congenital abnormalities or birth defects) should be recorded even if the study subject withdrew from the study. Infant's health status should be monitored where possible until 6 weeks, 6 months and 1 year old.

### 8.2.14. Other safety reports

Investigators will submit to LEC/IRB reports on other treatment safety aspects subject to immediate notification if they affect risk-benefit ratio, related to the treatment or may require relevant changes in the treatment within the study or study methodology.

In addition to urgent reports, Sponsor will annually prepare safety update reports on RPH-104 containing all the new relevant safety information obtained during the reporting interval. Summary of these reports will be sent to the investigators for submission to LEC/IRB of medical institutions on an annual basis.

# 9. Statistics

## 9.1. General provisions

Detailed description of statistical data analysis including last observation carried forward will be presented in statistical analysis plan (SAP). SAP development will be finalized until the study database lock. Any deviations from analysis planned in SAP should be justified in the clinical study report.

Any data will be generalized using descriptive statistics: number of the subjects, mean value, minimum and maximum, median and quartiles for continuous variables, frequency of observations with percentages - for qualitative variables.

## 9.2. Selection of data for the analysis

Statistical analysis will be conducted in the following study sets:

*Full analysis set (FAS) for the efficacy analysis*

Full analysis set (FAS) for efficacy analysis will include all randomized subjects who received the study products and underwent at least one hsCRP measurement after administration of the study products. This set is the main population for efficacy assessment.

*Per Protocol Set (PPS)*

ProtocolAll FAS subjects without important Protocol deviations affecting assessment of the primary efficacy parameter. Such Protocol deviations will be defined before breaking the blind in a blinded data review. This set is supplementary population for efficacy assessment.

*Safety set*

All randomized patients who have received the study drugs.

## 9.3. Statistical methods

### 9.3.1. Subjects disposition

The study report will contain the number of subjects enrolled (signed the ICF), the number of subjects randomized, the number and proportion of the subjects who completed the study per Protocol, the number and proportion of the subjects who withdrew early after randomization specifying the reasons. The number of screening failures will also be added specifying the reasons.

### 9.3.2. Demographic and other baseline characteristics

Demographic and other baseline characteristics including age, gender, race, anthropometric characteristics, medical history (time from STEMI debut) and other ones will be presented descriptively by treatment groups for FAS population. All data concerning demographic and other baseline characteristics will also be presented as lists. Analysis of group comparability by demographic and other baseline characteristics will be done.

### 9.3.3. Efficacy analysis

#### *9.3.3.1. Analysis of primary endpoint*

Primary endpoint is hsCRP area under curve (AUC) from Day 1 (baseline) until Day 14 [Visit 1 Day 1 – Visit 3 Day 14].

The following hypotheses will be tested for each RPH-104 dose level:

Null hypothesis H0: difference between mean $AUC_{1\text{-}14\ days}$ CRP in RPH-104 group and mean $AUC_{1\text{-}14\ days}$ CRP in placebo group is equal to 0.

Two-sided alternative hypothesis H1: difference between mean $AUC_{1\text{-}14\ days}$ CRP in RPH-104 group and mean $AUC_{1\text{-}14\ days}$ CRP in placebo group is different from 0.

Individual $AUC_{1\text{-}14\ days}$ CRP values will be calculated using trapezoidal method. Mean $AUC_{1\text{-}14\ days}$ CRP value will be compared between RPH-104 and placebo groups using analysis of variance ANOVA. Mean AUC values for RPH-104 80 mg, RPH-104 160 mg and placebo groups, differences in mean values and relevant two-sided 95% confidence intervals (CI) and well as *p*-values will be presented.

All hsCRP concentration values by study visits will also be presented as lists.

*9.3.3.2. Analysis of secondary endpoints*

- hsCRP area under curve (AUC) from Day 1 (baseline) until Day 28 [Visit 1 Day 1 – Visit 4 Day 28].
- BNP area under curve (AUC) from Day 1 (baseline) until Day 28 [Visit 1 Day 1 – Visit 4 Day 28].
- NT-pro-BNP area under curve (AUC) from Day 1 (baseline) until Day 28 [Visit 1 Day 1 – Visit 4 Day 28].

Analysis will be done similar to the analysis of the primary endpoint described above.

- Incidence of fatal outcomes (cardiac and non-cardiac) during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].
- Incidence of hospitalizations due to HF or other cardiac reasons not associated with HF, or due to non-cardiac reasons during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].
- Incidence of new cases of HF (defined as hospitalization due to HF or new onset of HF) during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].
- Incidence of "fatal outcome (due to any reason) or hospitalization due to HF or new onset of HF" during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].
- Incidence of "fatal outcome (due to any reason) or hospitalization due to HF" during 12-month follow-up period [Visit 1 Day 1 – Visit 6 Day 365].

The number and proportions of subjects (of the number of FAS subjects and valid %) with fatal outcomes, subjects with hospitalizations and subjects with new cases of HF will be presented by treatment groups. Intergroup comparisons will be performed using exact Fisher's test.

- Changes in levels of brain natriuretic peptide (BNP, NT-pro-BNP) during 12-month follow-up period compared to baseline [Visit 1 Day 1 – Visit 6 Day 365].

Changes in BNP, NT-pro-BNP levels will be presented by descriptive statistics by the study visits and treatment groups. Changes relative to baseline will be calculated for each visit.

Comparison of changes between the treatment groups after the treatment initiation, as well as the comparison of mean changes in BNP, NT-pro-BNP levels by Visits will be performed using a basic linear mixed model with the inclusion of the baseline as a covariate and the therapy group as a factor.

- Changes in structural and functional echocardiographic parameters after 12 months from the baseline [Visit 1 Day 1 - Visit 6 Day 365].

The parameters will be analyzed similar to the analysis of changes in brain natriuretic peptide level described above.

In case of significant deviations from the normal data distribution, data transformation (logarithmic or other) can be used. In case of using transformations, the relevant descriptive statistics will also include a geometric mean value.

*9.3.3.3. Analysis of exploratory endpoints*

- Changes in concomitant therapy [Visit 1 Day 1 – Visit 6 Day 365].

Number and proportion of subjects (of the number of FAS-subjects and valid %) with changes in the prescribed concomitant therapy with their causes will be presented by treatment groups.

- Interaction between STEMI outcomes and peculiarities of coronary bed lesion based on baseline CAG results [Visit 1 Day 1 – Visit 6 Day 365].

Detailed description of assessment methods will be presented in the SAP.

### 9.3.4. Safety analysis

Safety analysis will be carried out on safety set.

Scope of application will be presented specifying the following variables: the number of subjects receiving RPH-104 80 mg, the number of subjects receiving RPH-104 160 mg and the number of subjects receiving placebo.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of the subjects with AE/SAE, overall number and percentage of recorded AE/SAE, the number and percentage of AE/SAE resulting in early withdrawal will be presented by system organ class, preferred terms and treatment groups. The data will also be generalized by the number and percentage of AEs/SAEs with various categories of causality, expectedness and severity. All AEs will be additionally presented as listings.

Quantitative safety laboratory parameters will be presented using descriptive statistics by visits and treatment groups. Changes relative to baseline and abnormal laboratory values will also be provided. The data on the number of subjects with abnormal laboratory values will be generalized for the whole study period, by visits and treatment groups. All laboratory findings will be presented as lists.

Vital signs will be presented using descriptive statistics by visits and treatment groups. Changes relative to baseline will also be presented.

## 9.4. Sample size justification

Rationale for sample size will be based on testing the hypothesis of statistical superiority to compare hsCRP area under curve AUC between day 1 and day 14 (primary endpoint) between each RPH-104 group and placebo. Given exploratory nature of the study, adjustment of α-level due to multiple comparisons (two RPH-104 doses and placebo) will not be used.

Assuming that the expected mean hsCRP AUC will be 350±250 mg/L for the subjects with STEMI in placebo group (according to the pilot study (Van Tassell B.W. et al., 2018) and standardized effect size (d Cohan) 0.80 for the lowest dose (conservative estimate based on (Van Tassell B.W. et al., 2018), 34 randomized subjects in each treatment group (1:1:1) (102 randomized subjects in total) will assure the study power > 90% (2-sided level α = 0.05) for comparison of lower dose

with placebo and study power > 95% to detect the expected further hsCRP AUC 50% reduction by 50% and increased effect of the higher RPH-104 dose compared to placebo.

Given proportion of withdrawals and/or 20% statistical analysis (conservative estimate), the study power > 80% will be maintained for all comparisons.

Given potential screening failures of up to 30%, the study will enroll not more than 146 subjects.

## 9.5. Applied level of significance

Probability of type I error (two-sided level of significance) is established at 5% level for all comparisons. Due to exploratory nature of the study, adjustments for multiple comparisons are not planned.

## 9.6. Reporting deviations from the initial analysis plan

Deviations from the planned statistical analysis will be agreed with Sponsor and reflected in the study report.

## 9.7. Interim analysis

After the last subject completes 28-day follow-up period, an interim analysis of hsCRP, BNP and NT-pro-BNP will be performed after 14 and 28 days of the study. Based on this analysis, decision on the study termination will not be taken. The analysis results may be used to define the strategy for further RPH-104 development.

Population for performing an interim analysis – Full Analysis Set.

During the interim analysis the primary efficacy analysis will be performed (see section 9.3.3.1). This analysis will be performed only once and will not be repeated during the final analysis stage. Sensitivity analysis can't be done during the interim stage and will be performed during the final analysis stage.

Secondary efficacy variables (AUC from day 1 to day 28) will be derived and analysed for parameters hsCRP, BNP and NT-pro-BNP at the interim analysis stage (see section 9.3.3.2). This analysis will be performed only once and will not be repeated during the final analysis stage.

Values at visits (Day 1 – baseline, Days 3, 14 and 28) and changes from baseline (Days 3, 14 and 28) will be described for hsCRP, BNP and NT-pro-BNP parameters using descriptive statistics upported with graphics.

All individual subject's data will be kept blinded for the Sponsor and all other staff involved into the data review except unblinded statistician.

## 9.8. Independent study clinical outcome assessment committee

An independent study outcome assessment committee (ISOAC) will be arranged to assure reliability and quality of data on assessment of cardiovascular and other Protocol-defined outcomes as efficacy parameters. The committee will include three independent cardiologists with the relevant qualification for outcome classification according to terminology criteria 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials (Hicks K.A.et al., 2018) (see Attachment 1). Outcome classification will be blinded. ISOAC-defined outcome classification will be considered to be final for the purpose of the study result analysis. The committee shall convene in accordance with the approved work plan. The information on the composition, procedures and decisions of ISOAC will be included into the study report.

# 10. Quality control and quality assurance

## 10.1. General quality assurance information

Sponsor should establish relevant quality assurance and control system for the performance of this clinical study in accordance with the study Protocol, Good Clinical Practice and current regulations of the RF, EAEU and USA.

The study procedures specified in the Protocol should be followed strictly by Investigator and investigator's team members.

## 10.2. Quality assurance

According to ICH GCP and regulatory requirements, Sponsor, third party on his behalf, regulatory authorities or Ethics committees may perform audits (inspections) to assure quality at any time throughout the study or after the study termination. The investigator should provide auditors with direct access to the study-related documents including source documents and allow his own and his personnel time to cooperate with the auditors when discussing audit and inspection results and other issues.

## 10.3. Selection of the study sites

Selection of the study sites will be approved by Sponsor prior to the study to assure availability of the necessary personnel and evaluation of feasibility of the study by this personnel according to Good Clinical Practice guidelines adopted at the International Conference on Harmonization (ICH GCP E6 in the current version), applicable regulations of the RF, EAEU and USA.

## 10.4. Protocol compliance by the investigator

Prior to the study, the investigator should be familiar with the Protocol conditions, accept them and perform the study in accordance with the Protocol, ICH GCP and other applicable regulations of the participating country.

During the study, the Protocol deviations are not allowed except for the cases when it is necessary to prevent any direct risk for the subject.

The investigator should have enough time for accurate performance and completion of the study within the time frames agreed by Sponsor and have sufficient number of qualified employees and adequate equipment required for the study performance per Protocol.

Each co-investigator involved in the study should be familiar with the Protocol requirements and his obligations during the study. Delegation of any activities in the study to co-investigators will be documented by the principal investigator in writing in the relevant section of Investigator's Site File.

Decision on early withdrawal of the subject in each study site should be agreed by Sponsor.

If the decision to withdraw a subject was made by the Investigator, he should notify the Sponsor's representative by sending an email specifying the reason thereof. Within 48 hours excluding weekend and public holidays after the letter receipt, Sponsor will inform on his consent for the subject's withdrawal. If immediate withdrawal is required due to serious adverse events, the Investigator will notify Sponsor on SAE within 24 hours, however, without waiting for Sponsor's consent for the subject withdrawal.

In case of loss of contact with the subject or modification of doses of the study product not stipulated by the Protocol, the Investigator should notify Sponsor within 24 hours after becoming

aware of the violation to obtain instructions on further management of the subjects and recording deviations from the Protocol in CRF/source documents.

In case of violation of the above-mentioned agreement procedures or multiple Protocol deviations, temporary or final study termination in this study site will be considered.

## 10.5. Protocol deviations

Protocol deviation denotes any change, non-conformance or deviation from the study design or study Protocol procedures.

Any deviation from the Protocol during the clinical study should be recorded and added into study-related documents.

For the USA only. By signing a copy of the FDA 1572 form or other country-specific regulatory forms, the Principal Investigator confirms that he/she has received a copy of the Investigator's Brochure for RPH-104 and assures the Sponsor that he/she will comply with the Protocol and provisions included in the FDA 1572 form or other country-specific regulatory forms. No changes to this Protocol may be made without the written consent of the Sponsor.

## 10.6. Investigator's responsibility for Protocol violation

Non-compliance with the Protocol, standard operating procedures (SOPs) and/or relevant regulations by the Investigator/study site personnel, contract research organization (CRO) or Sponsor's officers should result in immediate Sponsor's actions designed to assure their fulfillment.

Where serious and/or recurrent cases of non-compliance with the relevant requirements by the Investigator/medical institution are identified during monitoring or audit, Sponsor should discontinue participation of the breaching party in the study. If participation of the Investigator/study site was terminated due to serious or recurrent cases of non-compliance, the Sponsor should notify the competent authorities thereof.

## 10.7. Study monitoring

The study will be monitored by blinded and unblinded monitors appointed by the Sponsor. The blinded monitor, as well as the blinded members of the study team, will not have access to any data that allows to determine the treatment group assigned by the IWRS to participants of the clinical study. The unblinded monitor will monitor the compliance of the study drug administration with the Protocol, as well as the accountability of the study drugs.

Prior to the study at the initiation visit to the site or at the meeting of Investigators representative of Sponsor (monitor or clinical study manager) or CRO appointed by Sponsor will conduct training in the Protocol and CRF completion for the Investigators and site personnel. During the study the study site monitor will make regular visits to the site to check completeness of the subject documents, accuracy of the information in CRF, compliance with the Protocol and Good Clinical Practice requirements, course of subject recruitment, product storage, issue and product reporting as per requirements. Remote monitoring may be used for these purposes, if necessary (for example, if administrative or sanitary and epidemiological restrictions are imposed in connection with the current epidemic situation associated with the SARS-CoV-2 coronavirus). The key site members should attend any monitoring visits to cooperate with the monitor and solve the issues arising.

Remote monitoring, if necessary, will be carried out using the appropriate module of the electronic data acquisition system. The investigator will upload anonymized copies of the source documents of patients to this module for verification of the source data, as well as copies of other documents required for remote verification by the monitor. These documents will be temporarily stored in the

data collection system, in the remote monitoring section. Upon completion of the scheduled check and resolution of all issues, copies of all documents will be removed from the system by the responsible data manager.

Monitoring of clinical study shall be carried out by Sponsor or authorized organization (CRO) for:

- assurance of protection of rights and health of the study subjects;
- control of accuracy and reliability of data in CRFs with respect to the data in source documentation;
- control of compliance of the investigator, members of Investigator's team with the approved Study Protocol, Amendments to the Protocol in the current version (if applicable), Good Clinical Practice and current regulations.

Clinical study monitoring shall be performed according to the approved plan. Clinical study monitor/manager should assure proper performance and documentation of the study. Clinical study monitor/manager will be responsible for the following:

- Check availability of the relevant Investigator's qualification and sufficient resources including laboratories, equipment and personnel throughout the study;
- Performs control the study product (conditions and terms of storage, sufficient amount of the products in the study site, correct prescription of the study product, product accounting);
- Check compliance of the approved Protocol and all amendments thereto by the Investigator (if applicable);
- Control timely, i.e. prior to the subject initiation of the study, signing Patient Information Sheet and ICF;
- Assure availability of the current version of the documents for the clinical study performance to the Investigator (Protocol, amendments thereto (if applicable), Investigator's Brochure, Patient Information Sheet and ICF);
- Assure sufficient awareness of the investigator and investigator's team members concerning the study;
- Monitor performance of the Investigator's and his team member's obligations according to the Protocol and other applicable agreements/contracts between Sponsor and Investigator/medical institution and independence of their roles (identification of delegation of Investigator's roles to unauthorized persons);
- Monitor compliance of selection criteria by the Investigator;
- Notifies Sponsor on the rate of subject recruitment into the study;
- Monitors accuracy and completeness of data in CRF, source documents and other study-related records by their reconciliation;
- Informs the Investigator on any errors, omissions and illegible records in CRFs;
- Controls observance of the terms of reporting adverse events determined by the Protocol;
- Checks keeping the main documents by the investigator;
- Notifies the Investigator on deviations from Protocol, SOPs, regulations and take necessary measures to prevent repetition of similar deviations.

The Investigator should keep source documents containing the data on each subject, and records made at the visits (hospital or clinic medical documents) including demographic and medical information, laboratory test findings, electrocardiograms and any other tests or examinations. Any CRF information should originate from the source documents of the subject. Furthermore, the Investigator should keep the original ICF (the second copy of signed ICF will be issued to the subject).

The Investigator should provide the monitor with access to all the subject's source documents for confirmation of compliance of source document data with CRF data. The Investigator should assure timely CRF filling prior to monitor or clinical study manager visit.

To confirm compliance of the study with Helsinki Declaration, ICH GCP, regulatory requirements of the member states and study Protocol as well as identity, accuracy and completeness of data, the clinical study monitor/manager will check CRFs and other study-related documents by verifying the source data.

By the end of the study, the Sponsor representative (clinical study monitor/manager) should make a visit to the site for Study termination visit.

## 10.8. Sponsor's audit

Sponsor's audit will be made separately and independently of the routine roles of monitoring and quality control of the clinical study. The audit purpose is to evaluate compliance of the study with the Protocol, SOPs and regulations.

To perform audit, the Sponsor defines the persons not related to the clinical study.

Sponsor should make sure that auditors are duly qualified to perform audit in the relevant manner. Auditor's qualification should be documented.

Sponsor or authorized company will develop the audit plan and the study audit procedures according to which the audit will be performed.

## 10.9. Study termination

Sponsor may suspend or terminate the study for safety, ethical reasons, for the Protocol compliance issues or for any other reasons. In case of such necessity, Sponsor will take measures to notify the site in advance. If the study is suspended or terminated, Sponsor and investigator will be responsible to inform Ethics Committees and regulatory authorities in a timely manner. In such cases, Sponsor should receive all the study-related data and all unused study products should be returned to Sponsor.

# 11. Ethics

## 11.1. Ethics aspects of the study

The study will be carried out in accordance with the ethical principles outlined in the Declaration of Helsinki of the World Medical Association, ICH GCP guideline and applicable regulations of the participating states.

The final version of the Protocol including Patient Information Sheet and ICF will be submitted for approval to regulatory authorities of the participating states and to ethics committees (see section below) of the study sites prior to the study start.

*All subsequent amendments to the Protocol* concerning not only administrative aspects should also be approved before their introduction in accordance with the procedure specified.

Obtaining informed consent from the subjects will be made prior to any study-related procedures. Patient Information will contain all the data on the clinical study required for making a reasonable and independent decision.

During the study all SAEs will be reported within 24 hours to the Sponsor who, based on analysis of the reports, may decide to suspend the study. The Ethics Committee will also be notified of SAEs, unexpected and related to the study product, according to the investigators.

The data identifying the subjects will be confidential and may only be disclosed in cases stipulated by law and on the decision of judicial authorities only. Study subjects will be insured according to local regulations.

## 11.2. Local Ethics Committee / Institutional Review Board

The study must be approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) formed according to the established procedure. Approval is required for the study Protocol, Protocol amendments, Patient Information Sheet with ICF, promotional materials. No study drugs will be sent to the site until the Sponsor or its representative receives a written permission from the IEC/IRB. The principal investigator or its designated person will provide the Sponsor or its representative with a copy of the approved Patient Information Sheet with ICF prior to the start of the study.

The investigator, in collaboration with the Sponsor or designated person, will be responsible for informing the IEC/IRB of all changes during the study, including amendments to the Protocol, updates to the investigator's brochures, IND safety reports (for the USA only), all unforeseen problems associated with risks for study participants, and termination of the study. The investigator will also be responsible for providing reports on the progress of the study to the IEC/IRB at regular intervals appropriate for the degree of risk to the participants involved, but at least once a year. Copies of all notifications and IEC/IRB approvals (if necessary) will be sent to the study monitor.

Only for the USA. The requirements for approval of study documents by the institution, as set out in section 21 of the Code of Federal Regulations (21 CFR), part 56, will be followed. The Protocol, Patient Information Sheet with ICF, investigator's brochure and other necessary documents must be approved by the Local Ethics Committee/Institutional Review Board (LEC/IRB) before the start of study enrollment. The sponsor or designated person must confirm that the LEC/IRB complies with the general standards regarding the composition, operation and responsibilities of the LEC/IRB as set forth in the ICH GCP Guideline, Sections 3.1 - 3.4, and 21 CFR, Part 56.

## 11.3. Confidentiality of the study subjects

The investigator will be responsible to observe confidentiality of the subjects, text of this Protocol and any other study materials and results.

The investigator should ensure confidentiality of the subjects. CRFs and other documents provided to Sponsor should identify the subjects by their identification numbers and codes rather than by their names or surnames.

The investigator should keep a special identification log of subjects' numbers, surnames, addresses and phones and numbers of case histories (if applicable). The investigator should observe strict confidentiality of the data not designed for submission to Sponsor.

All the study materials belonging to Sponsor may not be submitted to third parties except for the cases stipulated by applicable laws.

## 11.4 Informed Consent

Before obtaining an informed consent, the investigator or an authorized person should provide the subject with the study-related information in the language and at the complexity level understandable to the subject both verbally and in writing.

Prior to any study procedures are carried out, the subject should give his consent to participate in this study in writing by signing two copies of Informed Consent Form (ICF). The subject shall be

provided with Patient Information Leaflet with ICF reflecting complete, objective, authentic, adapted information on the study including the data on:

- absolutely voluntary nature of the decision to participate in the study and ability to discontinue the study at any time without explanation of reasons;
- purposes of the clinical study, its nature and all aspects;
- therapy options during the study and the chances to be randomly assigned into one of the study groups;
- study procedures;
- expected risks and benefit of participation in the study, study-related discomfort;
- subject's obligations during the clinical study;
- alternative treatments in addition to the one stipulated by the Protocol, available procedures and treatment methods;
- the number of subjects to be enrolled;
- suggested duration of the subject's participation in the study;
- presentation of additional information during the study;
- procedure of medical assistance to the subject or reimbursement of expenses to such assistance in case of health damage of the subject during the study, terms of medical assistance;
- insurance of the subject, insurance terms and any guarantees, provision of the insurance company address (if required by the local regulations);
- confidentiality terms.

The investigator will explain that the subject will be entitled to refuse to participate or recall their consent at any time without any consequences for their further therapy and without providing a reason.

Each subject should be given an opportunity to discuss the study or its alternatives with the investigator.

If a patient agrees to participate in the study, he/she has to sign and date the Informed Consent Form for participation in the study in two copies.

Investigator shall also sign and date both copies of ICF thus evidencing that the consent has been obtained and the subject had an opportunity to ask questions and received full answers.

The subject should have one dated original of the ICF. The second original copy should be added to the trial file by the investigator. When giving informed consent, the subject should provide a consent for direct access to his medical information for the study monitoring and audit and inspection by IEC/IRB and/or authorities.

The study subject should be informed in a timely manner on new information which may affect his/her willingness to participate in the study. Transfer of this information will be documented in new version of Patient information leaflet with ICF which should be signed by the study subject and investigator in two copies specifying the date.

# 12. Data handling and record keeping

## 12.1. Direct access to source data / documentation

Source data include the information contained in original medical records and their certified copies describing the results of clinical observations, examinations and other activities allowing reproducing the course of the clinical study and evaluating its quality. Source data are contained in source documentation (original or certified copies) and in electronic format. Source documents

include the original copies of documents related to the study, treatment, patient's medical history and the description of the patient's condition. For example, a medical record and discharge summaries with the results of laboratory tests are source documents.

The investigator or the study site should not interfere with direct access to the source data/documents for the study-related monitoring, audit, ethical inspection and inspection by competent authorities.

## 12.2. Record keeping in the study site

All the study-related documents should be archived in the study site or central archive of the Institution. Thorough list of all ID data on the study subjects is required.

According to ICH GCP, the requisite documents include: signed Protocol and all amendments thereto, copies of filled CRFs, signed ICFs of all the subjects, case histories and other source documents, approvals by ethics committees and regulatory authorities and all the correspondence with them including approved documents, product handling records, study correspondence and list of the subjects' surnames and addresses. This list is the key one in the documents to be stored by the investigator.

Accurate and precise records of the study course are the responsibility of the investigator. Source documents will be maintained according to the regulatory requirements. Records in the source documents will be made at each examination of the subject. The relevant data will be transferred to eCRF within the terms specified in SOPs of CRO/Sponsor/Clinical site or other documents.

If corrections in the source documents are required, the incorrect record should be deleted with a single horizontal line and the correct record will be written close to it specifying the date of correction, the correcting person's initials and signature. Any means deleting the previous record or making it illegible are not allowed.

## 12.3. Data collection

Electronic versions of CRF (eCRF) will be used in this study. Principal investigator will be responsible for completeness and accuracy of all the data in eCRF and timeliness of data entry and update.

The monitor will be responsible to check eCRF for completeness and accuracy of records, instruction of the site personnel on necessity to make relevant corrections or additions.

## 12.4. Database management and quality control

In the studies using eCRFs the Sponsor (or appointed CRO) representatives will analyze the data entered by the site personnel for accuracy and completeness. In case of discrepancies or missing values, queries for data will be generated specifying the nature of the issue and required clarification. These queries will be forwarded to the study site. The appointed study site officer is required to provide responses to the queries and make any necessary amendments immediately.

By the end of the study, any Protocol deviations will be determined. By the end of these actions and confirmation of database completeness and accuracy, it will be locked and prepared for data analysis.

After database lock, the Investigator will receive a CD or paper version of subject data for archiving in the study site.

## 12.5. Data confidentiality

Information about the study participants will be kept in compliance with confidentiality requirements. When processing it, applicable laws and regulations will be observed.

In order to prevent unauthorized access to confidential information about the study participants, security elements are built into the data collection system for this study to encrypt all data when they are transmitted in both directions. Access to the system will be controlled using a sequence of individually assigned user identification codes and passwords, which will be provided only to authorized employees.

In the case of remote monitoring, the investigator shall provide the monitor with depersonalized copies of the patients' source documents for verification of the source data. These source documents will be temporarily stored in the data collection system in the section for remote data verification. Upon completion of data verification and resolution of all questions regarding this data, the uploaded copies of the source documents will be deleted from the system by the responsible data manager. Data turnover during remote monitoring will be carried out in accordance with the regulatory requirements of the country where the study is being conducted.

## 12.6. Document archiving

The investigator must organize the retention of study documentation in the study site. The scope of documentation and its shelf life should comply with the requirements of the relevant regulatory authority, but should not be less than 2 years after receiving the first approval of the drug. In addition, the shelf life must meet the strictest applicable regulatory requirements. The investigator must take measures to prevent accidental or premature destruction of these documents.

By signing the Protocol, the Investigator shall give his consent to comply with the document storage and archiving procedures. Source documentation and investigator's site file will be subject to storage including subject identification list and study-related correspondence. The study subject documents will be archived according to the Study site rules.

The investigator should notify Sponsor on the place of storage of the relevant documents and contact Sponsor to obtain approval prior to destroying any of them. Investigator should take measures to prevent accidental or early destruction of these documents.

Sponsor will be responsible for archiving Clinical Trial Master File.

If Sponsor terminates clinical development of the study product, the Investigator and regulatory authorities will be notified thereof.

# 13. Financing and insurance

This clinical study will be financed by Sponsor.

The subjects will not be compensated for participation in this study.

During the study, the subjects will be insured as the study subjects according to the laws of the country participating in the study.

If health damage occurred due to administration of the study product or medical procedure per study Protocol, the subject will receive free qualified medical care as appropriate.

# 14. Protocol amendments

Modifications of the Protocol can only be done by the Sponsor, except in cases where it is necessary to reduce the inevitable risk for the subjects of the study. A change in the Protocol in order to prevent obvious acute danger to subjects may be made without delay, provided that the

LEC is informed within 5 days. Any fixed change to the Protocol will be in the form of an amendment. A proposed Protocol amendment should be submitted to the LEC and investigators should wait for its approval before starting to apply it. The Sponsor will file Protocol amendments with the relevant regulatory authorities for approval.

If, in the opinion of the IEC, investigators, or the Sponsor, a Protocol amendment significantly changes the design of the study, increases the potential risk for the study participants, or affects the inclusion of patients in the study, similar changes will need to be made to the current approved version of the ICF. In such cases, patients included in the study will need to sign a new approved version of the ICF.

# 15. Study report and publications

The investigator must understand that data obtained during the study can be used by the Sponsor or its agent for presentation to other investigators or governmental organizations. It should be understood that all data obtained during the study should be provided at the first request of the Sponsor.

The representative of the Sponsor, as well as the representatives of authorized state institutions, should have access to any primary sources of documents; however, the anonymity of the study participants should be respected as a professional requirement.

The Principal Investigator and his/her colleagues may subsequently publish additional results of this study in scientific journals or present them at scientific conferences, provided that the Sponsor is given the full opportunity to review any proposed abstract, manuscript or presentation of slides before they are submitted. This review is necessary to ensure that the Sponsor is aware of all oral or written representations of the data and does not imply any editorial revision or restriction of the contents of the presentation or use. The authorship of any publication will be agreed with all other investigators and the Sponsor. In accordance with the uniform requirements for manuscripts submitted to biomedical journals published by the International Committee of Medical Journal Editors, investigators whose contribution is solely in data collection will not be named individually as authors. Such investigators will rather be co-authored as the “RPH 104 Study Group” and will be indicated in a note.

The investigator must not publish results of this study, including those obtained at his/her study site, without the consent of the Sponsor. Results obtained in a separate study site should not be published before publication of the general results of the study.

The results of the study will be published to the extent and at the times established in accordance with the Sponsor's publication policy.

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# 17. Appendix 1. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials

(translation of extracts from publication by Hicks K.A.et al., 2018)

**Definition of cardiovascular death**

**Cardiovascular death** includes death due to acute myocardial infarction (MI), sudden cardiac death, death from heart failure (HF), death from stroke, death from cardiovascular (CV) procedures, death from CV hemorrhage and other CV death**.**

More specific classification of cardiovascular death (MI, sudden death, etc.) in outcome studies is not generally required. Furthermore, such classification is difficult as it refers to both principal cause (e.g. acute MI which may cause fatal arrhythmia or HF) and to death (sudden, arrhythmic; HF due to MI or aggravated HF) which are mostly overlapping. However, the following definitions may be used as necessary.

1. **Death due to acute myocardial infarction** belongs to any cardiovascular death (e.g. arrhythmia, sudden death, HF, stroke, pulmonary embolism, peripheral artery disease) within 30 days after MI[4] associated with direct consequences of MI including progressive HF and refractory arrhythmia. We noted that mechanisms of CV death may be currently under assessment, however, for convenience, if CV death occurs within 30 days post MI, it will be considered to be MI-related death.

   Acute MI should be confirmed by diagnostic criteria of acute MI where possible (see Definition of MI in publication by Hicks K.A.et al., 2018 and publication by Thygesen K. et al., 2018) or by the results of autopsy suggesting a previous MI or coronary artery thrombosis.

   Death due to MI therapy procedure (percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) or treatment of MI-related complication should also be considered as death due to acute MI.

   Death due to coronary procedure for the treatment of myocardial ischemia (i.e. chronic stable angina) or death due to MI as a result of CV examination/procedure/surgery should be considered as death due to treatment of CV pathology.

2. **Sudden cardiac death** means sudden death outside of 30-day period post acute MI. Sudden cardiac death includes the following scenarios:

[4] 30-day period is voluntary

a. Death which was certified and occurred without development or aggravation of symptoms

b. Death was certified within 60 min after development or aggravation of cardiac symptoms if the symptoms do not verify acute MI

c. Death certified and caused by identified arrhythmia (e.g. recorded at electrocardiogram (ECG), recorded on the monitor or not certified but detected at inspection of implantable cardioverter defibrillator)

d. Death after unsuccessful resuscitation at cardiac arrest (e.g. sudden cardiac death without response to implantable cardioverter defibrillator (ICD), electric activity arrest without pulse)

e. Death after successful resuscitation at cardiac arrest without determination of specific cardiac or non-cardiac etiology

f. Uncertified death of the subject who was seen alive and clinically stable within 24 hours before he/she was found dead, without any evidence of a specific non-cardiovascular cause of death (where appropriate, the information on the subject's clinical status should be provided)

**General provisions**

- If additional information does not suggest an alternative cause of death (e.g. other cardiovascular death), if the subject was seen alive within 24 hours before he/she was found dead, sudden cardiac death (2f criterion) should be recorded. For the subjects who were not seen alive within 24 hours before death, the cause of death should be recorded as undefined (e.g. the subject found dead in his/her bed if the family did not see him/her for more than 24 hours).

3. **Death from heart failure** means death due to clinical aggravation of the symptoms and/or signs of HF regardless of etiology of HF (see Heart failure definition). HF death may have various etiologies including single or recurring MI, ischemic or non-ischemic cardiomyopathy, hypertension or heart valve disease.

4. **Death from stroke** means death post stroke which is a direct consequence of stroke or its complication. Acute stroke should be verified using diagnostic stroke criteria where possible (see Appendix 8 of publication by Hicks K.A.et al., 2018).

5. **Death from cardiovascular procedures** means death caused by direct complications of a cardiovascular procedure**.**

6. **Death from cardiovascular hemorrhage** means death associated with a hemorrhage including non-stroke intracranial hemorrhage (e.g. subdural hematoma) (see Appendix 8 to publication by Hicks K.A.et al., 2018), non-procedural or non-traumatic vessel rupture (e.g. aorta aneurysm) or hemorrhage causing cardiac tamponage.

7. **Other cardiovascular death** refers to death from CV pathologies not included into the categories above where there is a certain known cause (e.g. pulmonary embolism or peripheral artery disease).

**Definition of non-cardiovascular death**

**Non-cardiovascular death** is any death with a specific cause which in its nature is not associated with a cardiovascular pathology as specified in Definition of cardiovascular death. Detailed recommendations on classification of non-CV causes of death are beyond this document. The required level of details and optimal classification will depend on the nature of the study population and expected number and type of non-CV deaths. Any specific expected safety issue should be added as an individual cause of death. Below is the recommended list of causes of non-CV death.

- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (including sepsis)
- Inflammatory (e.g. systemic inflammation response syndrome (SIRS)/Immune (including autoimmune) (may include environmental anaphylactic reaction (e.g. food allergy))
- Bleeding other than CV hemorrhage or stroke (see Definition of cardiovascular death, Section 6 and Appendix 8 of publication by Hicks K.A.et al., 2018)
- Procedure or surgery not associated with a CV pathology
- Injury (including murder)
- Suicide
- Response to OTC product or overdose
- Response to an OTC product or overdose (may include anaphylactic reaction)
- Neurological (non-CV) (other than CV death due to ischemic stroke, hemorrhagic stroke or stroke for unknown cause or CV hemorrhage into central nervous system)
- Malignant tumour (e.g. leukemia, lymphoma or another malignant tumour)

- Another non-CV cause (specify): _____

**Definition of uncertain cause of death**

**Undefined cause of death** refers to death not related to any of the CV or non-CV death categories above. Inability to classify the cause of death may be due to lack of information (e.g. the only available information is "the subject died") or due to deficit of additional information or data to determine the cause of death. Overall, most deaths should be classified as CV-related or non-CV-related, therefore this category of death is not encourage and should only be used in rare cases in well-designed clinical studies.

General analytical approach to analysis of death causes consists in assumption that all unexpected cases belong to CV category (e.g. supposed CV death, particularly "other CV death"). Nevertheless, the relevant classification and analysis of undefined causes of death depend on the population, study intervention, follow-up period and disease course (assumption that CV death is unlikely, e.g. in subjects with advanced oncology, advanced pulmonary disease, long-lasting infection, etc.). The approach should be pre-defined and described in the Protocol and other study-related documents including determination of endpoint and/or statistical analysis plan.

**Definition of hospitalization due to unstable angina**

**Unstable angina requiring hospitalization** includes

1. Ischemic discomfort (angina pectoris or equivalent symptoms) ≥ 10 minutes
    - at rest or
    - with increased intensity and frequent episodes associated with progressive reduction of physical exercise.

**AND**

2. Unscheduled hospitalization **within 24 hours** since the last symptom. Hospitalization is defined as admission to a hospital or intensive care unit with at least 24-hour stay (or change of calendar date if the time of hospitalization or time of discharge is lacking).

**AND**

3. At least one of the below-mentioned:

   a. New change in ST or T-wave or their aggravation on ECG at rest (with no confounding factors including left bunch branch block or left ventricular hypertrophy)

      - Temporary ST elevation (< 20 min)

        New ST elevation at J-point on two adjacent electrodes with separation point: ≥ 0.1 mV for all electrodes except for V2-V3 to which the following separation points are applicable: ≥ 0.2 mV for males aged ≥ 40 years old (≥ 0.25 mV for males aged < 40 years old) or ≥ 0.15 mV for females.

      - ST depression and modification of T-wave

        New horizontal or descending ST depression ≥ 0.05 mV on two adjacent electrodes and/or new inversion of T-wave ≥ 0.3 mV on two adjacent waves with marked R-wave or R/S > 1.

   b. Myocardial ischemia is definitely suspected by:

      - early positive physical exercise test, i.e. ST elevation or ST depression ≥ 2 mm up to 5 metabolic equivalents

      **OR**

      - stress-echocardiography (reversible wall movement deviation) **OR**
      - myocardial scintigraphy (reversible perfusion defect) **OR**
      - MRI (deficit of myocardial perfusion at pharmacological burden).

      **and** presumed association with the symptoms/signs of myocardial ischemia.

   c. Angiographic evidence of a new lesion site or aggravation a pre-existing site ≥ 70% (≥ 50% for left main site) and/or clot in epicardial coronary artery presumably responsible for myocardial ischemia symptoms/signs.

   d. Necessity in coronary revascularization (PCI or CABG) due to the site causing acute condition according to 3c criterion. This criterion will be met if revascularization was carried out during unscheduled hospitalization or after transfer to another facility without prior discharge.

**AND**

4. Negative cardiac biomarkers and lack of MI evidence

**General provisions**

1. Escalation of pharmacotherapy at ischemia including intravenous administration of nitrates or elevation of β-adrenoblocker dose should be considered as supporting but not diagnosing unstable angina. However, typical treatment and hospitalization with pharmacotherapy escalation without any additional results outlined in category 3 are insufficient to verify classification of hospitalization due to unstable angina.

2. If the subjects are admitted with suspected unstable angina and further testing reveals non-cardiac or non-ischemic etiology, this event should not be recorded as hospitalization due to unstable angina. Potential ischemic events meeting MI criteria should not be considered as unstable angina.

3. Scheduled hospitalization or repeated hospitalization for scheduled revascularization in subjects not meeting unstable angina criteria should not be considered as hospitalization due to unstable angina. For example,

- Hospitalization of a subject with stable effort angina for coronary angiography and PCI based on positive outpatient stress test should not be considered as hospitalization due to unstable angina.

- Repeated hospitalization of a subject meeting the criteria of unstable angina which has been stabilized, with further discharge and repeated hospitalization for revascularization is not a second hospitalization due to unstable angina.

4. A subject undergoing elective catheterization after coronary artery disease is diagnosed and further undergoing coronary revascularization does not meet hospitalization criteria for unstable angina.

**Definition of heart failure**

**Heart failure** includes hospitalization due to heart failure and may include emergency outpatient visits. Hospitalization due to HF should be isolated from emergency visits. If emergency visits are included into HF endpoint, the number of emergency visits should be specified separately from hospitalizations.

**Hospitalization due to heart failure** is an event meeting **ALL** the criteria below:

1) The subject is hospitalized with ***primary diagnosis*** of HF

2) Hospitalization period is **at least 24 hours** (or change of calendar date if admission and discharge time are lacking)

3) Upon admission the subject has new or aggravated pre-existing symptoms due to HF including **at least ONE** of the following:

   a. Dyspnea (exertional dyspnea, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
   b. Decreased exercise tolerance
   c. Fatigue
   d. Other symptoms of decreased perfusion of the target organ or volume overload (should be specified or described in the Protocol)

4) The subject has objective evidence of a new or aggravated pre-existing HF including **at least TWO** results of physical examination **OR** one result of physical examination and **at least ONE** laboratory test) including:

   a. Results of physical examination associated with heart failure including development of new or aggravation of pre-existing:

      i. Edema peripheral
      ii. Progressive bloating or ascites (without underlying liver disease)
      iii. Pulmonary rales/sounds
      iv. Increased jugular vein pressure and/or hepatojugular reflux
      v. Third heart sound gallop rhythm
      vi. Clinically relevant or rapid body weight gain presumably due to fluid retention

   b. Laboratory evidence of a new or aggravated pre-existing HF when obtained within 24 hours post admission including:

      i. Increased level of natriuretic peptide B (BNP)/N-terminal fragment BNP (NT-proBNP) correlates with heart failure decompensation (e.g. BNP > 500 pg/mL or NT-proBNP > 2000 pg/mL). Subjects with chronically increased natriuretic peptide level should have significant increase above baseline.

      ii. Radiological confirmation of pulmonary congestion

      iii. Non-invasive diagnostic evidence of clinically relevant increased left or right ventricular filling pressure or low cardiac output. E.g. echocardiographic criteria may include: septal or lateral E/e'> 15 or > 12, respectively; D-dominant nature of pulmonary venous inflow; plethoric inferior vena cava with minimum collapse at inspiration; or moderate

minute distance of left ventricular outflow tract (LVOT) (time-velocity integral [TVI])

**OR**

iv. Invasive diagnostic evidence with right cardiac catheterization demonstrating wedge pressure in pulmonary capillary (pulmonary artery occlusive pressure) ≥ 18 mm Hg, central venous pressure ≥ 12 mm Hg or cardiac index <2.2 L/min/$m^2$

**Note: All results of diagnostic tests should be reported if any, even if they do not meet the criteria above as they provide important information to decide on these events.**

5) The subject receives **at least ONE** of HF treatments below:

a. Significant intensification of oral diuretic therapy (e.g. doubling dose of a loop diuretic, initiation of supporting therapy with a loop diuretic, initiation of combined diuretic therapy)
b. Initiation of intravenous administration of a diuretic (even at a single dose) or vasoactive product (e.g. inotropic, vasoconstrictive, vasodilating agents)
c. Mechanic or surgical intervention including:
    i. Mechanical circulatory support (e.g. aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, artificial heart)
    ii. Mechanic fluid elimination (e.g. ultrafiltration, hemofiltration, dialysis)

**General considerations (hospitalization due to HF)**

Combined diuretic therapy may include 1) thiazide diuretic (e.g. hydrochlorothiazide, metolazone, chlorothiazide) + loop diuretic; or 2) mineralocorticoid receptor antagonist (MCRA) (e.g. spironolactone or eplerenone) + loop diuretic.

**Emergency visit due to heart failure** is an event meeting all the criteria below:

1) The subject seeks urgent unscheduled assistance from a physician or in an intensive care unit with the primary HF diagnosis but does not meet criteria for HF hospitalization.
2) The subject has all the signs and symptoms of HF hospitalization (i.e. 3), 4) results of physical examination/laboratory tests evidencing new or aggravated pre-existing HF as detailed above)
3) The subject receives **at least ONE** of HF treatments below:

    a. Initiation of intravenous administration of a diuretic or vasoactive product (e.g. inotropic, vasoconstrictive, vasodilating agents)*

    b. Mechanic or surgical intervention including:

i. Mechanical circulatory support (e.g. aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, artificial heart)
ii. Mechanic fluid elimination (e.g. ultrafiltration, hemofiltration, dialysis)

*** Note that significant intensification of oral diuretic therapy is NOT sufficient to meet urgent HF visit criteria.**

**General considerations (urgent HF visit)**

1. Clinical visits for ***scheduled*** therapy or procedures associated with HF (e.g. intravenous administration of diuretics, intravenous administration of vasoactive agents or mechanical fluid elimination) are **NOT** qualified as HF without hospitalization.

**Definition of Stroke and Transient Ischemic Attack**

**Introduction**

These definitions of Stroke and Transient Ischemic Attack apply to a wide range of clinical trials. They are general, overarching, and widely applicable definitions combined with a specific clinical measurement of disability. They are flexible in their application and consistent with contemporary understanding of the pathophysiology of stroke. This approach enables clinical trials to assess the clinically relevant consequences of vascular brain injury for determining the safety or effectiveness of an intervention.

The distinction between an Ischemic Stroke and a Transient Ischemic Attack is the presence of infarction. Persistence of symptoms is an acceptable indicator of acute infarction. Thus, duration of symptom persistence that will be used to distinguish between transient ischemia and acute infarction should be defined for any clinical trial in which it is used.

In trials involving patients with stroke, evidence of vascular central nervous system injury without recognized neurological dysfunction may be observed. Examples include microhemorrhage, asymptomatic infarction, and asymptomatic hemorrhage. When encountered, the clinical relevance of these findings may be unclear. If appropriate for a given clinical trial, however, they should be precisely defined and categorized.

Subdural hematomas are intracranial hemorrhagic events and not strokes.

**Transient Ischemic Attack**

Transient ischemic attack (TIA) is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, *without* acute infarction.

**Stroke**

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.

**Classification:**

**A. Ischemic Stroke**

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.

Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

**B. Hemorrhagic Stroke**

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

**C. Undetermined Stroke**

Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as either ischemic or hemorrhagic.

**Stroke Disability**

Disability should be measured by a reliable and valid scale in all cases, typically at each visit and 90 days after the event. For example, the modified Rankin Scale may be used to address this requirement:

| Scale | Disability |
|---|---|
| 0 | No symptoms at all |
| 1 | No significant disability despite symptoms; able to carry out all usual duties and activities |
| 2 | Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance |
| 3 | Moderate disability; requiring some help, but able to walk without assistance |
| 4 | Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance |
| 5 | Severe disability; bedridden, incontinent and requiring constant nursing care and attention |
| 6 | Dead |

**Interventional Cardiology Definitions**

**A. Clinical Definitions**

1. **Clinically-Driven Target Lesion Revascularization:** Revascularization is clinically-driven if the target lesion diameter stenosis is > 50% by quantitative coronary angiography (QCA) and the subject has clinical or functional ischemia which cannot be explained by another native coronary or bypass graft lesion. Clinical or functional ischemia includes any of the following:

   a. A history of angina pectoris, presumably related to the target vessel
   b. Objective signs of ischemia at rest (electrocardiographic changes) or during exercise test (or equivalent), presumably related to the target vessel
   c. Abnormal results of any invasive functional diagnostic test [e.g., coronary flow reserve (CFR) or fractional flow reserve (FFR)]

   ***Comment:*** *Target lesion revascularization (TLR) of a > 70% diameter stenosis by QCA in the absence of the above signs or symptoms may be considered clinically-driven.*

   ***Comment:*** *In the absence of QCA data or if a ≤ 50% stenosis is present, TLR may be considered clinically-driven by the Clinical Events Committee (CEC) if severe ischemic signs and symptoms attributed to the target lesion are present.*

2. **Non-Target Lesion and Non-Target Lesion Revascularization:** A lesion for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.

3. **Non-Target Vessel and Non-Target Vessel Revascularization:** A vessel for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.

4. **Percutaneous Coronary Intervention (PCI) Status:**

   a. **Elective:** The procedure can be performed on an outpatient basis or during a subsequent hospitalization without significant risk of myocardial infarction (MI) or death. For stable in-patients, the procedure is being performed during this hospitalization for convenience and ease of scheduling and **NOT** because the patient's clinical situation demands the procedure prior to discharge.

   b. **Urgent:** The procedure should be performed on an inpatient basis and prior to discharge because of significant concerns that there is risk of myocardial ischemia, MI, and/or death. Patients who are outpatients or in the emergency department at the time that the cardiac catheterization is requested would warrant hospital admission based on their clinical presentation.

   c. **Emergency:** The procedure should be performed as soon as possible because of substantial concerns that ongoing myocardial ischemia and/or MI could lead to death. "As soon as possible" refers to a patient who is of sufficient acuity that one would cancel a scheduled case to perform this procedure immediately in the next available room during business hours, or one would activate the on-call team were this to occur during off-hours.

   d. **Salvage:** The procedure is a last resort. The patient is in cardiogenic shock when the PCI begins (i.e., the time at which the first guide wire or intracoronary device is introduced into a coronary artery or bypass graft for the purpose of mechanical revascularization) **OR** within the last ten minutes prior to the start of the case or during the diagnostic portion of the case, the patient has also received chest compressions or has been on unanticipated circulatory support (e.g., intra-aortic balloon pump, extracorporeal membrane oxygenation, or cardiopulmonary support).

5. **Percutaneous Coronary Intervention (PCI):** Placement of an angioplasty guide wire, balloon, or other device (e.g., stent, atherectomy catheter, brachytherapy delivery device, or thrombectomy catheter) into a native coronary artery or coronary artery bypass graft for the purpose of mechanical coronary revascularization. In the assessment of the severity of coronary lesions with the use of intravascular ultrasound, coronary flow

reserve (CFR), or fractional flow reserve (FFR), insertion of a guide wire will **NOT** be considered PCI.

6. **Procedural Success:** Achievement of < 30 % residual diameter stenosis of the target lesion assessed by visual inspection or QCA and no in-hospital major adverse cardiac events (MACE, a composite of death, MI, or repeat coronary revascularization of the target lesion). Ideally, the assessment of the residual stenosis at the end of the procedure should be performed by an angiographic core laboratory.

   ***Comment:*** *For some device interventions (e.g., balloon angioplasty), achievement of < 50% diameter stenosis by visual inspection or QCA is an acceptable definition for procedural success.*

7. **Target Lesion:** Any lesion treated or attempted to be treated during the PCI with the study device. The target lesion includes the arterial segment treated with the study device (stent, in most cases) plus 5 mm proximal and 5 mm distal to the treatment site.

8. **Target Lesion Failure (TLF):** The composite of ischemia-driven revascularization of the target lesion, MI related to the target vessel, or cardiac death related to the target vessel. If it cannot be determined with certainty whether the MI or death was related to the target vessel, it is considered a TLF.

9. **Target Lesion Revascularization (TLR):** Any repeat percutaneous intervention of the target lesion (including 5 mm proximal and 5 mm distal to the target lesion) or surgical bypass of the target vessel performed for restenosis or other complication involving the target lesion. In the assessment of TLR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the CEC for review upon request.

10. **Target Vessel:** A major native coronary artery (e.g., left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery, or right coronary artery) or bypass graft containing the target lesion. A native coronary artery target vessel includes the arterial segments upstream and downstream to the target lesion plus major side branches.

11. **Target Vessel Failure (TVF):** The composite of ischemia-driven revascularization of the target vessel, MI related to the target vessel, or cardiac death related to the target vessel. If it cannot be determined with certainty whether the MI or death was related to the target vessel, it is considered a TVF.

12. **Target Vessel, Non-Target Lesion, and Target Vessel, Non-Target Lesion Revascularization:** Any lesion or revascularization of a lesion in the target vessel other than the target lesion, respectively.

13. **Target Vessel Revascularization (TVR):** Any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. In the assessment of TVR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the CEC for review upon request.

14. **Vascular Complications:**

- **Access site hematoma:** Development of a new, localized collection of blood at a vascular access site sufficient to produce a palpable mass within 72 hours of a procedure.
- **Arteriovenous fistula:** Development of a new, unintended communication between an artery and a vein occurring at a vascular access site within 72 hours of a procedure.
- **Peripheral ischemia:** Development of new arterial insufficiency sufficient to produce clinical signs or symptoms of ischemia (pallor, pain, paresthesia) distal to a vascular access site within 72 hours of a procedure.
- **Peripheral nerve injury:** Development of new sensory or motor loss of peripheral nerve function from external nerve compression (e.g., as a result of positioning during a procedure), or internal compression or direct nerve damage from the procedure, occurring within 72 hours of a procedure.
- **Pseudoaneurysm:** Development of a new localized collection of blood with a persistent communication (neck) originating at a vascular access site and occurring within 72 hours of a procedure.
- **Retroperitoneal hemorrhage:** Development of new bleeding into the retroperitoneal space originating at a vascular access site and occurring within 72 hours of a procedure.

**B. Angiographic Definitions**

1. **Abrupt Closure:** New intra-procedural severely reduced flow (TIMI grade 0-1) within the target vessel that persists and requires intervention by stenting or other treatment, or results in MI or death. Abrupt closure requires an association with a vascular dissection, thrombus, or severe spasm at the treatment site or within the instrumented vessel.

2. **Coronary Lesions Treated**

| Coronary Artery Segments | Definition |
|---|---|
| **Right coronary artery ostium** | **Origin of the right coronary artery, including the first 3 mm of the artery** |
| **Proximal right coronary artery** | **Proximal portion of the right coronary artery, from the ostium of the right coronary artery to** |

| | |
|---|---|
| | **the origin of the first right ventricular branch (pRCA)** |
| **Mid right coronary artery** | **Middle portion of the right coronary artery, from the origin of the first right ventricular branch to the acute margin (mRCA)** |
| **Distal right coronary artery** | **Distal portion of the right coronary artery, from the acute margin to the origin of the posterior descending artery (dRCA)** |
| **Right posterior descending artery** | **In right dominant and mixed circulations, the vessel that runs in the posterior interventricular groove and supplies septal perforator branches (PDA)** |
| **Posterolateral segmental artery** | **In right dominant circulations, the distal continuation of the right coronary artery in the posterior atrioventricular groove after the origin of the right posterior descending artery (PLSA)** |
| **First right posterolateral branch** | **In right dominant circulations, the first posterolateral branch originating from the right posterior atrioventricular artery (RPL1)** |
| **Second right posterolateral branch** | **In right dominant circulations, the second posterolateral branch originating from the right posterior atrioventricular artery (RPL2)** |
| **Third right posterolateral branch** | **In right dominant circulations, the third posterolateral branch originating from the right posterior atrioventricular artery (RPL3)** |
| **Posterior descending septal perforator** | **Septal perforator vessel originating from the posterior descending artery** |
| **Right ventricular branch** | **Branch arising from the right coronary artery to supply the right ventricular wall (RV)** |
| **Left main coronary artery ostium** | **Origin of the left coronary artery, including the first 3 mm of the artery** |
| **Left main coronary artery body** | **Body of the left main coronary artery, from the ostium to the bifurcation (LM)** |
| **Left main coronary artery bifurcation** | **Distal end of the left main, including the terminal 3 mm through the bifurcation of the left main into the left anterior descending and left circumflex arteries** |

| | |
|---|---|
| **Left anterior descending artery ostium** | **Origin of the left anterior descending coronary artery, including the first 3 mm of the artery** |
| **Proximal left anterior descending artery** | **Proximal portion of the left anterior descending coronary artery, from the ostium to the origin of the first septal (pLAD)** |
| **Mid left anterior descending artery** | **Middle portion of the left anterior descending coronary artery, from the origin of the first septal artery to the origin of the third septal artery (mLAD)** |
| **Distal left anterior descending artery** | **Distal portion of the left anterior descending coronary artery, from the origin of the third septal artery to the terminus (dLAD)** |
| **First diagonal branch** | **First of the three longest branches originating from the left anterior descending artery to supply the anterolateral wall of the left ventricle (D1)** |
| **First diagonal lateral branch** | **Branch of the first diagonal branch** |
| **Second diagonal branch** | **Second of the three longest branches originating from the left anterior descending artery to supply the anterolateral wall of the left ventricle (D2)** |
| **Second diagonal lateral branch** | **Branch of the second diagonal branch** |
| **Third diagonal branch** | **Third of the three longest branches originating from the left anterior descending artery to supply the anterolateral wall of the left ventricle (D3)** |
| **Third diagonal lateral branch** | **Branch of the third diagonal branch** |
| **Anterior descending septal perforator** | **Septal perforator vessel originating from the left anterior descending artery to supply the interventricular septum** |
| **Left circumflex artery ostium** | **Origin of the left circumflex coronary artery, including the first 3 mm of the artery** |
| **Proximal left circumflex artery** | **Proximal portion of the left circumflex coronary artery, from the ostium to the origin (or the nominal location of) the first marginal branch (pLCX)** |
| **Mid left circumflex artery** | **Middle portion of the left circumflex coronary artery, from the origins of (or nominal locations** |

| | |
|---|---|
| | **of) the first marginal to the second marginal (mLCX)** |
| **Distal left circumflex artery** | **Distal portion of the left circumflex coronary artery, from the origin of (or the nominal location of) the second marginal to the terminus (in right dominant systems), or to the origin of the 1st left posterolateral in all other dominance systems (dLCX)** |
| **First obtuse marginal branch** | **First of the three longest branches originating from the left circumflex artery to supply the lateral wall of the left ventricle (OM1)** |
| **First obtuse marginal lateral branch** | **Branch of the first marginal branch** |
| **Second obtuse marginal branch** | **Second of the three longest branches originating from the left circumflex artery to supply the lateral wall of the left ventricle (OM2)** |
| **Second obtuse marginal lateral branch** | **Branch of the second marginal branch** |
| **Third obtuse marginal branch** | **Third of the three longest branches originating from the left circumflex artery to supply the lateral wall of the left ventricle (OM3)** |
| **Third obtuse marginal lateral branch** | **Branch of the third marginal branch** |
| **Left atrioventricular artery** | **In left dominant and mixed circulations, the distal continuation of the left circumflex coronary artery in the posterior atrioventricular groove** |
| **Left posterior descending artery** | **In left dominant circulations, the vessel that arises from the distal continuation of the left atrioventricular artery, travels in the posterior interventricular groove, and supplies septal perforator branches (LPDA)** |
| **First left posterolateral branch** | **In left dominant and mixed circulations, the first posterolateral branch originating from the posterior atrioventricular left circumflex artery (LPL1)** |
| **Second left posterolateral branch** | **In left dominant and mixed circulations, the second posterolateral branch originating from the posterior atrioventricular left circumflex artery (LPL2)** |

| | |
|---|---|
| **Third left posterolateral branch** | **In left dominant and mixed circulations, the third posterolateral branch originating from the posterior atrioventricular left circumflex artery (LPL3)** |
| **Ramus intermedius branch** | **Branch vessel whose origin bisects the origins of the left anterior descending and circumflex arteries (RI)** |
| **Ramus intermedius lateral branch** | **Branch of the ramus intermedius branch** |

3. **Dissection:**

   **Based on the National Heart, Lung, and Blood Institute (NHLBI) Dissection Classification System:**

   - **Grade A:** Minor radiolucencies within the lumen during contrast injection with no persistence after dye clearance
   - **Grade B:** Parallel tracts or double lumen separated by a radiolucent area during contrast injection with no persistence after dye clearance
   - **Grade C:** Extraluminal cap with persistence of contrast after dye clearance from the lumen
   - **Grade D:** Spiral luminal filling defect with delayed but complete distal flow
   - **Grade E:** New persistent filling defect with delayed antegrade flow
   - **Grade F:** Non-A-E types with total coronary occlusion and no distal antegrade flow

   **Note:** Grade E and F dissections may represent thrombus

4. **Late Loss:** Minimum lumen diameter (MLD) assessed at follow-up angiography minus the MLD assessed immediately after the index procedure. MLDs are measured by QCA.

5. **Minimum Lumen Diameter (MLD):** The mean minimum lumen diameter (typically measured in-lesion, in-stent, and in-segment) derived from two orthogonal views by QCA.

6. **No Reflow:** An acute reduction in coronary flow (TIMI grade 0-1) in the absence of dissection, thrombus, spasm, or high-grade residual stenosis at the original target lesion.

7. **Percent Diameter Stenosis (% DS):** The value calculated as 100 x (1 – MLD/RVD) using the mean values determined by QCA from two orthogonal views (when possible).

8. **Reference Vessel Diameter (RVD):** Defined as the average of normal segments within 10 mm proximal and 10 mm distal to the target lesion from two orthogonal views using QCA.

9. **Restenosis:** Re-narrowing of the vessel following the treatment of a prior stenosis

   - **Binary restenosis:** A diameter stenosis of > 50% at the previously treated lesion site, including the originally treated site plus the adjacent vascular segments 5 mm proximal and 5 mm distal to the site.

   - **In-stent restenosis (ISR):** A previously stented lesion with a > 50% diameter. stenosis.

10. **Thrombus (Angiographic):** A discrete, mobile, intraluminal filling defect with defined borders with or without associated contrast staining.

11. **TIMI (Thrombolysis in Myocardial Infarction) Flow Grades:**

    - **Grade 0 (no perfusion):** There is no antegrade flow beyond the point of occlusion.

    - **Grade 1 (penetration without perfusion):** The contrast material passes beyond the area of obstruction but “hangs up” and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence.

    - **Grade 2 (partial perfusion):** The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) is perceptibly slower than its entry into or clearance from

comparable areas not perfused by the previously occluded vessel (e.g., the opposite coronary artery or the coronary bed proximal to the obstruction).

- **Grade 3 (complete perfusion):** Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved bed in the same vessel or the opposite artery.

**12. Vessels**

- Left main coronary artery (LMCA)
- Left anterior descending artery (LAD) with septal and diagonal branches
- Left circumflex artery (LCX) with obtuse marginal branches
- Ramus intermedius artery
- Right coronary artery (RCA) and any of its branches
- Posterior descending artery
- Saphenous vein bypass graft(s)
- Arterial bypass graft(s): Right internal mammary graft, left internal mammary graft, radial artery graft, and gastroepiploic artery graft.