

# Clinical study protocol

Multi-center randomized double-blind placebo-controlled Phase II study of efficacy and selection of dose of Seroguard, solution (JSC Pharmasyntez, Russia) used for prevention of pelvic adhesions

**Name of the test drug:** Seroguard

**Dosage form and dosage:** Solution, 0.41 mg/mL

**Study phase:** II

**Study Sponsor:** JSC Pharmasyntez, Russia

**Protocol ID:** SG-2/1215

**Protocol revision:** 3.2 dated 06.03.2017.

## Confidentiality agreement

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## Page of protocol approval by the study Sponsor

Study title                      Multi-center randomized double-blind placebo-controlled  
Phase II study of efficacy and selection of dose of Seroguard,  
solution (JSC Pharmasyntez, Russia) used for prevention of  
pelvic adhesions

Protocol                              SG-2/1215                              revision 3.2 dated 06.03.2017.

Prepared by                      N.A. Dvoynikova, Clinical Pharmacologist

Date 06 March 2017                      Signature   /signed/  

Agreed by                              A.S. Guschin,  
R&D Director Advisor

Date 06 March 2017                      Signature   /signed/  

Approved by                              M.G. Shurygin,  
R&D Director

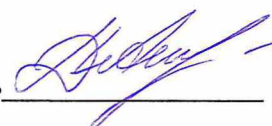
Date 06 March 2017                      Signature   /signed/

## Страница утверждения протокола спонсором исследования


Наименование исследования Многоцентровое рандомизированное двойное слепое плацебо-контролируемое исследование II фазы по изучению эффективности и подбору дозы препарата Серогард, раствор (АО «Фармасинтез», Россия), применяемого для профилактики спаячной болезни малого таза.

Протокол SG-2/1215 версия 3.2 от 06.03.2017 г.


Разработал Двойникова Н. А., клинический фармаколог

Дата 6.03.2017 Подпись 

Согласовал Гуцин А. С.,  
советник по науке и инновационной деятельности

Дата 6.03.17 Подпись 

Утвердил Шурыгин М. Г.,  
директор по науке и инновационной деятельности

Дата 06.03.2017 Подпись 

Study title	Multi-center randomized double-blind placebo-controlled Phase II study of efficacy and selection of dose of Seroguard, solution (JSC Pharmasyntez, Russia) used for prevention of pelvic adhesions.
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Protocol SG-2/1215 revision 3.2 dated 06.03.2017.

I, the undersigned, am responsible for conducting the study in this site and agree with the following:

I certify that I have read the latest revision of the present protocol, including all the annexures as well as Patient information leaflet of the test drug/the reference drug and have understood the information specified in these documents.

I have sufficient time for correct performance and completion of the study within the stipulated period of the study performance, and I have sufficient number of qualified employees and adequate equipment for the planned study procedures.

I agree to perform the study by me and my employees according to conditions, terms and procedures of the present protocol, complying with the requirements of national and international requirements of ICH GCP (Good Clinical Practice) and all the applicable requirements of authorities and government legislation.

Principal Investigator

Full name

## DESIGNATION, ORGANIZATION

Phone:

Fax:

E-mail:

Date \_\_\_\_\_ Signature \_\_\_\_\_

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## Synopsis

<b>Study title</b>	Multicenter randomized double-blind placebo-controlled Phase II study of efficacy and selection of dose of Seroguard, solution (JSC Pharmasyntez, Russia) used for prevention of pelvic adhesions.
<b>Protocol ID</b>	SG-2/1215
<b>Study purposes and objectives</b>	<p>The present study is aimed at evaluation of efficacy of the drug Seroguard, solution, used for prevention of pelvic adhesions.</p> <p><b>Main study objectives:</b></p> <ol style="list-style-type: none"> <li>1. To determine change in number of pelvic adhesions based on MRI data in post-surgical period in comparison to pre-surgical MRI data</li> <li>2. To determine change in thickness of pelvic adhesions based on MRI data in post-surgical period in comparison to pre-surgical MRI data</li> <li>3. To determine frequency of limited displaceability of pelvic organs in post-surgical period (based on results of transvaginal ultrasound investigation).</li> <li>4. To determine frequency of hyperechoic linear lesions in post-surgical period based on results of transvaginal ultrasound investigation.</li> <li>5. To determine changes in frequency of detecting limited displaceability in comparison to baseline (absolute change and in % of baseline value).</li> <li>6. To determine changes in frequency of detecting hyperechoic linear lesions based on repeated transvaginal ultrasound investigation in comparison to baseline.</li> <li>7. To determine frequency of detecting complete absence of USI – signs of adhesion process in pelvis in post-surgical period (defined as absence of limited displaceability of pelvic organs and absence of hyperechoic linear lesions)</li> <li>8. To determine number of adhesions during surgery.</li> <li>9. To determine number of dense adhesions during surgery.</li> <li>10. To determine percentage of female patients with any adverse reactions.</li> <li>11. To determine percentage of female patients with any serious adverse reactions.</li> </ol>

	<ol style="list-style-type: none"> <li>12. To determine percentage of female patients with adverse reactions, relation of which to use of the test drug or the placebo is “definite”, “probable” or “possible”.</li> <li>13. To determine percentage of female patients with serious adverse reactions, relation of which to use of the test drug or the placebo is “definite”, “probable” or “possible”.</li> <li>14. To determine percentage of female patients with mild adverse reactions.</li> <li>15. To determine percentage of female patients with moderate adverse reactions.</li> <li>16. To determine percentage of female patients with severe adverse reactions.</li> <li>17. To determine percentage of female patients with clinically significant changes in results of physical examination.</li> <li>18. To determine percentage of patients with clinically significant changes in vital signs.</li> <li>19. To determine percentage of female patients with clinically significant changes on electrocardiogram (ECG).</li> <li>20. To determine percentage of female patients with clinically significant changes in laboratory parameters.</li> </ol>
<b>Study methodology</b>	The present study will be performed as multicenter double-blind randomized placebo-controlled Phase II study.
<b>Study duration</b>	<p>Screening period (up to 15 days before the surgery)</p> <p>Treatment period (Day 0)</p> <p>Interim safety evaluation (Day 6±1)</p> <p>Evaluation of treatment efficacy (Day 30±4 days)</p>
<b>Number of subjects</b>	<ol style="list-style-type: none"> <li>1) Placebo group, 1.5 mL/kg – up to 30 screened female patients which corresponds to 26 randomizations and 24 completed cases</li> <li>2) Placebo group, 2.4 mL/kg – up to 30 screened female patients which corresponds to 26 randomizations and 24 completed cases</li> <li>3) Seroguard group, 1.5 mL/kg – up to 30 screened female patients which corresponds to 26 randomizations and 24 completed cases</li> </ol>

	4) Seroguard group, 2.4 mL/kg – up to 30 screened female patients which corresponds to 26 randomizations and 24 completed cases
<b>Inclusion and non-inclusion criteria</b>	<p><b>Inclusion criteria</b></p> <ol style="list-style-type: none"> <li>1. Female patients aged from 18 to 45 years with confirmed diagnosis of pelvic adhesions with indications for surgery (laparoscopic adhesiolysis)</li> <li>2. Voluntarily and personally signed and dated Form of Informed Consent to participate in the study</li> <li>3. Female patients with pelvic adhesions confirmed by gynecological examination and USI</li> </ol> <p><b>Non-inclusion criteria</b></p> <ol style="list-style-type: none"> <li>1. Female patients having contraindications to operative treatment (including acute or exacerbated chronic adnexal inflammatory process)</li> <li>2. Body mass index 30.0 kg/m<sup>2</sup> and more</li> <li>3. Known hypersensitivity to components of the test drug (Seroguard)</li> <li>4. Pregnancy, lactation or planning for pregnancy during the clinical study</li> <li>5. Refusal to use effective contraception methods throughout the study</li> <li>6. Positive HIV, RW, HBV or HCV test results.</li> <li>7. Alcohol abuse, drug addiction, and toxicomania (except for smoking)</li> <li>8. Category III and higher by physical status classification of the American Society of Anesthesiologists (ASA).</li> <li>9. Purulent process in the abdominal cavity</li> <li>10. Disseminated endometriosis</li> <li>11. Elevated WBC count in complete blood count exceeding 10*10<sup>9</sup>/L</li> <li>12. Necessity of using any other drugs during the surgery (except for 0.02% chlorhexidine aqueous solution throughout the</li> </ol>

	<p>surgery, as well as the test drug or the placebo (0.9% sodium chloride) in the end of surgery) administered intraperitoneally</p> <p>13. Concomitant diseases that may require conversion of the surgical intervention by other indications</p> <p>14. Type I or II diabetes mellitus</p> <p>15. Deep vein thrombosis and/or PATE at screening or in the history</p> <p>16. Renal impairment (reduced glomerular filtration rate below 60 mL/min/1.73 m<sup>2</sup> evaluated by the CKD-EPI equation)</p> <p>17. Liver disorders determined as more than 2-fold elevation of the upper limit of normal of one of the following enzymes: ALT, AST, GGTP, AP, or more than 2-fold elevation of total bilirubin level</p> <p>18. Myocardial infarction within 6 months before screening</p> <p>19. Any concomitant diseases accompanied by heart failure.</p> <p>20. Clinically significant changes in ECG (in Investigator's opinion).</p> <p>21. Any concomitant diseases accompanied by respiratory failure</p> <p>22. Any oncology disease within 3 years before enrollment into the study.</p> <p>23. Systemic inflammatory diseases.</p> <p>24. Diseases associated with chronic hemorrhages</p> <p>25. Blood diseases (anemias of any origin, hemoglobinopathies, inherited and acquired coagulopathies, hemostasis disorders, thrombocytopenias, and thrombocytopathias, any hemoblastoses)</p> <p>26. Any other disease, that, in the Investigator's opinion, may distort the study results or present an additional threat to well-being of female patient after administration of the study drug</p> <p>27. Administration of anticoagulants, antiaggregants (except for acetylsalicylic acid at the dose of less than 325 mg/day) at the moment of inclusion into the study or planning to do so during the study.</p> <p>28. Administration of drugs with pronounced hemato-, hepato-, or nephrotoxic action, drugs of biological origin</p>
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	<p>29. Necessity of administration of cytostatics, systemic glucocorticosteroids and other immunosuppressive agents in the period of participation in the study.</p> <p>30. Participation in another clinical study within 30 days before screening</p> <p>31. Contraindications for performance of MRI (presence of implants or implanted electronic devices)</p> <p>32. Impossibility or inability to comply with the requirements of the protocol, including those for physical, psychic or social reasons, in Investigator's opinion</p> <p><b>Withdrawal criteria</b></p> <ol style="list-style-type: none"> <li>1. Withdrawal of informed consent by female patient</li> <li>2. Female patient's non-compliance with the rules of participation in the study.</li> <li>3. Pregnancy occurrence.</li> <li>4. Necessity of conversion during surgical intervention</li> <li>5. Necessity of surgery during the period between adhesiolysis surgery and Visit 3</li> <li>6. Other reasons occurring during the study and interfering with the study performance in accordance with the protocol.</li> <li>7. Necessity of drain tube installation revealed during the surgery</li> </ol>
<b>Study drug</b>	<p><b>Test drug:</b></p> <p>Seroguard, solution 0.41 g/L, JSC Pharmasintez, Russia, in the volume of 1.5 or 2.4 mL/kg</p> <p><b>Reference drug:</b></p> <p>Sodium chloride, solution for infusion 0.9%, CJSC EAST-PHARM, Russia, in the volume of 1.5 or 2.4 mL/kg</p>
<b>Dosage regimen and route of administration of the study drug</b>	<p>Administration of the drug is performed at the final stage of surgical intervention. After an adequate sanitation of the abdominal cavity with warm normal saline in the quantity of 100 mL, the drug Seroguard, solution in the concentration of 0.41 g/L or placebo is administered through trocar with the help of a metal tube 25 cm long with inner diameter of 4 mm with a silicone nozzle 5 cm long, which is tightly</p>

	<p>connected to Janet syringe containing an anti-adhesion solution/placebo.</p> <p>The test drug/placebo should be applied onto the operated surface in the quantity of 2.4 mL/kg body weight or 1.5 mL/kg body weight by means of forced pressing the plunger of the syringe.</p> <p>In order to create the maximum afflux of anti-adhesion agent into the pelvis, all the patients should be recommended to practice active behavior (getting up and walking) in the end of the first day after the surgery and supine position with the head kept up by the bed head elevation during rest.</p> <p>At the post-operative period, for all the groups, patient management is performed in accordance with the established standards.</p>
<p><b>Main parameters of efficacy and safety assessment</b></p>	<p><b>Primary efficacy endpoint:</b> achieving clinical efficacy determined as:</p> <p>Frequency of reducing number of adhesions after repeated MRI by 3 or more (in female patients with 10 and less adhesions at the baseline) or by 30% and more (in patients with &gt;10 adhesions at the baseline)) in comparison to baseline MRI data</p> <p><b>Secondary efficacy endpoints:</b></p> <ol style="list-style-type: none"> <li>1. Change in thickness of pelvic adhesions by repeated MRI in comparison to baseline MRI data</li> <li>2. Frequency of limited displaceability of pelvic organs in post-surgical period (based on results of transvaginal ultrasound investigation) on Day 30±4 after the surgery</li> <li>3. Frequency of hyperechoic linear lesions in post-surgical period based on results of transvaginal ultrasound investigation</li> <li>4. Change in frequency of detecting limited displaceability of pelvic organs in comparison to baseline (absolute change and in % of baseline value)</li> <li>5. Changes in frequency of detecting hyperechoic linear lesions based on repeated transvaginal ultrasound investigation in comparison to baseline</li> <li>6. Frequency of detecting complete absence of USI – signs of adhesion process in the pelvis in post-surgical period (defined as absence of limited displaceability of pelvic organs and absence of hyperechoic linear lesions)</li> </ol> <p><b>Safety parameters:</b></p> <ol style="list-style-type: none"> <li>7. Vital signs (body temperature, BP, HR, RR)</li> </ol>

	<p>8. Laboratory parameters:</p> <p>Blood chemistry – total protein, glucose, ALT, AST, total bilirubin, alkaline phosphatase, amylase, creatinine</p> <p>Complete blood count – RBC count, WBC count, platelet count, hemoglobin, hematocrit, WBC differential, ESR</p> <p>Coagulogram – coagulation time, international normalized ratio (INR), thrombin time, activated partial thromboplastin time (APTT)</p> <p>Urinalysis – color, transparency, pH, specific gravity, protein, glucose, WBC, RBC, bacteria, casts, salts</p> <p>9. ECG data – heart rate [HR], PR, QRS, QT intervals and calculated QTc interval.</p> <p>10. USI data</p> <p>11. Incidence of adverse reactions</p> <p>12. Incidence of serious adverse reactions</p> <p>13. Incidence of unexpected adverse reactions</p> <p>14. Incidence of adverse and serious adverse reactions caused termination/withdrawal from the study</p>
<b>Study procedures</b>	<p><b>Visit 0 – Screening</b></p> <ul style="list-style-type: none"> <li>• Obtaining informed consent</li> <li>• Collection of history, demographic data</li> <li>• Gynecological history</li> <li>• Collection of previous therapy information</li> <li>• Physical examination with evaluation of vital signs</li> <li>• Laboratory investigation: complete blood count, blood chemistry, coagulogram, urinalysis, pregnancy test (performed not earlier than on the day 7 before surgical intervention), HIV, HBV, HCV and RW blood test</li> <li>• ECG</li> <li>• USI of the abdominal cavity</li> <li>• USI of the pelvic organs (transvaginal) (in the second phase of the menstrual cycle)</li> <li>• MRI of the abdominal cavity and the pelvic organs</li> </ul>

	<ul style="list-style-type: none"> <li>• Gynecological examination and colposcopy</li> <li>• Cytological examination (Pap-smears)</li> <li>• Microscopic (bacterioscopic examination) examination of the smear stained by Gram's method</li> <li>• Assessment of the inclusion/non-inclusion criteria compliance</li> <li>• Only for female patients included into the study with diagnosis "infertility" - hysterosalpingography (Day 7-10 of the menstrual cycle), use of hysterosalpingography results obtained on Day 7-10 of the menstrual cycle within 6 months before screening visit is permissible</li> </ul> <p><b>Visit 1 (Day 0)</b></p> <p><i>Before the surgery:</i></p> <ul style="list-style-type: none"> <li>• Physical examination with evaluation of vital signs</li> <li>• Actualization of the information on concomitant therapy</li> <li>• Actualization of the information on concomitant disease</li> <li>• Reassessment of inclusion/non-inclusion criteria</li> <li>• Randomization</li> <li>• Surgical intervention using the test drug or the placebo</li> <li>• Evaluating severity of baseline adhesion process (intraoperative)</li> </ul> <p><i>After the surgery:</i></p> <ul style="list-style-type: none"> <li>• Physical examination with evaluation of vital signs</li> <li>• Local status assessment (description of postsurgical wound)</li> <li>• Adverse reaction assessment</li> </ul> <p><b>Visit 2 Interim safety assessment (Day 6±1)</b></p> <ul style="list-style-type: none"> <li>• Physical examination with evaluation of vital signs</li> <li>• Laboratory investigations: complete blood count, blood chemistry, urinalysis</li> <li>• Local status assessment (description of postsurgical wound)</li> <li>• USI of the abdominal cavity</li> <li>• ECG</li> </ul>
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	<ul style="list-style-type: none"> <li>• Adverse reaction assessment</li> </ul> <p><b>Visit 3 (30±4 days after the surgery)</b></p> <ul style="list-style-type: none"> <li>• Physical examination with evaluation of vital signs.</li> <li>• Local status assessment (description of postsurgical wound)</li> <li>• Adverse reaction assessment</li> <li>• Laboratory investigations: complete blood count, blood chemistry, coagulogram, urinalysis, pregnancy test</li> <li>• ECG</li> <li>• USI of the pelvic organs (transvaginal) with the adhesion severity evaluation</li> <li>• USI of the abdominal cavity</li> <li>• MRI of the abdominal cavity and the pelvis</li> </ul>
<p><b>Statistical analysis (sample size justification)</b></p>	<p>In the studies of the drug Adept® (Innoventica plc), maximally close to the test drug by mechanism of action (FDA Executive Summary (Version 2): P050011 Innovata plc Adept® Adhesion Reduction Solution (4% Icodextrin Solution, 2006), a primary endpoint was used. It was determined as a decrease in number of adhesions during second look diagnostic laparoscopy by 3 or more (in patients with 10 or less adhesions at the baseline) or by 30% and more (in patients with &gt;10 adhesions at the baseline)) is 45%.</p> <p>Performance of second look laparoscopy under the present study is unacceptable from the ethical point of view, MRI will be used for evaluation of primary end point. As per the publication (Ghonge, N.P.; Ghonge, S.D. Computed tomography and magnetic resonance imaging in the evaluation of pelvic peritoneal adhesions: What radiologists need to know? Indian J Radiol Imaging. 2014 Apr-Jun; 24(2): 149–155), MRI data highly correlate with laparoscopy picture (both pre-surgical and post-surgical studies during repeated laparoscopies). The exclusions are the thinnest adhesions that may not be seen on MRI which may be compensated by use of high-field MRI.</p> <p>As per the above publication, MRI allows to visualize adhesions qualitatively and quantitatively and to obtain data with the same degree of detalization as during laparoscopic investigation before and after the surgery.</p> <p>Thus, calculation of sample size will be based on efficacy of similar drugs studied based on laparoscopic data, however, MRI control will be</p>

	<p>used in the study, first of all due to ethical considerations and due to strong correlation between MRI data and laparoscopy data.</p> <p>Accordingly, as per the above studies of the drug Adept®, efficacy related to achieving primary end point (clinical efficacy determined as decrease in number of adhesions during repeated diagnostic laparoscopy by 3 and more (in patients with 10 or less adhesions at the baseline) or by 30% and more (in patients with &gt; 10 adhesions at the baseline)) is 45%. In the control group (placebo) based on literature review and metha-analysis (Ahmad G. et al., Fluid and pharmacological agents for adhesion prevention after gynaecological surgery (Review), 2014) achieving clinical efficacy is recorded in not more than 10% cases.</p> <p>Using these baseline data, the following assumptions were introduced (as per the method specified in the FDA Guidance for Industry: Non-Inferiority Clinical Trials):</p> <ul style="list-style-type: none"> <li>• The study will be conducted as a <i>superiority trial</i>, i.e. at least one dosage of Seroguard must be more efficient than the placebo, whereby the <i>superiority margin</i> will be 5% and more (definition of endpoint and superiority margin from the main study of Adept® was used). Comparison with placebo will be performed for each dosage of the drug separately. Comparison of dosages by efficacy between them is not planned and will be a subject of the study in the Phase III of clinical studies of the drug</li> <li>• Expected rates of achieving the primary endpoint in the groups with different dosages will be considered initially equal</li> <li>• First type error (<math>\alpha</math>) = 5 % (0.05) for <i>superiority</i> hypothesis</li> <li>• Second type error (<math>\beta</math>) = 20 % (0.2), that corresponds to 80 % power.</li> <li>• Expected withdrawal from the study will make 15% at screening and 10% after randomization</li> </ul> <p>Null and alternative hypotheses for the <i>superiority testing</i> stage are worded as follows:</p> <ol style="list-style-type: none"> <li>1. Null hypothesis (<math>H_0</math>) holds that the difference in the rate of the primary endpoint achievement for one of the dosages of the drug Seroguard and the placebo will not exceed 5% in favor of the drug <div style="text-align: center;"> <math display="block">H_0: p_1 - p_0 \leq 0.05</math> </div> </li> <li>2. Alternative hypothesis (<math>H_A</math>) holds that the difference in the rate of the primary endpoint achievement of one of the dosages of the</li> </ol>
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	<p>drug Seroguard and the placebo will exceed 5% in favor of the drug</p> $H_A: p_1 - p_0 > 0.05$ <p>Where <math>p_0</math> and <math>p_1</math> are the rates of the primary endpoint achievement in the groups of the placebo and Seroguard (of any dosage), respectively.</p> <p>For the purpose of calculation of the sample size in each group in this case, the formula is applied which is given in <i>Chow S, Shao J, Wang H. 2008. Sample Size Calculations in Clinical Research. 2nd Ed. Chapman &amp; Hall/CRC Biostatistics Series. page 90</i></p> $n = (p_1 \times (1 - p_0) + p_0 \times (1 - p_0)) \times \left( \frac{z_{1-\alpha} + z_{1-\beta}}{p_1 - p_0 - \delta} \right)^2$ <p>where</p> <p><math>n</math> is the size of one group;</p> <p><math>z</math> is the value of the normal distribution function with the given <math>\alpha</math> and <math>\beta</math> levels;</p> <p><math>\delta</math> is superiority margin 5%;</p> <p><math>p_1</math> is the expected proportion in the active drug group (one of the dosages) – 45%</p> <p><math>p_0</math> is the expected proportion in the placebo group – 10%</p> <p>Applying the above data in this formula, we obtain the minimum number of patients in the placebo group without considering withdrawal: 24 completed cases which corresponds to 26 randomizations and 30 screenings.</p> <p>Thus, the total number to be enrolled in the study is:</p> <ol style="list-style-type: none"> <li>1) Placebo group, 1.5 mL/kg – up to 30 screened female patients that corresponds to 26 randomizations and 24 completed cases</li> <li>2) Placebo group, 2.4 mL/kg – up to 30 screened female patients that corresponds to 26 randomizations and 24 completed cases</li> <li>3) Seroguard group, 1.5 mL/kg – up to 30 screened female patients that corresponds to 26 randomizations and 24 completed cases</li> <li>4) Seroguard group, 2.4 mL/kg – up to 30 screened female patients that corresponds to 26 randomizations and 24 completed cases</li> </ol>
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	Thus, total of 120 female patients are to be screened and at least 104 female patients are to be randomized for the study.
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## Acronyms

ALT	Alanine Aminotransferase
Ap	Alkaline Phosphatase
APTT	Activated Partial Thromboplastin Time
AR	Adverse Reaction
ASA	American Association of Anaesthetists
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
BP	Blood Pressure
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
DP	Drug Product
ECG	Electrocardiography
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
FL	Federal Law
GCP	Good Clinical Practice
GGTP	Gamma-Glutamyl Transpeptidase
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICD	International Classification of Diseases
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International Normalized Ratio
ITT	Intent-to-treat
LEC	Local Ethics Committee
MOH	Ministry of Health
PATE	Pulmonary Artery Thromboembolism
PP	Per protocol

RNA	Ribonucleic Acid
RR	Respiratory Rate
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
USI	Ultrasound Investigation
WHO	World Health Organization
WMA	World Medical Association

## **1 General information**

### **1.1 Protocol title, ID and date**

Study title Multi-center randomized double-blind placebo-controlled Phase II study of efficacy and selection of dose of Seroguard, solution (JSC Pharmasyntez, Russia) used for prevention of pelvic adhesions

Protocol SG-2/1215 revision 3.2 dated 06.03.2017

### **1.2 Name and address of the Sponsor and monitor**

Joint Stock Company Pharmasyntez

Legal address: Krasnogvardeyskaya str., 23, off. 3, Irkutsk, 664007, Russia.

Actual address: Rosa Luxemburg str., 184, Irkutsk, 664040, Russia.

Phone: +7(3952)55-03-28

Fax: (495)737-03-30

### **1.3 Name and designation of persons authorized on behalf of the Sponsor to sign the protocol and amendments to the protocol**

Natalya Anatolyevna Dvoynikova

Clinical pharmacologist, JSC Pharmasyntez

### **1.4 Name, designation, address and phone number of Medical reviewer of the present study appointed by the Sponsor**

Michael Gennadyevich Shurygin

R & D Director, JSC *Pharmasyntez*

Rosa Luxemburg str., 184, Irkutsk, 664040, Russia.

Phone: +7(3952)55-03-28 ext. 189

### **1.5 Name and designation of investigators responsible for the study performance, as well as addresses and phone numbers of clinical sites**

#### **1. Government-Owned Health Institution of Moscow, Municipal clinical hospital No 12, Moscow City Health Department**

Address: Bakinskaya str., 26, Moscow, 115516

Phone: 8(495) 321-54-92

E-mail: gkb12@zdrav.mos.ru

**Principal Investigator:** Vera Dmitriyevna Petrova

**2. State Educational Government-Financed Institution of Higher Professional Education, I.M. Sechenov First Moscow State Medical University, Ministry of Health of the Russian Federation**

Address: Yelanskogo str., 2, bldg. 1, Moscow, 119435

Phone: +7 (499) 372-00-15

E-mail: mgmukliniki@mma.ru

**Principal Investigator:** Natalya Ivanovna Borisova

**3. State Educational Government-Financed Institution of Higher Professional Education, Kazan state medical university, Ministry of Health of the Russian Federation (SEGFI of HPE, Kazan SMU, Ministry of Health of the Russian Federation)**

Address: Butlerova str., 49, Kazan, the Republic of Tatarstan, 420012

Phone: +7 (843) 2360451

E-mail: goszak-chief@kgmu.kcn.ru

**Principal Investigator:** Albir Almazovich Khasanov

**4. State Educational Government-Financed Institution of Higher Professional Education, A.I. Evdokimov Moscow State University of Medicine and Dentistry, Ministry of Health of the Russian Federation**

Address: Delegatskaya str., 20, bldg. 1, Moscow, 127473

Phone: 8 (495) 609-67-00

E-mail: msmsu@msmsu.ru

**Principal Investigator:** Vladimir Nikolayevich Kuzmin

**5. Federal state institution, V.I. Kulakov Research Center for Obstetrics, Gynecology, and Perinatology, Ministry of Health of the Russian Federation.**

Address: Academician Oparin str., 4, Moscow, 117997

**Principal Investigator:** Inna Anatolyevna Apolikhina.

**6. Krai Government-Owned Publicly Funded Health Care Institution, Krai clinical hospital**

Address: Partizana Zheleznyaka str., 3 "A", Krasnoyarsk, 660022



**Principal Investigator:** Alexey Ivanovich Gritsan.

**7. Federal State Educational Government-Financed Institution of Higher Professional Education, I.P. Pavlov Ryazan state medical university, Ministry of Health of the Russian Federation (Government-owned health institution, Ryazan regional clinical hospital)**

Address: Vysokovltnaya str., 9, Ryazan, 390026

**Principal Investigator:** Dmitry Viktorovich Seliverstov

**8. Government-Owned Health Institution, Leningrad regional clinical hospital**

Address: Lunacharskogo prospekt, 45-49, Saint-Petersburg, 194291

**Principal Investigator:** Irina Vladimirovna Sergeyeva.

**9. State-Funded Health Care Facility of Moscow, V.M. Buyanov Municipal Clinical Hospital, Moscow City Health Department**

Address: Bakinskaya str., 26, Moscow, 115516

**Principal Investigator:** Vera Dmitriyevna Petrova.

**1.6 Names and addresses of clinical laboratories and other medical and/or technical services and/or organizations involved into the study**

Central laboratory for evaluation of MRI data: Center of computed tomography

Address: Krasnoyarskaya str., 11 B, Irkutsk, 664009

Tel/fax: (3952) 500-557

responsible person: Viktor Anatolyevich Shanturov, Chief Physician, D. Sc., professor.

## 2 Justification of the study

The seriousness of problematics of serosal injury is related to increase in number of invasive medical procedures accompanied by traumatization (surgical procedures in thoracic and abdominal cavities, endoscopic diagnostic procedures, etc.). An inflammatory process is developed in response to injuries. It leads to formation adhesion which significantly causes abnormality of organs covered with serous membrane.

After surgeries, adhesions are formed on the abdominal cavity organs with a rate from 20% to 80%. Meanwhile, “peritoneal adhesions” are developed with characteristic clinico-morphological complex of symptoms. It’s the most common and threatening complication is an acute adhesive ileus comprising more than 40% among different types of acquired ileus, lethality for this abnormality achieves 8-19%. Formation of adhesions in the pelvis leads to infertility.

Moreover, in 65% cases of infertility, the reason is female reproductive system abnormality, whereby one of the most common (30% - 35%) pathogenetic mechanisms of infertility is abnormality of transportation of egg, as well as of sperm cell and gestational sac through fallopian tubes, including due to pelvic abnormality involving peritoneum and formation of adhesive process in the pelvis – tubal or tubo-peritoneal factor (1,2). Diseases causing such complications, first of all, include inflammatory diseases of the pelvis, including acute salpingitis. In their etiological structure, infections caused by Chlamydia trachomatis, Neisseria gonorrhea and anaerobic bacteria prevail. Infertility risk is increased after each such disease: 10%-12% after the first one, 23%-35% - after the second one and 54%-75% - after the third one, and the 6-7 fold risk of extrauterine pregnancy after an inflammatory disease of the pelvis (3,4). Other widespread reasons of tubo-peritoneal infertility is endometriosis (7%-14%, disease is accompanied by chronic inflammation and cicatrization in the pelvis involving Fallopian tubes, similar to that appearing after infection diseases) (5), in the developing countries – tuberculous salpingitis (in 10%-12% patients with pulmonary tuberculosis) (6), post-surgical adhesive process in the pelvis (in particular, after surgeries for perforated appendicitis, the risk of tubo-peritoneal infertility is increased by 4.8-fold; in most cases, pelvic surgeries cause development of adhesive process in the pelvis) (7,8).

Standard methods of diagnosing infertility reasons are hysterosalpingography, hysteroscopy and laparoscopy, whereby the last two methods are also used for treatment (9). In the study by Neerja et al. (10), laparoscopy was performed in 140 of 200 women with primary or secondary infertility aged from 20 to 30 years. In 38 cases (27.14%), a laparoscopic adhesiolysis was performed, a fallopian tube surgery was directly performed in 53 cases (37.86%), electrocoagulation or removal of lesions of endometriosis – in 25 cases (17.86%), drilling of polycystic ovaries – in 24 cases. Laparoscopy allowed to diagnose tubo-peritoneal cause of infertility in 30 women, in which abnormality was not found based on hysterosalpingography data, meanwhile the surgery allowed 64 (45,7%) women to become pregnant. Thus, laparoscopic interventions are one of the most efficient methods of diagnostics and treatment of infertility in women.

In the meantime, the most common complication after pelvic surgeries is formation of adhesions. After second look laparoscopy in women previously underwent gynecological surgeries, adhesions

were found in 56%-100% cases (8), whereby, involvement of fallopian tubes in adhesion process is typical (11,12). Thus, the topicality of searching for means for prevention of adhesions during any gynecological surgeries, as well as for prevention of their relapse after adhesiolysis is unmistakable. Despite multiple, presently offered means and recommendations for prevention of post-surgical adhesions, no reliable and efficient means have been found, and the result of using the administered drugs is fairly doubtful, because in the clinical practice there are no methods of objective control for post-surgical adhesions, evaluation of their efficacy is performed by indirect signs (13,14,15). JSC Pharmasynitez has developed a new drug Seroguard, solution (hereafter Seroguard or the test drug), mechanism of action of which is related to suppression of p38-mitogen-activated protein kinase activity (p38 MAPK). Role of these intracellular regulators in inflammatory processes is well known, their participation in pathogenesis of such inflammatory diseases as rheumatoid arthritis, Crohn's disease, psoriasis, bronchial asthma, is described, search for the drugs suppressing p38 MAPK is going on (16). As inflammation underlies the adhesions, suppression of p38 MAPK in the abdominal cavity may reduce activity of adhesive process. This assumption is based on the results of several pre-clinical studies. Thus, Ward et al. in the study of rats showed that suppression of MAP KAP kinase II (MK2) which is activated by p38 MAPK causes decrease of inflammation and intra-abdominal adhesion severity (17). Katada et al. in the study of mice showed that in case of injured caecum, a p38 MAPK activity is increased, and administration of p38-MAPK inhibitor prevents formation of adhesions (18). The pre-clinical studies of the drug Seroguard also demonstrated high antiadhesive activity with no significant toxicity. Development of a new anti-adhesive drug Seroguard for clinical use is actual, justified by pathogenetic reasons and promising results of pre-clinical studies. In a double-blind placebo-controlled Phase I clinical study, a tolerability of the drug Seroguard was evaluated in patients after laparoscopic cholecystectomy (19). Seroguard was administered into abdominal cavity of patients at the end of the surgery at the dose of 2.4 mL/kg. Comparison to similar volume of placebo (0.9% sodium chloride) showed that incidence of adverse reactions in the both groups was comparable.

In the studies of the drug Adept® (Innoventica plc), maximally close to the test drug (20) by mechanism of action, a primary endpoint was used. It was determined as a decrease in number of adhesions during second look diagnostic laparoscopy by 3 or more (in patients with 10 or less adhesions at the baseline) or by 30% and more (in patients with >10 adhesions at the baseline), which is an adequate reflection of an expected mechanism of the drug action and allows to justify sample size required for performance of the study. Meanwhile, performance of second look laparoscopy in conditions of a similar study in the Russian Federation is ethically unacceptable, due to which using MRI is supposed for evaluation of the given endpoint. As per the publication data of Ghonge et al. (21), MRI data of the study sufficiently correlate with laparoscopic picture (including both pre-surgical and post-surgical studies with second look laparoscopies). The exclusion are the thinnest adhesions that may not be seen by MRI, which may be compensated by using high-field MRI. This allows to use MRI investigation as an analogue of second look laparoscopy while maintaining required accuracy of evaluating the primary endpoint.

Presently, considering safety of the drug Seroguard when administered into abdominal cavity proved in the Phase I clinical study, it is planned to perform a Phase II clinical study, in which it is supposed to evaluate safety and efficacy of Seroguard for prevention of adhesions in the pelvis after laparoscopy adhesiolysis due to tubo-peritoneal infertility caused by pelvic adhesions.

## 2.1 Name and description of the study drugs

The test original drug Seroguard, solution manufactured by JSC Pharmasyntez, is a drug for administration into serous cavities, containing conjugate of hydrochloride 4-[4-(4-fluorophenyl)-2-[4-methylsulfinyl)phenyl]-1H-imidazol-5-pyridine with poly-1-vinylimidazole as an active ingredient. The following is information as per the draft instruction for medical use.

### Structural formula

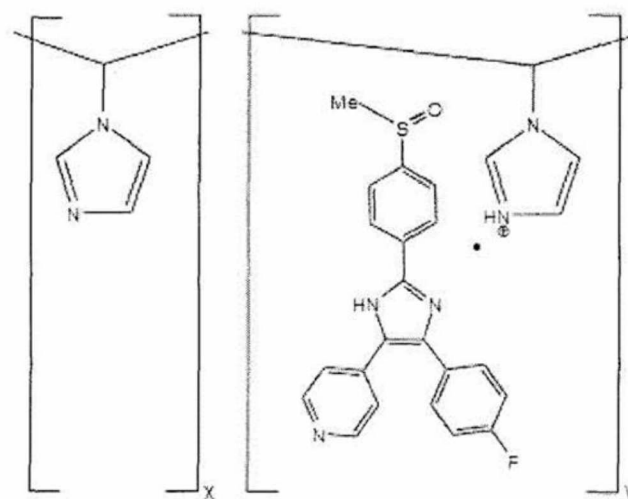


Figure 1 – Structural formula of the active ingredient of the drug Seroguard, solution

**Pharmacotherapeutic group:** Selective immunosuppressants

**ATC code:** L04AA

### Pharmacodynamics

The drug doesn't exert systemic influence on organs and systems of the body. It exerts local action. It is known that in case of injured serous membrane, in particular, in case of peritoneal trauma, a hyperexpression of a set of genes is observed. They are responsible for synthesis of biologically active substances (interleukins, integrines, growth factors, signaling cascades), which launch inflammatory process and process of reparation. Hyperexpression of genes responsible for synthesis of collagen is observed from Day 3 to Day 14, maximum on Day 3. A set of gene co-expressions changed during reparative process in response to abdominal alteration is known.

Administration of Seroguard significantly modifies response of cells to alteration causing significant decrease in anti-inflammatory cytokine gene expression by Week 2 of the process, a sharp decrease of Csf3 colony-stimulating factor activation, interruption of second wave of

activation of growth factor expression, suppression of a set of genes (Egf, Pdgfa, Tgfa). Activity of Wisp1 gene happens which codes main chain of WISP signaling pathway, maintaining proliferative activity of fibroblasts and activation of Col5a3 collagen gene is significantly decreased.

Experimental studies demonstrated that during administration of Seroguard, solution, cell response is significantly changed in the site of abdomen injury from the point of view of gene activity coding proteins of focal adhesion. Main fixed shifts are an earlier activation of these gene transcription (starting from Day 1 of the process in comparison to Day 3 in control), after which an activity is sharply decreased and is left less than in control group up to the end of follow-up. Decreased expression of membrane proteins of adhesion and related proteins of cytoskeleton, probably, interferes with interaction of cells with each other and with interstitial matrix in time corresponding to conversion of fibrin adhesions into fibrous adhesions.

p38 ( $\beta$ ,  $\gamma$ ,  $\delta$  subunits), p44 and JNK3 kinases similar by 3-dimensional structural organization act as main biological targets in the mechanism of Seroguard action, which allows to consider MAP kinase inhibition to be main in the mechanism of action of the drug.

### **Pharmacokinetics**

After intravenous administration to rats at the dose of 6.15 mg/kg, peak of concentration is observed at about 15 minutes after administration and is  $38.89 \pm 2.50$   $\mu\text{g/mL}$ .

Half-life is  $4.25 \pm 0.07$  h.

Mean retention time is about 5.9 hours.

Volume of distribution is about 1300 mL/kg.

After intraperitoneal administration to rats at the dose of 6.15 mg/kg, the drug in blood plasma is not observed by HPLC method, which evidences absence of its significant absorption after by the given route of administration.

### **Indications**

Prevention of adhesions

### **Contraindications**

Allergy to the drug components.

Intra-abdominal administration — purulent process in the abdominal cavity and the pelvis.

Gynecological surgery — purulent process in the abdominal cavity and the pelvis.

Intrapericardial administration — presence of infectious pericarditis.

Intra-articular administration — presence of infected wounds, abrasions in the joint; joint infection; venous or lymphatic stasis from the side of injured joint.

Not tested in pregnant patients, patients under 18, patients with hepatic or renal failure.

Studies in animals did not show any toxic activity or negative effect on reproductive function, fertility and teratogenic effect by Seroguard.

## **Posology and method of administration**

Administered into serous cavity by method of single irrigation (by syringe, without injuring abdominal mesothelium) in aseptic conditions before completion of surgery. Re-administration is not recommended.

Before administration, aspirate all remaining fluids (blood, exudate, solutions administered intraoperatively).

Before use, heat the solution until body temperature.

Doses for adults:

For abdominal cavity surgery, the drug is administered at the dose of 2.4 mL/kg body weight into abdominal cavity.

For gynecological surgery, the drug is administered into abdominopelvic cavity at the dose of 1.5 to 2.4 mL/kg providing post-surgical position preventing discharge of the drug from the pelvic cavity.

For surgeries related to pericardium dissection, the drug is administered intrapericardially at the dose of 0.05 mL x left ventricular stroke output.

For administration into joint cavity during arthroscopy - up to 2 mL depending on the volume of joint.

The drug is intended only for administration into serous cavity, intravenous administration is unacceptable. Do not mix with other drugs. Do not use as a vehicle of other drugs as antibiotics, chemotherapeutic agents, etc.

## **Side effect**

In the Phase I clinical study, general incidence of side effects on administration of the drug Seroguard was similar to those during administration of the placebo. During the study, the following side effects possibly related to administration of the drug were found: hyperthermia (1.8 %), pain in infraclavicular region (0.9 %), increased WBC count in blood (0.9 %).

## **Overdose**

No information on overdose of the drug Seroguard is available.

## **2.2 Results of pre-clinical and clinical studies significant for the given study**

### **2.2.1 Pre-clinical studies**

Experimental studies of safety of Seroguard, solution were performed. They were aimed at evaluating acute and chronic toxicity, irritant properties, allergenicity, immunotoxicity, reproductive toxicity, mutagenicity and risk of carcinogenic action.

The test drug was proved to be low toxic, to have a high therapeutic index and safe after long-term (180 days) daily intraperitoneal administration to endotherm animals (rodents and dogs). Solution

of the drug does not exert irritant action at the site of administration and is apyrogenic. It was shown that the drug does not have specific types of toxicity.

The performed studies showed that administration of Seroguard during modelling aseptic and purulent peritonitis had a marked therapeutic action and contributed to prevention of adhesions.

After intravenous administration to rats at the dose of 6.15 mg/kg, peak concentration is observed about at 15 minutes after administration and is  $38.89 \pm 2.50 \mu\text{g/mL}$ . Half-life is  $4.25 \pm 0.07 \text{ h}$ . Average retention time is about 5.9 hours. Distribution volume is about 1300 mL/kg. After intraperitoneal administration to rats at the dose of 6.15 mg/kg, the drug is not observed in blood plasma which evidences absence of its significant absorption during the given route of administration.

According to hazard classification of drug products for clinical use, Seroguard, solution is referred to class III of low-toxic (low-hazard) drugs.

### **2.2.2 Clinical studies**

Seroguard, solution is a new original drug that has passed pre-clinical studies, Phase I clinical study was also performed (19). Multi-center double-blind placebo-controlled study included patients of both genders at the age from 18 to 75 years having indications for planned laparoscopic cholecystectomy. Treatment group (Seroguard) included 24 patients, and placebo group (0.9% sodium chloride) - 23 patients. Seroguard, solution 0.41 g/L, JSC Pharmasyntez, Russia or its respective placebo were administered into abdominal cavity at the end of laparoscopic cholecystectomy at the dose of 2.4 mL/kg. Incidence, nature and severity of adverse reactions (including clinically significant abnormalities of physical examination, vital signs, instrumental investigations, clinical laboratory parameters) were evaluated. 206 adverse reactions (AR) were recorded in the study: 110 (53,4%) – in the group of treatment with Seroguard and 96 (46.6%) – in the placebo group. 14 cases of adverse reactions (6.8%) were moderate and one was severe, remaining adverse reactions were mild. 194 (94.2%) ARs were doubtfully related to administration of the drug, 8 (3,9%) – conditionally related, and 4 ARs (1,9%) in the treatment group were evaluated as possibly related to the drug administration. 196 of 206 ARs (95.2%) completed by recovery of patient, in the remaining 10 cases (4.9%), a significant amelioration was observed. 4 serious ARs were also recorded in three patients of both groups in the study.

No statistically significant changes, except for level of eosinophils and lymphocytes in the placebo group, were recorded in most of complete blood count and blood chemistry parameters. A statistically significant elevation ( $p = 0.0297$ ) was noted in the level of eosinophils in the placebo group by Visit 11 (Day 28), however, it was not clinically significant. Similarly, elevation in lymphocytes ( $p = 0,0148$ ) was observed by Visit 11 (Day 28), which was not clinically significant.

The performed analysis of coagulogram data did not reveal statistically significant differences in any parameter between the Visits ( $p > 0.05$ ). Analysis did not also show any statistically significant variations in vital signs ( $p > 0.05$ ).

Thus, a good tolerability (comparable to that of placebo) of the drug Seroguard, solution 0.41 g/L, JSC Pharmasyntez, Russia was proved after administration into abdominal cavity at the end of laparoscopic cholecystectomy at the dose of 2.4 mL/kg in the Phase I study.

More detailed information on results of pre-clinical studies is provided in the Investigator's Brochure.

## **2.3 Known and potential risks and benefit for the study subjects**

### **2.3.1 Risks and inconveniences related to participation in the study**

ARs related to administration of the test drug and characteristic for the group of p38 MAPK inhibitors may be observed as well as AR not previously noted (known ARs during treatment with p38 MAPK inhibitors are provided in section 2.2.2.) may be noted during this study. Safety profile of p38 MAPK inhibitors is satisfactory even during systemic use, and considering the absence of Seroguard absorption from the abdominal cavity according to pre-clinical data, it is possible to calculate good tolerability of the drug. Based on results of the Phase I clinical study, safety profile of the drug Seroguard was comparable to that of placebo. Thus, AR incidence in the group of treatment with the test drug is expected not to exceed the similar parameter in the placebo-control group (risk related to the underlying disease which is an indication for surgery, risk of surgery and anesthesia).

Blood sampling for clinical laboratory investigations (see section 4.2.3.5) may be accompanied by mild pain which is fleeting and/or ecchymoses may be formed at the site of needle injection. A thrombus may be formed in vein or infectious complication may be developed significantly rarer. Dizziness and/or fatigue may be observed during and soon after blood sampling.

Electrocardiographic examination (see section 4.2.3.6) is a painless examination, however rash or irritation may develop on patient's skin at the sites of gel application and using sticky electrodes for ECG.

Ultrasound investigation (see section 4.2.3.6) – In the present study, USI of the abdominal cavity is performed by transabdominal access and USI of the pelvis - by transvaginal access. The latter may be accompanied by mild painful sensations.

Hysterosalpingography. Rare complications of performing HSG include development of acute or chronic endometritis (in cases when bacteria along with contrast agent get from vagina into the uterine cavity), as well as allergy to contrast agent (contrast contains iodine, that's why presence of allergy to iodine should be specified in all women before HSG). Exceedingly rare complication of HSG is injury of fallopian tubes and/or uterine. In addition, during HSG a woman receives a small dose of X-ray irradiation (control of maximum individual effective irradiation dose is required).

Study procedures performed under the protocol, including blood sampling and electrocardiographic investigation, are routine in general clinical practice. Frequency of their performance does not make any significant additional load for female patient.



In order to minimize risks, the study will include female patients meeting inclusion criteria (section 5.1) and not having non-inclusion criteria (section 5.2). All the study subjects before signing informed consent to participate in the given study will be informed on possible risks and discomfort as well as on necessity to inform the Medical Investigator on health problems, if any. Medical Investigator will perform close monitoring of the study participants during the study. If necessary (for example, development of ARs), Medical Investigator will take required measures to perform respective investigations and/or administration of the therapy required.

#### **2.3.2 Possible benefit related to participation in the study**

In the study, no money compensation is planned for female patients, however, they will have possibility to take adequate treatment and investigation under the protocol. Decreased incidence, prevalence and severity of adhesions in abdominal cavity as a result of administration of the study drug, i.e. reduced risk of developing post-surgical complications related to adhesive process, which increases chances of becoming pregnancy and/or reduces probability of pelvic adhesions, is possible (but not obligatory) during the study.

Throughout the study, female subjects of the study will be under close control of employees of healthcare institution participating in conducting the study.

Considering the above, as well as pre-clinical data on safety of the drug Seroguard, the results of the Phase I clinical study and clinical data on administration of p38 MAPK inhibitors, risk/benefit ratio in the present study may be considered to be acceptable for patients who will participate in it.

### **2.4 Description and justification of route of administration, dosages, dosage regimen and therapy course**

The test drug Seroguard is administered once into serous cavity in aseptic conditions before completion of surgery. Repeated administrations are not recommended. The drug is ready for administration. Before administration, aspirate all the remaining liquids from serous cavity (blood, exudates, solutions administered intraoperatively). Before use, heat the drug to body temperature. After an adequate sanitation of the abdominal cavity with warm normal saline in the quantity of 100 mL, the drug Seroguard, solution in the concentration of 0.41 g/L is administered through trocar with the help of a metal tube 25 cm long with inner diameter of 4 mm with a silicone nozzle 5 cm long, which is tightly connected to Janet syringe containing an anti-adhesion solution/placebo.

The study drug shall be applied onto the operated surface in the quantity of 2.4 mL/kg body weight or 1.5 mL/kg body weight by means of forced pressing the plunger of the syringe.

In order to create the maximum afflux of anti-adhesion agent into the pelvis, all the patients should be recommended to practice active behavior (getting up and walking) in the end of the first day after the surgery and supine position with the head kept up by the bed head elevation during rest.

At the post-operative period, for all the groups patient management is performed in accordance with the established standards.

The drug is intended only for administration into serous cavity, intravenous administration is unacceptable. Do not mix with other drugs. Do not use as a vehicle of other drugs as antibiotics, chemotherapeutic agents, etc.

Selection of dosage is based on principle of Seroguard action – the drug acts at the site of its administration. Seroguard should cover the surface of abdomen in order to form an efficient liquid barrier which causes launch of apoptosis of activated fibroblasts, interrupting development of adhesive process at the site of abdomen injury.

In the studies by diZerega (22,23), area of abdomen and volume of liquid required for its complete coverage were determined. For a human being, a maximum weight coefficient is approximately 2.4 mL/kg (that is, for patient with weight of 80 kg,  $80 \times 2.4 = 192$  mL minimum). Thickness of boundary layer, in which reaction to injury is developed, which causes adhesions, and in which it is necessary to block activity of kinase cascade, is about  $h = 0.3$  mm based on morphometry data. Thus, the volume of boundary layer is equal to multiplication of thickness of boundary layer by area of abdomen surface ( $V = S \times h$ ). Activity of cascades in cells of deeper layers is unfavorable to be suppressed, because of ongoing process of surgical wound healing.

For gradually released active component of  $IC_{50}$  value related to MAPK p38 fibroblasts,  $IC_{50} = 300$  nM,  $M = 413.9$  g ( $IC_{50} = 413.9 \times 300 \times 10^{-9} = 0.00012417$  g/L = 0.12417 mg/L) (24).

Area of abdomen (approximately equal to body surface) of a person with weight of 80 kg and height of 180 cm is about 2 m<sup>2</sup>. Volume of boundary layer is  $2 \times 0.0003 = 0.0006$  m<sup>3</sup> = 0.6 dm<sup>3</sup> (the drug will be distributed at this volume).

Based on  $T_{1/2}$  coding RNA for MAPK (25) for 3-day exposure (based on absence of active absorption of conjugate in abdominal cavity):

$$0.12417 \text{ mg/L} \times 0.6 \text{ L} \times 24 = 1.79 \text{ mg}$$

Considering additional 10 % (200 mL of liquid is administered), a dose administered should be  $1.79 \times 1.1 = 1.997$  mg. Thus, for a person with weight of 80 kg and height of 180 cm, a quantity of the conjugate administered should contain about 2 mg of the drug, and the volume should be about 200 mL, which is 2.4 mL/kg. Efficacy and safety of the dose 1.5 mL/kg will be also evaluated in the study considering that the drug will exert its action not on the whole surface of the abdomen, but mainly in the pelvis.

Maximum dose administered to rats in the toxicological study is 30 mL/kg intravenously and intraperitoneally, meanwhile neither death of animals, nor abnormal general condition or behavior of animals were noted. In the study in dogs, the maximum administered dose of Seroguard was 12 mL/kg intraperitoneally, whereby no abnormal functioning of organs and systems of animals was observed. After recalculation for human being (26), both dosages exceed the above doses for the Phase II study for at least twice.

Sodium chloride, solution for infusion 0.9% (CJSC EAST-PHARM, Russia) was selected as the placebo). Selection of the drug is based on requirements to placebo in the given study:

- The drug may be used for irrigation of the abdominal cavity during the surgery;

- The drug does not exert effect on the body of patient after selected route of administration in the dosage selected.

Sodium chloride solution is widely used in abdominal surgery as placebo (27,28,29,30), it does not also exert significant pharmacological action and may not influence on parameters of safety of patients, that's why its use as a placebo is justified.

## **2.5 Normative-regulatory base for conducting the clinical study**

The present document is a protocol of a clinical study which is planned to be conducted as per the principles of Declaration of Helsinki of the World Health Association (adopted by 18th WMA General Assembly, Helsinki, June 1964, amended by 64<sup>th</sup> General Assembly, Fortaleza, October, 2013), tripartite guideline for Good Clinical Practice (ICH GCP) and is regulated by acting legislation of the Russian Federation (RF):

- Federal Law dated 12.04.2010 No 61-Φ3 “On drug circulation” as amended.
- Federal Law dated 27.07.2006 No 152-Φ3 “On personal data” as amended.
- RF national standard GOST P52379-2005 “Good Clinical Practice”.
- RF government decree No 714 dated 13.09.2010 (as amended by the RF government decree dated 18.05.2011 No 393, dated 04.09.2012 No 882) “On the approval of model rules of mandatory health and safety insurance for patients participating in a clinical drug study”.
- Order of RF Ministry of Healthcare dated 29<sup>th</sup> of November, 2012 No 986H “On approval of regulation on ethics board”
- Order of RF Ministry of Healthcare dated 01.04.2016 N 200H “On approval of Good Clinical Practice requirements”.

## **2.6 Description of the study population**

The study population will be hospitalized patients with confirmed diagnosis of pelvic adhesions. The study will include female patients aged from 18 to 45 years after signing informed consent. Patients meeting inclusion criteria, without non-inclusion criteria (sections 5.1 and 5.2), passed all the screening procedures, will be included into the study and randomized into one of the study groups

# **3 Purposes and objectives of the study**

## **3.1 Purpose**

The present study is aimed at evaluating efficacy of the drug Seroguard, solution, used for prevention of pelvic adhesions.

**Main purposes of the study:**

Comparison of efficacy of the drug Seroguard, solution, administered in the volume of 1.5 mL/kg or 2.4 mL/kg and placebo (0.9% sodium chloride) in the volume of 1.5 mL/kg or 2.4 mL/kg by presence, severity and prevalence of adhesions during laparoscopic treatment of pelvic adhesions.

Study of safety profile of the drug Seroguard, solution administered in the volume of 1.5 mL/kg or 2.4 mL/kg, in comparison to placebo (0.9% sodium chloride) in the volume of 1.5 mL/kg or 2.4 mL/kg during laparoscopic treatment of pelvic adhesions.

### **3.2 Study objectives**

1. To determine change in number of pelvic adhesions based on MRI data in post-surgical period in comparison to data of pre-surgical MRI data
2. To determine change in thickness of pelvic adhesions based on MRI data in post-surgical period in comparison to data of pre-surgical MRI data
3. To determine frequency of limited displaceability of pelvic organs in post-surgical period (based on results of transvaginal ultrasound investigation).
4. To determine frequency of hyperechoic linear lesions in post-surgical period based on results of transvaginal ultrasound investigation.
5. To determine changes in frequency of detecting limited displaceability in comparison to baseline (absolute change and in % of baseline value).
6. To determine changes in frequency of detecting hyperechoic linear lesions based on repeated transvaginal ultrasound investigation in comparison to baseline.
7. To determine frequency of detecting complete absence of USI – signs of adhesion process in pelvis in post-surgical period (defined as absence of limited displaceability of pelvic organs and absence of hyperechoic linear lesions)
8. To determine number of adhesions during surgery.
9. To determine number of dense adhesions during surgery.
10. To determine percentage of female patients with any adverse reactions.
11. To determine percentage of female patients with any serious adverse reactions.
12. To determine percentage of female patients with adverse reactions, relation of which to use of the test drug or the placebo is “definite”, “probable” or “possible”.
13. To determine percentage of female patients with serious adverse reactions, relation of which to use of the test drug or the placebo is “definite”, “probable” or “possible”.
14. To determine percentage of female patients with mild adverse reactions.
15. To determine percentage of female patients with moderate adverse reactions.
16. To determine percentage of female patients with severe adverse reactions.
17. To determine percentage of female patients with clinically significant changes in results of physical examination.
18. To determine percentage of patients with clinically significant changes in vital signs.
19. To determine percentage of female patients with clinically significant changes in electrocardiogram (ECG).
20. To determine percentage of female patients with clinically significant laboratory parameters.

## 4 Design of the study

### 4.1 Primary and secondary endpoints evaluated in the study

Primary endpoints evaluated in the study will be efficacy and safety parameters after single administration of the test drug or the placebo.

**Primary endpoint:** achieving clinical efficacy determined as:

Frequency of reducing number of adhesions after repeated MRI by 3 or more (in female patients with 10 and less adhesions at the baseline) or by 30% and more (in patients with >10 adhesions at the baseline)) in comparison to baseline MRI data

**Secondary efficacy endpoints:**

1. Change in thickness of pelvic adhesions by repeated MRI in comparison to baseline MRI data
2. Frequency of limited displaceability of pelvic organs in post-surgical period (based on results of transvaginal ultrasound investigation) on Day 30±4 after the surgery
3. Frequency of hyperechoic linear lesions in post-surgical period based on results of transvaginal ultrasound investigation
4. Change in frequency of detecting limited displaceability in comparison to baseline (absolute change and in % of baseline value)
5. Changes in frequency of detecting hyperechoic linear lesions based on repeated transvaginal ultrasound investigation in comparison to baseline
6. Frequency of detecting complete absence of USI – signs of adhesion process in the pelvis in post-surgical period (defined as absence of limited displaceability of pelvic organs and absence of hyperechoic linear lesions)

**Safety parameters:**

- Vital signs (body temperature, BP, HR, RR)
- Laboratory parameters:

Blood chemistry – total protein, glucose, ALT, AST, total bilirubin, alkaline phosphatase, amylase, creatinine

Complete blood count – RBC count, WBC count, platelet count, hemoglobin, hematocrit, WBC differential, ESR

Coagulogram – coagulation time, international normalized ratio (INR), thrombin time, activated partial thromboplastin time (APTT)

Urinalysis – color, transparency, pH, specific gravity, protein, glucose, WBC, RBC, bacteria, casts, salts

- ECG data – heart rate [HR], PR, QRS, QT intervals and calculated QTc interval.
- USI data

- Incidence of adverse reactions
- Incidence of serious adverse reactions
- Incidence of unexpected adverse reactions
- Incidence of adverse and serious adverse reactions caused termination/withdrawal from the study.

## **4.2 Description of the study design, graphical scheme of the study design, procedures and stages of the study**

### **4.2.1 Description of the study design**

A multicenter randomized double-blind placebo-controlled clinical study of efficacy and selection of dose of the drug Seroguard, solution (JSC Pharmasyntez, Russia) used for prevention of pelvic adhesions will be performed.

After successful completion of screening procedures, a female patient will undergo a planned laparoscopic surgery. Randomization of female patients into groups will be performed on the day of surgery using an online IWRS system (Interactive Web Response System). The test drug or the placebo are used at the final stage of the surgery. A female patient is planned to be under control in the hospital for 6 days after completion of the surgery. On Day 7 of the study, a female patient may be discharged from the hospital, if there are no any contraindications, in this case a follow-up of a female patient is performed on outpatient basis. Follow-up lasts for 4 weeks, up to Day 28 of the study. Then a complete evaluation of treatment efficacy after repeated MRI-investigation of the abdominal cavity and the pelvis is performed.

Study procedures aimed at evaluating safety and efficacy of the test drug and the placebo will be identical in all the groups:

- 1) Placebo group, 1.5 mL/kg – up to 30 screened female patients which corresponds to 26 randomizations and 24 completed cases
- 2) Placebo group, 2.4 mL/kg – up to 30 screened female patients which corresponds to 26 randomizations and 24 completed cases
- 3) Seroguard group, 1.5 mL/kg – up to 30 screened female patients which corresponds to 26 randomizations and 24 completed cases
- 4) Seroguard group, 2.4 mL/kg – up to 30 screened female patients which corresponds to 26 randomizations and 24 completed cases

#### 4.2.2 Graphical scheme of the study design

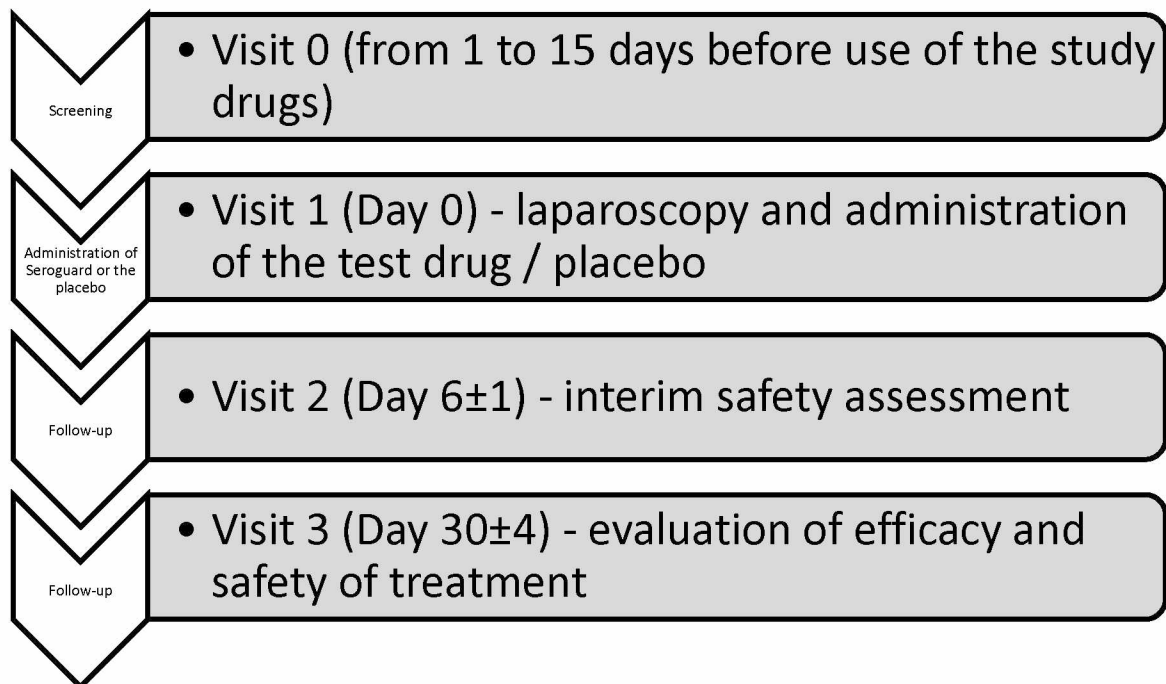


Figure 2 – Graphical scheme of the study

### 4.2.3 Description of the study procedures

**Table 1 – Schedule of the study procedures**

Procedures	Screening	Surgery	Follow-up		Unscheduled visit <sup>1</sup>	Withdrawal visit
	Visit 0	Visit 1	Visit 2	Visit 3		
	Day from -15 to -1	Day 0	Day 6±1	Day 30±4		
Informed consent	+					
Evaluation of inclusion, non-inclusion criteria	+	+				
Evaluation of withdrawal criteria			+		+	
Collection of medical and pharmacotherapeutic analysis	+					
Collection of demographic and anthropometric data	+					
Physical examination	+	+	+	+	+	+
Evaluation of local status		+	+	+	+	+ <sup>2</sup>
Measurement of vital signs <sup>3</sup>	+	+	+	+	+	+
HIV, RW, HBV and HCV blood test	+					
Pregnancy test	+			+		+
Randomization		+				
Complete blood count	+		+	+	+	+
Blood chemistry	+		+	+	+	+
Coagulogram	+			+		+
Urinalysis	+		+	+	+	+
MRI of abdominal cavity and pelvic organs	+			+		+
USI of abdominal cavity	+		+			+
USI of pelvic organs	+			+		+
Gynecological examination and colposcopy	+					
Cytological examination (Pap-smears)	+					
Smear microscopy	+					
Hysterosalpingography <sup>4</sup>	+					
12-lead ECG	+		+	+	+	+
Evaluation of concomitant therapy		+	+	+	+	+
Administration of the test drug/placebo		+				
Detection of ARs	+	+	+	+	+	+

<sup>1</sup> Any additional study procedure may be performed in case of indications, at the discretion of the Principal Investigator.

<sup>2</sup> If applicable

<sup>3</sup> Blood pressure, heart rate at the radial artery, respiration rate, body temperature will be measured.

<sup>4</sup> Performed at the discretion of a doctor for women included into the study with diagnosis “infertility”.



#### **4.2.3.1 Collection of demographic data and history, anthropometry**

During screening visit after signing informed consent, the following data will be collected from all the patients:

- Race, age (birth date).
- Body weight (kg), height (cm), BMI (kg/m<sup>2</sup>).
- Detailed medical history, including:
  - previous surgeries and traumas;
  - previous diseases
  - allergy history;
  - drugs used within the previous 30 days or 5 half-lives (which is longer) before visit of screening and used concomitantly, as well as herbal drugs and additives.
- Collection of gynecological anamnesis:
  - Beginning of menses and their nature;
  - Date of beginning of the last menses;
  - Presence/absence of previous pregnancies, their course and outcome;

Female patients signing informed consent should also provide consent to comply with efficient contraception throughout the study. Effective methods of contraception are use of one of the following methods (considering inclusion/non-inclusion criteria for the present study):

- Complete abstinence.
- Double barrier method: condom or occlusive cap (diaphragm or cervical/vault cap) plus spermicide (foam/gel/film/creme/suppository).

Women are obliged to comply with an adequate method of contraception throughout the whole study period.

#### **4.2.3.2 Physical examination**

Physical examination will be performed at all the visits in order to reveal normal or changed physical data of patients, that were before administration of the study drug, as well as to reveal possible changes during and after its use. Acceptable terms of investigation performance are specified in section 4.2.4.

Physical examination includes:

- general condition of female patient;
- condition of skin;
- musculoskeletal system;
- lymphatic nodes;
- thyroid;
- upper respiratory tract and lungs;
- heart, blood vessels;

- abdominal cavity organs, kidneys;
- psycho-neurological status.

#### **4.2.3.3 Evaluation of vital signs**

Evaluation of vital signs will be performed at each visit. Acceptable terms of performance are specified in section 4.2.4. Evaluation includes:

- measurement of axillary temperature;
- measurement of systolic and diastolic blood pressure (BP);
- count of heart rate per 1 minute;
- count of respiration rate (RR) per 1 minute.

Measurements are performed in seated or semirecumbent position after 5 minutes of rest on one and the same hand (for measurement of BP and heart rate) and, if possible, by one and the same specialist of a clinical site during participation of a particular female patient in the study.

#### **4.2.3.4 Evaluation of local status (condition of postsurgical wounds)**

To be evaluated:

- Palpatory tenderness
- Hyperemia
- Edema
- Presence of discharge

#### **4.2.3.5 Laboratory investigations**

Scheduled blood and urine tests will be performed at screening (after signing informed consent) (Visit 0) and during visits 2 and 3, as well as in case of unscheduled visit and withdrawal visit. The following laboratory parameters will be determined/evaluated for the given studies:

- Blood chemistry – total protein, glucose, ALT, AST, total bilirubin, alkaline phosphatase, amylase, creatinine.
- Complete blood count – RBC, WBC, platelet count, hemoglobin, hematocrit, WBC differential, ESR.
- Coagulogram – coagulation time, international normalized ratio (INR), thrombin time, activated partial thromboplastin time (APTT) – *performed only at visits 0, 3 and at withdrawal visit.*
- Complete urinalysis with sediment microscopy - color, transparency, pH, specific gravity, protein, glucose, WBC, RBC, bacteria, casts, salts.
- HIV, RW, HBV and HCV blood tests – *only at screening.*

Clinical laboratory investigations will be performed by local laboratory of a clinical site according to the standards of a respective site (including methods of biological sample collection and performance of laboratory investigations). Medical Investigator will obtain the study results,

review, evaluate clinical significance of each parameter deviation from normal values (used in the local laboratory), put date and signature and store as a primary documentation. Samples of blood and urine for laboratory investigations are taken in fasting conditions, i.e. within 10 hours before sampling, a female patient of the study should not eat and drink anything, except for water.

**Pregnancy test** will be performed at screening (Visit 0) and at Visit 3, as well as at withdrawal visit, in a clinical site using strip-test (lateral flow immunoassay of beta-chorionic gonadotropin in urine).

**Cytological examination (Pap-smear) and microscopic (bacterioscopic examination) examination of smears stained by Gram's method.** Smears for microscopy are taken from cervical canal, vagina and urinary tract. Smear is taken by spatula which does not injure mucosa of the specified organs and collect discharge in their lumen. Before collection of smears, gynecologist introduces a gynecological speculum into vagina. A material taken is applied on a glass slide and is sent to laboratory.

#### **4.2.3.6 Instrumental studies**

##### **Electrocardiography**

Acceptable terms of ECG performance are specified in section 4.2.4.

Standard 12-lead ECG (with measurement of heart rate [HR], PR, QRS, QT intervals and calculation of QTc) will be performed in prone position after 5 minutes of rest. Recording rhythm in the respective leads should contain evaluable data of at least three cardiac cycles. All the changes in ECG should be subjected to evaluation by a primary care physician.

If any changes in ECG, Medical Investigator should evaluate their clinical significance. If clinically significant deviations at screening, Medical Investigator should evaluate possibility of inclusion of patient into the present study, at Visit 2 and 3 or in case of unscheduled visit or withdrawal visit – to evaluate conformity to AR criteria (see section 8.2).

##### **Ultrasound investigation of abdominal cavity and retroperitoneum**

It is performed twice at Visits 0 and 2 as well as at withdrawal visit of the study as per the unique method presented in the separate guideline.

##### **Performance of pelvic USI**

Pelvic USI is performed at Visits 0 and 3 as well as at withdrawal visit of the study as per the unique method presented in the separate guideline, using transvaginal probe. Video recording of the performed investigation is required! Disc with the study results is attached to the primary documentation.

##### **Performance of MRI of abdominal cavity and pelvis**

The study is performed under fasting conditions (a female patient should starve before the investigation for at least 4 hours). 0.5 – 1.0 hours before the investigation, a female patient should

void the bladder and colon. Before the investigation, features of abdominal cavity and pelvic MRI performance will be explained to a female patient in detail.

MRI of the abdominal cavity and the pelvis is performed at Visits 0 and 3, as well as at withdrawal visit as per the protocol of MRI investigation which will be provided in a separate guideline along with evaluation of adhesion severity according to the following method defined by the Sponsor:

Prevalence in abdominal cavity:

1. absence of adhesions;
2. one floor (up to 3 segments of one level);
3. two floors;
4. total adhesive process.

Prevalence in pelvic cavity:

1. Absence;
2. One region (right lateral space, left lateral space, pouch of Douglas or vesicouterine pouch);
3. Two regions;
4. Subtotal adhesive process in the pelvis (3 regions);
5. Total adhesive process in the pelvis.

Maximum severity of adhesions:

1. Thin (filmy or filiform);
2. Severe;
3. Severe with impaired passage through organs involved into the process (narrowing of the intestines for more than ½ of the lumen or hydrosalpinx).

Score of assurance evaluation is given for every adhesion in its presence:

absolute assurance, that the adhesion is present – 4;

adhesion is, probably, present – 3;

adhesion is, possibly, present – 2;

difficult to determine whether adhesion is present or absent – 1.

Pelvic adhesion index is determined:

**PAI (pelvic adhesions index) = (A+B)\*Ccp,**

Determine as per the Tables A and B:

A – Prevalence of pelvic adhesive process		B – Maximum severity of adhesions	
Absence	0	Absence	0

One region (right lateral space, left lateral space, pouch of Douglas or vesicouterine pouch)	1	Thin (filmy or filiform)	1
2 regions	2	Severe	2
Subtotal adhesive process in the pelvis (3 regions)	3	Severe with impaired passage through organs involved into the process	3
Total adhesive process in the pelvis	4		

Ccp value is an arithmetic mean of assurance evaluation score during description of each detected adhesion.

Record of MRI-investigation results in DICOM-format will be sent to the study Sponsor for centralized evaluation in independent laboratory. Meanwhile, information on female patient by whom it could be identified, including therapy group, will remain blinded.

### Hysterosalpingography

Hysterosalpingography is performed at Visit 0 at the discretion of a doctor only for female patients included into the study with diagnosis of infertility. May not be performed in case of hysterosalpingography results obtained on Day 7-10 of menstrual cycle at least 6 months before visit 0.

Water-soluble contrast agents are most commonly used for hysterosalpingography (50, 70% solutions of Cardiotrast, 60, 76% solutions of Triombtrastum, 60, 70% solutions of Urotrast, 76% solution of Verografin, etc.). Performed using radiotransparent urological examination chair by digital radiography equipment which permits to decrease radiation dose for patient. She is put on the edge of a table in a position comfortable for vaginal procedures. After treatment of vulva with disinfectant, a bimanual pelvic examination is performed. Spoon-shaped vaginal speculum is introduced into vagina. Its walls are wiped by dry cotton ball, and then by cotton ball moistened with alcohol. Anterior lip of cervix uteri is caught by bullet forceps, without piercing cervical canal mucosa reach with receptors.

Schultz cannula consisting of a tube 30-35 cm length is used for hysterosalpingography. Its internal diameter is 1.5-2.0 mm. One end of tube is connected to 10 or 20-gramm syringe. A cone-shaped tip is fixed on the other end; it is introduced into cervical canal in order to close external orifice of the uterus. There is a "rider" with a screw on the tube, on which ends of bullet forceps are fixed so as to firmly retain the tip in the cervix. Cannula is filled with contrast agent heated up to the body temperature. After ensuring in tightly closed external orifice by introducing a small quantity of contrast agent into uterine cavity a speculum is removed, and the woman is placed on the table so as to permit a central roentgen ray to pass through the upper edge of the uterus. In order to protect a doctor from roentgen radiation along with X-ray protection apron, fixed on radiography equipment for urological investigations, a mobile lead screen protecting the body and legs of a doctor is used. 2-3 mL of contrast agent are used for obtaining a first image in order to get a uterine cavity three-dimensional image. After treatment and examination of the first image, 3-4 more mL of contrast agent are added and the second image is obtained. In this case tighter filling of uterine cavity is obtained, and the contrast agent gets into tubes and abdominal cavity. After examination

of a second image, a third image is obtained, if needed. 10-20 mL of contrast agent are usually used for the whole procedure. During hysterosalpingography using radiography equipment with electro-optical converter on a TV screen, gradual filling of uterine cavity and tubes, movement of contrast agent into abdominal cavity may be seen, images are made while filling uterine cavity and tubes. On the day of procedure, it is required to shave pubic hair, and if no stool, perform cleansing enema. Before the procedure, void the bladder. After the procedure, patients should have rest on a couch for 40-60 min.

### **Gynecological examination**

Gynecological examination of vulva, vagina and cervix is performed at Visit 0 as per the medical-economical standard (the study using speculum and bimanual examination) with obligatory recording of the following parameters:

- color of vaginal and cervical mucosa;
- presence or absence of abnormal changes (scars, polyps, erosions);
- form of cervix (conical, cylindrical, deformed);
- form of exterior mouth of the uterus (round, slit-like);
- nature of discharge

### **Colposcopy**

Colposcopy represents a diagnostic examination of vaginal orifice, vaginal walls and portio vaginalis using colposcope (lightening device and binocular with 40-fold magnification). Before the procedure, a woman should abstain from sex, vaginal douche, use of vaginal tablets and other topical drugs several days before the visit to a doctor. On the day of the procedure, a woman should wash her genitals with warm water and soap. There are not restrictions on the day of menstrual cycle.

Procedure of colposcopy is the following – after a careful introduction of speculum, examine cervix and remove mucus. When introducing speculum and wiping cervix with cotton wool ball, try not to traumatize mucosa, otherwise it will be impossible to evaluate epithelium changes correctly. After introduction, a colposcope is fixed at the distance of 20-25 cm from the surface examined. Beam of light is directed on the cervix and, looking through the colposcope, ocular lenses are fixed so as to obtain a clear image of mucosa vaginal part of cervix, vaginal walls or vulva. Cervix is examined clockwise or by zones.

Then, 3% acetic acid is applied on uterine cervix, under its effect, mucosa is removed, and epithelium cells become whitish-grey. Acetic acid solution starts to act 30-60 seconds after application of mucosa and lasts for 3-4 minutes. Then 2% Lugol's aqueous solution is applied, after that a healthy mature stratified squamous epithelium of uterine cervix is colored into dark-brown color (positive Shiller's test). All the abnormal sites of tissue after exposure of Lugol's solution are not colored or colored into slightly-yellowish.

#### **4.2.4 Description of periods and visits of the study**

##### ***4.2.4.1 Screening period***

#### **Visit 0 (from Day -15 to -1 of the study)**

The following will be performed at the visit:

- Obtaining informed consent (see section 12.2). All the screening procedures will be performed only after obtaining informed consent.
- Collection of history, demographic and anthropometric data, gynecologic history (see section 4.2.3.1).
- Collection of information on previous therapy (see section 4.2.3.1).
- Physical examination (see section 4.2.3.2).
- Evaluation of vital signs (see section 4.2.3.3).
- Laboratory investigations: complete blood count, blood chemistry, urinalysis, coagulogram, pregnancy test, HIV, HBV, HCV and RW blood test (see section 4.2.3.5).
- ECG (see section 4.2.3.6).
- USI of the abdominal cavity, pelvis (see section 4.2.3.6).
- MRI of the abdominal cavity and the pelvis (see section 4.2.3.6).
- Gynecological examination and colposcopy (see section 4.2.3.6).
- Cytological examination (PAP-smears) (see section 4.2.3.5).
- Microscopic (bacterioscopic examination) examination of the smear stained by Gram's method (see section 4.2.3.5).
- Hysterosalpingography (see section 4.2.3.6).
- Evaluation of inclusion/non-inclusion criteria compliance (see section 5).
- Evaluation of AR (see section 8).

##### ***4.2.4.2 Therapy period***

#### **Visit 1 (Day 0)**

*Before the surgery:*

- Physical examination (see section 4.2.3.2).
- Evaluation of vital signs (see section 4.2.3.3).
- Actualization of the information on concomitant therapy.
- Actualization of the information on concomitant diseases.

- Re-evaluation of inclusion/non-inclusion criteria (see section 5).
- Randomization (see section 4.3.1).
- ***Surgical intervention using the test drug or the placebo***

*After the surgery:*

- Physical examination (see section 4.2.3.2).
- Evaluation of vital signs (see section 4.2.3.3).
- Evaluation of local status (condition of postsurgical wounds). (see section 4.2.3.4)
- Evaluation of AR (see section 8).

#### **Visit 2 Interim safety assessment (Day 6±1)**

- Physical examination (see section 4.2.3.2).
- Evaluation of vital signs (see section 4.2.3.3).
- Evaluation of local status (condition of postsurgical wounds). (see section 4.2.3.4) .
- Evaluation of withdrawal criteria (see section 5.3)
- Laboratory investigations: complete blood count, blood chemistry, urinalysis (see section 4.2.3.5).
- USI of the abdominal cavity (see section 4.2.3.6).
- ECG (see section 4.2.3.6).
- Actualization of the information on concomitant therapy.
- Actualization of the information on concomitant diseases.
- Evaluation of AR (see section 8).

#### **Visit 3 (30±4) Evaluation of safety and efficacy**

- Physical examination (see section 4.2.3.2).
- Evaluation of vital signs (see section 4.2.3.3).
- Evaluation of local status (condition of postsurgical wounds).
- Laboratory investigations: complete blood count, blood chemistry, coagulogram, urinalysis, pregnancy test (see section 4.2.3.5).
- USI of pelvic organs (transvaginal) (see section 4.2.3.6).
- MRI of the abdominal cavity and the pelvis (see section 4.2.3.6).
- ECG (see section 4.2.3.6)
- Actualization of the information on concomitant therapy.



- Actualization of the information on concomitant diseases.
- Evaluation of AR (see section 8).

#### **4.2.4.3    *Unscheduled visit***

Unscheduled visit may be performed at the discretion of the Investigator in case of ARs for performance of the required investigations. During each unscheduled visit regardless of its reason, the Investigator performs the following procedures and completes respective pages of CRF (Additional/Unscheduled visit):

- Physical examination (see section 4.2.3.2).
- Evaluation of vital signs (see section 4.2.3.3).
- Evaluation of local status (condition of postsurgical wounds).
- Evaluation of withdrawal criteria (see section 5.3)
- Laboratory investigations: complete blood count, blood chemistry, urinalysis (see section 4.2.3.5).
- ECG (see section 4.2.3.6).
- Actualization of the information on concomitant therapy.
- Evaluation of AR (see section 8).

If any indications, any study procedure may be performed additionally (see section 4.2.3). Respective pages of CRF are completed in this case.

#### **4.2.4.4    *Withdrawal visit***

Medical aid is performed as per the standards accepted in the specific healthcare institution in case of withdrawal of patient from the study. Visit of withdrawal from the study will be similar to completion Visit 3 by contents.

- Physical examination (see section 4.2.3.2).
- Evaluation of vital signs (see section 4.2.3.3).
- Evaluation of local status (condition of postsurgical wounds) (see section 4.2.3.4) .
- Evaluation of AR (see section 8).
- USI of pelvic organs (transvaginal) (see section 4.2.3.6).
- MRI of the abdominal cavity and the pelvis (see section 4.2.3.6).
- USI of the abdominal cavity (see section 4.2.3.6).
- Laboratory investigations: complete blood count, blood chemistry, coagulogram, urinalysis, pregnancy test (see section 4.2.3.5).
- ECG (see section 4.2.3.6).

If a female patient is withdrawn from the study before discharge from the hospital, withdrawal visit is performed on the same day. If a female patient is withdrawn from the study already after discharge from the hospital, the visit should be performed within 5 days after it became known on withdrawal of a female patient. If a hospitalized patient refuses to pass the visit procedures, it may be limited by collection of information on AR. If an ambulatory patient refuses to come to a withdrawal visit, a phone contact (in exceptional cases) is accepted.

A follow-up will be performed for patients withdrawn from the study voluntarily and with ARs. The follow-up will last until recovery of the study patient condition, until stabilization or establishing chronic AR.

### **4.3 Measures aimed at minimization of subjectivity**

#### **4.3.1 Randomization procedure**

After signing informed consent for participation in the present study by female patient, confirmation of inclusion criteria presence and non-inclusion criteria absence, all the study subjects will be distributed into groups of treatment by method of centralized block randomization in 1:1:1:1 ratio, without stratification by center using online IWRS system (Interactive Web Response System). Randomization ID of patient will be assigned to a female patient as per the order of access to IWRS system. Whereby randomization IDs corresponding to administration of the test drug or the placebo will be randomly assigned to the equal number of patients.

1. Placebo group, 1.5 mL/kg – up to 30 screened female patients which corresponds to 26 randomizations and 24 completed cases
2. Placebo group, 2.4 mL/kg – up to 30 screened female patients which corresponds to 26 randomizations and 24 completed cases
3. Seroguard group, 1.5 mL/kg – up to 30 screened female patients which corresponds to 26 randomizations and 24 completed cases
4. Seroguard group, 2.4 mL/kg – up to 30 screened female patients which corresponds to 26 randomizations and 24 completed cases

A block generation of randomization sequence will be used for generation of randomization list. Randomization list will be generated in statistics software using random number generator at the stage of preparation for the study

Only randomization ID of the study female patient will be recorded in CRF without specifying the drug administered.

The Investigators will pass an online training on using IWRS system.

Register of screened and randomized female patients will be performed for all the sites. Form of register is provided in the Study Site File. Completion of the form should be performed by the Investigator on a regular basis with entering all the required data.



## 4.4 Description of the drugs used in the study – description of the dosage form, packing and labeling

### 4.4.1 Dosage form, composition and clinical-pharmacological characteristics

**Trade name:** Seroguard

**International non-proprietary name of the drug – not determined**

**Chemical name:** conjugate of hydrochloride 4-[4-(4-fluorophenyl)-2-[4-methylsulfinyl)phenyl]-1H-imidazol-5-pyridine with poly-1-vinylimidazole.

**Dosage form:** Solution for intracavitary administration.

**Composition** per 1 mL of solution.

<i>Active ingredients:</i>	<i>Quantity</i>
Hydrochloride 4-[4-(4-fluorophenyl)-2-[4-methylsulfinyl)phenyl]-1H-imidazol-5-pyridine (functional imidazolinium salt)	0.01 mg
Poly-1-vinylimidazole	0.4 mg
<i>Excipient:</i>	
Water for injection	up to 1 mL
Theoretical osmolality	0.073 mOsm/L

#### **Active ingredient:**

conjugate of hydrochloride 4-[4-(4-fluorophenyl)-2-[4-methylsulfinyl)phenyl]-1H-imidazol-5-pyridine with poly-1-vinylimidazole - 0.41 mg/mL.

#### **Description**

Transparent colorless liquid.

#### **Pharmacotherapeutic group:**

**ATC code:** L04AA

#### **Pharmacological properties**

##### **Pharmacodynamics**

The drug doesn't exert systemic influence on organs and systems of the body. It exerts local action. It is known that in case of injured serous membrane, in particular, in case of peritoneal trauma, a hyperexpression of a set of genes is observed. They are responsible for synthesis of biologically active substances (interleukins, integrines, growth factors, signaling cascades), which launch inflammatory process and process of reparation. Hyperexpression of genes responsible for synthesis of collagen is observed from Day 3 to Day 14, maximum on Day 3. A set of gene co-expressions changed during reparative process in response to abdominal alteration is known.

Administration of Seroguard significantly modifies response of cells to alteration causing significant decrease in anti-inflammatory cytokine gene expression by Week 2 of the process, a sharp decrease of Csf3 colony-stimulating factor activation, interruption of second wave of activation of growth factor expression, suppression of a set of genes (Egf, Pdgfa, Tgfa). Decreased activity of Wisp1 gene happens which codes main chain of WISP signaling pathway, maintaining proliferative activity of fibroblasts, and decreases activation of Col5a3 collagen gene is significantly decreased.

Experimental studies demonstrated that during administration of Seroguard, solution, cell response is significantly changed in the site of abdomen injury from the point of view of gene activity coding proteins of focal adhesion. Main fixed shifts are an earlier activation of these gene transcription (starting from Day 1 of the process in comparison to Day 3 in control), after which an activity is sharply decreased and is left less than in control group up to the end of follow-up. Decreased expression of membrane proteins of adhesion and related proteins of cytoskeleton, probably, interferes with interaction of cells with each other and with interstitial matrix in time corresponding to conversion of fibrin adhesions into fibrous adhesions.

p38 ( $\beta$ ,  $\gamma$ ,  $\delta$  subunits), p44 and JNK3 kinases similar by 3-dimensional structural organization act as main biological targets in the mechanism of Seroguard action, which allows to consider MAP kinase inhibition to be main in the mechanism of action of the drug.

### **Pharmacokinetics**

After intravenous administration to rats at the dose of 6.15 mg/kg, peak of concentration is observed at about 15 minutes after administration and is  $38.89 \pm 2.50$   $\mu\text{g/mL}$ .

Half-life is  $4.25 \pm 0.07$  h.

Mean retention time is about 5.9 hours.

Volume of distribution is about 1300 mL/kg.

After intraperitoneal administration to rats at the dose of 6.15 mg/kg, the drug in blood plasma is not observed, which evidences absence of its significant absorption by the given route of administration.

### **Indications**

Prevention of adhesions

### **Contraindications**

Allergy to the drug components.

Intra-abdominal administration — purulent process in the abdominal cavity and the pelvis.

Gynecological surgery — purulent process in the abdominal cavity and the pelvis.

Intrapericardial administration — presence of infectional pericarditis.

Intra-articular administration — presence of infected wounds, abrasions in the joint; joint infection; venous or lymphatic stasis from the side of injured joint.

Not tested in pregnant patients, patients under 18, patients with hepatic or renal failure.

Studies in animals did not show any toxic activity or negative effect on reproductive function and fertility by Seroguard.

### **Posology and method of administration**

Administered into serous cavity by method of single irrigation (from syringe, without injuring abdominal mesothelium) in aseptic conditions before completion of surgery. Re-administration is not recommended.

Before administration, aspirate all remaining fluids (blood, exudate, solutions administered intraoperatively).

Before use, heat the solution to body temperature.

Doses for adults:

For abdominal cavity surgery, the drug is administered at the dose of 2.4 mL/kg body weight into abdominal cavity.

For gynecological surgery, the drug is administered into abdominopelvic cavity at the dose of 1.5 to 2.4 mL/kg providing post-surgical position preventing discharge of the drug from the pelvic cavity.

For surgeries related to pericardium dissection, the drug is administered intrapericardially at the dose of 0.05 mL x left ventricular stroke output.

For administration into joint cavity during arthroscopy - up to 2 mL depending on the volume of joint.

The drug is intended only for administration into serous cavity, intravenous administration is unacceptable. Do not mix with other drugs. Do not use as a vehicle of other drugs as antibiotics, chemotherapeutic agents, etc.

### **Side effect**

In the Phase I clinical study, general incidence of side effects on administration of the drug Seroguard was similar to those during administration of the placebo. During the study, the following side effects possibly related to administration of the drug were found: hyperthermia (1.8 %), pain in infraclavicular region (0.9 %), increased WBC count in blood (0.9 %).

### **Overdose**

No information on overdose of the drug Seroguard is available.

#### **4.4.2 Packing and labeling**

Primary packing: 50 mL, 100 mL, 150 mL, 200 mL, 230 mL, 250 mL into type I-III USP dark glass vials. Vials are sealed with butylrubber stopper, crimped with aluminum cap.

Secondary packing: 1 vial along with package insert into consumer's carton pack.

### ***Labeling of the study drugs***

Labeling should provide security of the study subject, possibility of tracking and identification of the drug and the study and it should contribute to correct use of the drug in the study.

The following information should be provided on the label of the test drug/placebo:

- dosage form, route of administration, number of dosage units;
- code for identification of contents;
- number (code) of the study, information on the Investigator, Visit No;
- identification No (ID) of female patient of the clinical study – entered in the study site after access to IWRS system and before delivery of the drug for surgery performance;
- signature: “For clinical studies”;
- storage conditions;
- period of use with specifying month and year so as to avoid any confusion (data until which the drug should be used, expiry date or retest date may be specified);

Symbols and pictograms may be used in order to clarify the above information. An additional information, warning and/or package insert may be provided.

Name, address and phone number of the Sponsor, contract research organization or the Investigator contractually employed (main contact to obtain information on the drug, the clinical studies and for urgent decodification) will be specified on a card which will be kept by a female patient throughout the clinical study.

If it is necessary to change the date of using the drug, it's necessary to apply an additional label on the pack. On an additional label, there should be a new date until which the drug should be used as well as Batch No should be specified again. An additional label may be applied on a previous date of use, but it should not cover an initial Batch No which is related to quality control. This procedure may be performed at the manufacturing site which has a right to do it. If necessary, this may be performed in the study institution by pharmacist performed clinical studies or under his/her control, as well as by other medical staff as per the requirements of the acting legislation. If it is impossible, the procedure may be performed by a person who has passed respective training. The procedure should be performed as per the GMP requirements according to the special and standard methods and, if required, by the contract; the procedure should be controlled by a second person. An additional labelling should be thoroughly documented both in clinical study documents and in Batch protocols.

#### **4.4.3 Storage conditions**

Store in the original manufacturer's container at the temperature from 2 to 8°C.

Keep out of reach of children.

Shelf life: 18 months. Do not use after an expiry date specified on pack.

#### **4.4.4 Principles of the study drug dosing**

The test drug or the placebo are administered into abdominal cavity at the end of the surgery at the dose of 1.5 mL/kg or 2.4 mL/kg according to the draft package insert. Justification of the dose is provided in section 2.4.

#### **4.4.5 Additional therapy methods**

- Immediate mobilization

- During post-surgical period for all the groups, management of patients is as per the accepted standards

#### **4.5 Expected duration of participation of female patients in the study**

Screening period (up to 15 days before the surgery)

Treatment period (Day 0)

Interim safety evaluation (Day 6±1)

Evaluation of treatment efficacy (Day 30±4 days)

Considering the given periods, the minimum duration of the study for female patient is 28 days, and the maximum duration is 50 days.

#### **4.6 Description of “termination rules” or “withdrawal criteria” for separate subjects or the study, in general.**

Withdrawal criteria for separate subjects of the study are described in section 5.3.

According to the Article 40 of the FL No 61-Φ3 “On drug circulation” dated 12.04.2010 as amended and the requirements of the Good Clinical Practice of the Russian Federation, approved by the order of the Ministry of Health of the RF dated 19.06.2003 No 266, a clinical study may be discontinued or terminated, if in the process of its performance, hazard to life, health of patients is revealed. In case of revealed hazard to life, health of a female patient of the clinical study, investigators are obliged to inform on this a head of healthcare institution or organization that obtained permission of authorized federal agency for conducting the clinical study of the drug. Decision on discontinuation of the clinical study of the medical drug is made by a head of the healthcare institution and (or) the Sponsor of the study (or CRO)<sup>1</sup>, decision on termination of such a study is made by an authorized federal agency based on written report by the head of medical organization or organization of the study Sponsor (or CRO).

Report on completion, discontinuation or termination of the clinical study of the medical drug is sent to an authorized federal agency as per the form established by it within five working days from the date of such completion, discontinuation or termination of the clinical study.

The Investigator must immediately inform the study subjects on discontinuation or termination of the study, provide them adequate medical care and follow-up. Upon termination of the study the Investigator must assure that interests of the study subjects are adequately protected.

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<sup>1</sup> Organization obtained permission from an authorized federal agency for organization of the clinical study of the medical drug.



The Investigator and (or) healthcare institution should immediately inform the Sponsor of the study (or CRO) on termination or discontinuation of the study with detailed explanation of reasons in the written form.

If the study Sponsor (or CRO) discontinues or terminated the study, the Investigator should immediately inform the administration of the healthcare institution on this.

The Investigator and (or) healthcare institution should immediately inform Ethics Committee on discontinuation or termination of the study with detailed explanation of reasons in the written form.

If Ethics Committee finally or temporarily recalls decision on the study performance, the Investigator should inform the administration of the healthcare institution on this.

The Investigator and (or) healthcare institution should immediately inform an organization-developer on final or temporary recall of decision for performance of the clinical study with detailed written explanation of reasons.

The clinical study may be discontinued or terminated, if an authorized federal agency provides a conclusion on performance of the clinical study with violation of Good Clinical Practice requirements based on results of checking activity of one or several healthcare institutions performing clinical studies of the drug.

The study performance in a separate clinical site may be terminated, if the Sponsor or its representatives, Investigator, regulatory bodies or LEC of a clinical site consider it to be necessary for any reason.

## **4.7 Procedures for accounting the study drugs**

### **4.7.1 Preparation and distribution of the study drugs**

Quantity of the study drugs (Seroguard and placebo) will be sufficient for the whole therapy period. Every participating clinical site should use the study drugs only for the purposes under the present clinical study in strict compliance with the study protocol.

The Sponsor or its representative will provide all clinical sites with special forms of accounting receipt, distribution and return of the study drugs for facilitation of physical inventory procedure.

An employee of a clinical site responsible for circulation of the study drugs should maintain a log for accounting the study drugs. Date when the drugs were received in the clinical site, distribution among female patients and return of unused drugs are recorded in the log. Account of the study drug number should be documented throughout the study.

In case of unreasonable delay in the study performance, an authorized employee of the site responsible for circulation of the drugs in the study should confirm that their shelf life is not over.

Compliance with the dosage regimen of the study drugs will be provided by the nature of the study – the drugs will be administered to patients in the hospital.

The Medical Investigator is responsible for the study drugs:

- to be used only for the female patients of the present study;
- to be kept locked up and in a safe place having access only for employees taking part in the study before administration to a female patient of the study;
- to be strictly accounted, and the account of the drugs is documented with indication of the ID of a study subject who used the drug.

#### **4.7.2 Supplies, disposal, accounting the study drugs**

The study drugs packed and labeled according to the current requirements (see section 4.4.2) will be provided by the Sponsor in the amount sufficient for performance of the whole study. A clinical site receives the study drugs from the study Sponsor as per the acceptance certificate.

The Investigator should keep records in the Log for accounting the study drugs reflecting number of used and unused drug in order. An authorized representative of the Sponsor regularly checks how the Investigator uses the drugs by counting their number.

After completion of the study, an employee of a clinical site responsible for circulation of the test drug and the placebo should provide the Sponsor or the study monitor with the originals of completed forms of receipt, distribution and return of the study drugs. Upon completion of the study, it is necessary to perform count of the drugs and to provide a written explanation in case of any non-conformances. Packs of the used drugs and the unused drugs should be returned to the Sponsor. Return is performed as per the acceptance certificate.

The Sponsor confirms a final report on accounting the drugs, one original of which is placed into the Investigator file.

The Sponsor is responsible for disposal of the unused and/or returned drug products for the study. It is not accepted to dispose drug products for the clinical studies without permission from the Sponsor. In case of drug disposal, the Sponsor should be provided a certificate of destruction with date or another document on disposal. Batch Nos and/or patient IDs (or possibility of their tracking should be provided), and number of the drugs disposed should be specified in these documents.

### **4.8 Storage of randomization codes**

See also section 4.3.1

The Principal Investigator will be provided an envelope with information for decoding the group of patient by randomization ID. The Principal Investigator will be responsible for storage of envelope with decoding information so as to provide confidentiality and integrity of information, but with preserved possibility of access, if it is necessary to disclose randomization ID. Upon completion of the study, the Principal Investigator must return the envelope to the Sponsor despite the fact whether it was opened or not.

In case of unintentional unblinding of female patient or staff of the clinical site, the Sponsor should be informed immediately.

In cases when unblinding of the treatment group and the drug administered is required to provide safety of the study subject (for example, in case of AR development), unblinding should be

performed after approval and consent of the Sponsor's medical expert. If it is technically impossible, and unblinding is required by vital indications, the medical expert of the Sponsor should be informed on the given fact as soon as possible.

Unblinding of randomization ID, in general, will be performed upon completion of the study and database shutdown.

#### **4.9 List of data recorded directly in the CRF and considered as primary**

All the data will be initially entered into primary documentation (medical history or medical record) of female patient, and only then they will be transferred into CRF of the study patient.

### **5 Selection and exclusion of the study subjects**

#### **5.1 Inclusion criteria**

1. Female patients aged from 18 to 45 years with confirmed diagnosis of pelvic adhesions with indications for surgery (laparoscopic adhesiolysis)
2. Voluntarily and personally signed and dated Form of Informed Consent to participate in the study
3. Female patients with pelvic adhesions confirmed by gynecological examination and USI

#### **5.2 Non-inclusion criteria**

1. Female patients having contraindications to operative treatment (including acute or exacerbated chronic adnexal inflammatory process)
2. Body mass index  $30.0 \text{ kg/m}^2$  and more
3. Known hypersensitivity to components of the test drug (Seroguard)
4. Pregnancy, lactation or planning for pregnancy during the clinical study
5. Refusal to use effective contraception methods throughout the study
6. Positive HIV, RW, HBV or HCV test results.
7. Alcohol abuse, drug addiction, and toxicomania (except for smoking)
8. Category III and higher by physical status classification of the American Society of Anesthesiologists (ASA).
9. Purulent process in the abdominal cavity
10. Disseminated endometriosis
11. Elevated WBC count in complete blood count exceeding  $10 \times 10^9/\text{L}$

12. Necessity of using any other drugs during the surgery (except for 0.02% chlorhexidine aqueous solution throughout the surgery, as well as the test drug or the placebo (0.9% sodium chloride) in the end of surgery) administered intraperitoneally
13. Concomitant diseases that may require conversion of the surgical intervention by other indications
14. Type I or II diabetes mellitus
15. Deep vein thrombosis and/or PATE at screening or in the history
16. Renal impairment (reduced glomerular filtration rate below 60 mL/min/1.73 m<sup>2</sup> evaluated by the CKD-EPI equation)
17. Liver disorders determined as more than 2-fold elevation of the upper limit of normal of one of the following enzymes: ALT, AST, GGTP, AP, or more than 2-fold elevation of total bilirubin level
18. Myocardial infarction within 6 months before screening
19. Any concomitant diseases accompanied by heart failure.
20. Clinically significant changes in ECG (in Investigator's opinion).
21. Any concomitant diseases accompanied by respiratory failure
22. Any oncology disease within 3 years before enrollment into the study.
23. Systemic inflammatory diseases.
24. Diseases associated with chronic hemorrhages
25. Blood diseases (anemias of any origin, hemoglobinopathies, inherited and acquired coagulopathies, hemostasis disorders, thrombocytopenias, and thrombocytopathias, any hemoblastoses)
26. Any other disease, that, in the Investigator's opinion, may distort the study results or present an additional threat to well-being of a female patient after administration of the study drug
27. Administration of anticoagulants, antiaggregants (except for acetylsalicylic acid at the dose of less than 325 mg/day) at the moment of inclusion into the study or planning to do so during the study.
28. Administration of drugs with pronounced hemato-, hepato-, or nephrotoxic action, drugs of biological origin
29. Necessity of administration of cytostatics, systemic glucocorticosteroids and other immunosuppressive agents in the period of participation in the study.
30. Participation in another clinical study within 30 days before screening
31. Contraindications for performance of MRI (presence of implants or implanted electronic devices)

32. Impossibility or inability to comply with the requirements of the protocol, including those for physical, psychic or social reasons, in Investigator's opinion

### **5.3 Withdrawal criteria**

1. Withdrawal of informed consent by female patient
2. Female patient's non-compliance with the rules of participation in the study.
3. Pregnancy occurrence.
4. Necessity of conversion during surgical intervention
5. Necessity of surgery during the period between adhesiolysis surgery and Visit 3
6. Other reasons occurring during the study and interfering with the study performance in accordance with the protocol.
7. Necessity of drain tube installation revealed during the surgery

#### **5.3.1 Early withdrawal**

Patients willing to terminate their participation in the study (recall of informed consent) are withdrawn from the study. Each female patient has a right to terminate her participation in the study at any time without explaining the reasons.

After randomization and beginning of a clinical phase, the Medical Investigator may prematurely exclude a female patient from the study in case of:

- Female patient's refusal to continue participation in the study.
- Occurrence of reasons/appearance of situations threatening safety of female patient found during the study (for example, hypersensitivity reactions, serious life-threatening adverse reactions related to the drug administration, pregnancy of female patient).
- Development of diseases in a female patient described in non-inclusion criteria, required administration of the drugs not permitted by the protocol.
- Appearance of another reasons during the study interfering with performance of the study according to the protocol.

Detection of reasons of withdrawal from the study in patients included into the study leads to their exclusion from the study at the stage of detection of these reasons. In any case of early termination by female patient/withdrawal of female patient from the study, the Medical Investigator should make a respective record in the CRF with obligatory indication of early termination or withdrawal from the study as well to inform the Sponsor's representative.

#### **5.3.2 Collection of data on the study participants early terminated their participation in the study**

All the cases of withdrawal of female patients from the study will be documented. The Investigator should specify date and reason of early withdrawal from the study in the primary documentation and the CRF in section for the study completion.

If a patient terminates participation in the study voluntarily, the Investigator should try to find out the reason. If an early termination of a female patient is related to AR or serious adverse reaction (SAR), the Investigator should make every effort for collection of information on its outcome and to record it in the CRF, section on AR/SAR. If exclusion/withdrawal from the study was related to SAR, it is necessary to follow the procedure on notification of the Sponsor on SAR (see section 8.3).

All ARs developed during the study in female patients withdrawn from the study, including ARs to the moment of terminating participation of female patient in the study will be analyzed and included into a final report on the study performance.

If withdrawal/exclusion from the study was after administration of the study drug to a female patient, her data collected before the moment of withdrawal/exclusion from the study will be analyzed during analysis of safety and, if possible, during analysis of efficacy. Approaches to analysis of data on the study participants early terminated their participation in the study are described in section 9.5.

#### **5.3.3 Substitution procedure**

Female patients withdrawn before randomization will be substituted by new female patients (in the volume considered by the calculated number of female patients screened). Female patients withdrawn from the study after randomization and beginning of the therapy will not be replaced by new ones, and their data will be considered in the final analysis (see section 9.5).

#### **5.3.4 Follow-up of female patients early terminated the study**

Follow-up of female patients withdrawn from the study is not planned intentionally. See also section 4.2.4.4.

If a female patient was withdrawn from the study due to the reason of AR/SAR, she is followed up due to resolution of the AR/SAR or until the Investigator considers it to be “chronic” or “stable”. The follow up of female patients of the study withdrawn from the study and, in the meantime, having ARs or having other parameters of safety, which could cause therapy termination, is described in section 8.4.

## **6 Treatment of the study subjects**

### **6.1 Dosage regimen of the test drug and the placebo**

See section 4.4.4.

### **6.2 Previous and concomitant therapy**

Previous therapy is intake of the drugs or non-drug therapy by a female patient *before the moment of inclusion into the study* (an information on the drugs received by female patient within 30 days before Visit 0 is collected).

Concomitant therapy is intake of the drugs or non-drug therapy by a female patient *at the moment of her inclusion into the study and in the period of participation in the study*.

Information on *previous therapy* will be collected and evaluated by Medical Investigator based on data of patient record/medical history and patient's questionnaire (collection of medical history) during selection of candidates for participation in the study and during screening period (Visit 0).

Information on *concomitant therapy* will be collected and evaluated by Medical Investigator based on data of patient record/medical history and patient's questionnaire of the study during the following periods:

- Administration of the test drug or the placebo (Visit 1);
- Follow-up visit (Visits 2-3).

Data on the drugs used for previous and concomitant therapy, dose, route and frequency of administration, dates of beginning and completion of the therapy, should be entered into primary documentation and into the CRF. Information on the test drug/placebo will be entered into a separate/specified for this section of the CRF.

#### 6.2.1 Permissible previous and concomitant therapy

Any previous therapy, except for described in section **Ошибка! Источник ссылки не найден.**, is acceptable.

Female patients also may receive any drugs administered by a doctor and required for treatment of concomitant diseases/contraception, except for the drugs that may interfere with interpretation of new data obtained during the study (see section **Ошибка! Источник ссылки не найден.**). Decision on administration of the concomitant therapy drugs will be made by the Medical Investigator at his/her discretion and in case justified necessity of such an administration. Continuation of therapy with drugs not included into the list of forbidden therapy should be agreed before inclusion of patient into the study.

#### 6.2.2 Forbidden previous and concomitant therapy

- During the surgery, it is forbidden to use any drugs intraperitoneally, except for normal saline or 0.02% chlorhexidine bigluconate as well as the test drug and the respective placebo before suture of surgical wound.
- Systemic glucocorticosteroids, cytostatics and other immunosuppressors.
- Anticoagulants, antiaggregants (except for acetylsalicylic acid at the dose of less than 325 mg/day).
- Oral contraceptives (combined drugs, containing estrogen component and progestogen, or progestogen only), used for at least 4 weeks/1 menstrual cycle before the first use and 4 weeks/1 menstrual cycle after the last use of the drugs compared.
- Injectable progestogen.
- Implants with progestogen.
- Vaginal ring containing estrogen and progestogen components.
- Transdermal system containing estrogen and progestogen components.

- Copper-containing intrauterine system.
- Levonorgestrel-releasing intrauterine system.

If during the study, it becomes necessary or it is established that the drugs or therapy methods specified in the present section are used, a female patient should be withdrawn from the study.

#### **Use of forbidden or not specified by the protocol drugs and therapy methods**

In case of single and/or irregular administration of the drugs specified in the present section, decision on inclusion of patient into the study is made by the Medical Investigator.

If during the study, it becomes necessary or it is established that the drugs or therapy methods specified in the present section are used, a female patient should be withdrawn from the study.

### **6.3 Methods of control for compliance with the procedures by the study subjects**

#### **6.3.1 Measures to provide compliance**

In the present clinical study, the test drug and its respective placebo will be administered into cavity of the pelvis at the final stage of the surgery by the Medical Investigator once at Visit 1. Due to this, control of patient compliance with treatment is not required.

In order to provide compliance with the visit schedule, a coordinator of the clinical site preliminarily, before the scheduled outpatient visit, reminds the study subject on date and time of visit (phone call, fax, e-mail, etc.). If it is impossible to contact with the study subject, a phone call is made to a relative or connected person of the study subject. Attempts to contact with the study subject, her relative or connected person are made thrice.

Regardless of contact type, the Investigator receives a confirmation on received reminder from the study subject, on which a record is made in the Log of phone calls.

If the study subject can not visit the study site at the next scheduled visit, a possible postpone of visit is discussed considering acceptable deviations.

#### **6.3.2 Evaluation of compliance**

Not applicable. The drug is administered once, intraperitoneally by the staff of the clinical site.

## **7 Efficacy evaluation**

### **7.1 List of efficacy parameters**

**Primary endpoint:** achieving clinical efficacy determined as:

- Frequency of reducing number of adhesions after repeated MRI by 3 or more (in female patients with 10 and less adhesions at the baseline) or by 30% and more (in patients with >10 adhesions at the baseline)) in comparison to baseline MRI data



### **Secondary efficacy endpoints:**

1. Change in thickness of pelvic adhesions by repeated MRI in comparison to baseline MRI data
2. Frequency of limited displaceability of pelvic organs in post-surgical period (based on results of transvaginal ultrasound investigation) on Day 30±4 after surgery
3. Frequency of hyperechoic linear lesions in post-surgical period based on results of transvaginal ultrasound investigation
4. Change in frequency of detecting limited displaceability in comparison to baseline (absolute change and in % of baseline value)
5. Change in frequency of detecting hyperechoic linear lesions in comparison to baseline (4 and less) based on repeated transvaginal ultrasound investigation
6. Frequency of detecting complete absence of USI – signs of adhesion process in the pelvis in post-surgical period (defined as absence of limited displaceability of pelvic organs and absence of hyperechoic linear lesions)

## **7.2 Methods and terms of evaluation, recording and analysis of efficacy parameters**

Evaluation of efficacy of the study drugs Seroguard, solution 0.41 g/L (JSC Pharmasyntez, Russia) and the Placebo will be performed for all the study subjects at Visit 3 based on considering parameters specified in section 8.1

## **8 Evaluation of safety**

### **8.1 List of safety parameters**

- Vital signs (body temperature, BP, HR, RR)
- Laboratory investigations:
  - Blood chemistry – total protein, glucose, ALT, AST, total bilirubin, alkaline phosphatase, amylase, creatinine
  - Complete blood count – RBC, WBC, platelet count, hemoglobin, hematocrit, WBC differential, ESR
  - Coagulogram – coagulation time, international normalized ratio (INR), thrombin time, activated partial thromboplastin time (APTT)
  - Urinalysis – color, transparency, pH, specific gravity, protein, glucose, WBC, RBC, bacteria, casts, salts
- ECG data – heart rate [HR], PR, QRS, QT intervals and calculated QTc interval

- USI data
- Incidence of adverse reactions
- Incidence of serious adverse reactions
- Incidence of unexpected adverse reactions
- Incidence of adverse and serious adverse reactions caused treatment discontinuation/withdrawal from the study

## **8.2 Methods and terms of evaluation, recording and analysis of safety parameters**

Evaluation of safety of the study drugs Seroguard, solution 0.41 g/L (JSC Pharmasyntez, Russia) and the Placebo will be performed for all the study subjects at Visits 1-3, based on account of parameter, specified in section 8.1. Detection of adverse reactions (ARs) happens from the moment of signing informed consent to visit 3 inclusive. In addition, each study subject will be provided a phone number of the Investigator for contact in case of any problems with health. Clinical symptoms that will be developed after signing informed consent, but before use of the test drug or the placebo will be recorded as concomitant disease.

If the Investigator finds/receives information on AR, an unscheduled visit at the study site will be appointed in the nearest time (if required). At the moment of receiving information on AR, after analysis of AR and evaluation of risk for the study subject, the Investigator comes to a decision on delivery of required medical care. At the unscheduled visit, the Investigator makes decision on possibility of further participation of female patient in the study.

In case of indications, by the decision of the Medical Investigator or the physician, additional clinical and/or laboratory-instrumental investigations may be performed at unscheduled visits (see section 4.2.4.5).

The Investigator is responsible for notification of the Sponsor on any event considered as unusual, even if this event may be considered as unexpected benefit for the study subject.

### **Adverse reactions**

AR means “any unintended and unfavorable reaction of the body which may be related to the drug administration” (Federal Law dated 12.04.2010 No 61-Φ3 “On drug circulation”).

### **AR severity grades**

AR severity grade will be established as per the below classification:

- **Grade 1: mild.** Asymptomatic (detected at physical or laboratory-instrumental investigation) or with minimally pronounced symptoms, easily tolerable by a subject, causing minimum discomfort and not interfering with normal activity, not requiring special treatment;

- **Grade 2: moderate.** Causing discomfort, limiting normal activity; requiring medical aid without invasive interventions (for example, applying a dressing);
- **Grade 3: severe.** Making normal activity impossible; disabling; requiring invasive intervention; requiring hospitalization; life-threatening; death.

### **Causal relation of AR to administration of the study drugs**

Causal relation of AR to administration of the study drugs will be evaluated based on criteria of the World Health Organization (WHO):

- **Definite.** Clinical manifestations of AR, including laboratory abnormalities, observed during administration of the drugs, which may not be explained by presence of current diseases and influence of other factors and chemical compounds. Side reaction manifestation regress after the drug withdrawal and develop after re-administration.
- **Probable.** Clinical manifestations of AR, including laboratory abnormalities, related to time of the drug administration, which are unlikely related to concomitant diseases or other factors and which regress after the drug withdrawal. Response reaction to re-administration is unknown.
- **Possible.** Clinical manifestations of AR, including laboratory abnormalities, related to time of the drug administration, which may be explained by presence of concomitant diseases or administration of the other drugs and chemical compounds. Information on reaction to withdrawal of the drug is unclear.
- **Unlikely.** Clinical manifestations of AR, including laboratory abnormalities, which develop with no clear temporary relation to the drug administration; there are other factors (drugs, diseases, chemical substances), that may be a reason of their development.
- **Conditional.** Clinical manifestations of AR, including laboratory abnormalities, related to “side reactions”, that require obtaining additional data (for accurate estimate) or these obtained data are analyzed at present.
- **Unclassified.** Reports on suspected side reaction may not be evaluated, because the information is not sufficient or it is contradictory.

### **Serious adverse reaction or unexpected adverse reaction**

Serious AR (SAR) is an adverse reaction of the body related to the administration of the drug that led to death, congenital anomaly or birth defects or life-threatening, requiring hospitalization or incapacitating and (or) disabling (Federal Law dated 12.04.2010 No 61-Φ3 “On drug circulation”).

In case of SAR development in the study subject, administration of the study drug is discontinued, the Medical Investigator completes the respective section of the CRF of the study subject and SAR Report Form.

If SAR develops, the Investigator (if required) must take actions to provide respective qualified medical assistance to the study subject, including performance of clinical and/or laboratory-instrumental investigations.

In this case, follow up of the study subject should be continued before resolution/stabilization of the SAR observed.

### **Unexpected adverse reaction**

Unexpected AR (UAR) is an adverse reaction of the body which is related to administration of the drug at the doses recommended in the protocol of the clinical study, Investigator' brochure, or to administration of the drug at the doses recommended in the package insert on its use for prevention, diagnostics, treatment of diseases or medical rehabilitation of patient, and nature, severity and outcome of which do not correspond to information on the drug, contained in the protocol of the clinical study, Investigator's brochure or in package insert of the drug (Federal Law dated 12.04.2010 No 61-Φ3 "On drug circulation")

### **Pregnancy**

See section 8.3.

### **Deviations in values of laboratory and instrumental investigation parameters**

Deviations from the normal (values accepted in the respective clinical site) results of laboratory or instrumental investigations are considered as clinically significant and, respectively, as ARs, if they are:

- confirmed in repeated investigation;
- accompanied by clinical manifestations or symptoms;
- accompanied by withdrawal of a female patient from the study;
- confirm development of disease/manifestation of toxic properties of the study drug;
- require appointing unscheduled visits, additional diagnostic procedures and/or therapeutic measures;

### **AR outcome**

AR outcome is indicated to the moment of time when it is documented as per the following categories:

- recovered/resolved (no signs of AR completely);
- recovering/resolving (regress of sign/symptom of AR, incomplete disappearance);
- recovered/resolved with sequelae;
- not recovered/not resolved (AR existing at the moment of documentation or at the moment of death of the study subject due to any reason or due to development of another AR);
- lethal outcome (death due to developed AR);
- no data (for example, if the study subject did not come for final examination or follow-up visit and cannot be contacted).

### **8.3 Requirements to reports, procedures for recording and reporting adverse reactions and intercurrent diseases**

#### **Adverse event recording**

If any AR develops, the Investigator should complete the respective sections of the CRF of the study subject, evaluate feasibility of continuing the study by female patient (exclude the study subject or continue participation of female patient in the study). ARs will be recorded from the moment of the study drug administration and to completion of the final visit (Visit 3).

For each AR, the following information should be recorded in the primary medical documentation:

- AR nature as per the ICD-10 terminology system (International Classification of Diseases 10<sup>th</sup> revision);
- severity grade (mild/ moderate/ severe AR);
- causal relation to administration of the test drug/reference drug (definite/ probable/ possible/ unlikely/ conditional/ unclassified);
- duration (start date and time / stop date and time);
- outcome (resolved/ resolving/ resolved with sequelae/ not resolved / lethal outcome/ no data);
- is AR serious.

#### **Report on serious adverse reaction to the Sponsor**

In case of SAR, it is necessary to record the fact of SAR development in the primary documentation and complete respective pages of the CRF of the study subject.

Information on SAR should be sent to the pharmacovigilance officer of JSC Pharmasyntez, Natalya Anatolyevna Dvoynikova within 24 hours:

- Phone: 8 (3952) 55-03-28;
- Fax: 8 (3952) 55-03-25;
- E-mail: n.dvoynikova@pharmasyntez.com.

A special form of serious adverse reaction is completed in this case (see section 17.1), original of which is sent to JSC Pharmasyntez to the following address: Rosa Luxemburg str., 184, Irkutsk 664040, Russia.

Notification form should be sent, even if the Investigator has incomplete volume of information on SAR. However, after the primary report on SAR, the Investigator should always inform on evaluation of degree of SAR relation to the administration of the study drug (see section 8.2). The Investigator should receive confirmation that the information is delivered.

If provided by the current requirements, the Sponsor will send respective notifications on AR to appropriate healthcare authorities.

## **Pregnancy during the study**

Before the study beginning, female patients are instructed on effective methods of contraception used throughout the study. All the study subjects pass pregnancy test at Visit 0, 3 or at Withdrawal Visit (see section 4.2.3.5), they are also instructed on required obligatory notification of the Investigator at any time when pregnancy is suspected. In this case, during the next/unscheduled visit, a pregnancy test is repeated (using test-strip, see section 4.2.3.5) and, if required, a concentration of beta-chorionic gonadotropin in blood is determined, and examination by gynecologist is performed. If fact of pregnancy is confirmed, female patient discontinues her participation in the study (see section **Ошибка! Источник ссылки не найден.**).

## **8.4 Method and duration of follow-up of the study subjects after adverse reactions**

Information on all newly developed/continuing ARs is recorded at each next/unscheduled visit. In case of repeated report on continuing AR, it is necessary to complete a new template of AR Report Form with note of date of a primary report on continuing AR.

All ARs should be traced until their resolution or until the Investigator considers them as “chronic” or “stable” (AR outcomes in such cases are classified as resolving/resolved with sequelae/ not recovered). Information on this should be recorded in the primary documentation, CRF of a female patient and the final AR Report Form.

At the final visit (Visit 3), the Investigator instructs the study subject on necessity to report on any ARs subsequently which, in the opinion of a female patient or her physician may be related to the administration of the test drug/reference drug.

## **8.5 Modification of the study drug dosage regimen**

In the present study, modification of the study drug dosage regimen is not considered which is provided by the purposes and design of the present study.

## **9 Statistics**

### **9.1 Description of statistical methods to be used, including terms of each planned interim analysis**

Statistical analysis will be performed using a specialized software, selection of which will be performed at the stage of preparation of statistical analysis plan.

Continuous (quantitative) data will be presented using a number of observations, arithmetic mean, 95 % confidence interval (CI) for the mean (unless otherwise specified), standard (mean square) deviation, median, interquartile range, minimum and maximum.

Serial, categorical and qualitative data will be provided using absolute frequency (number of observations), relative frequencies (percent) and 95 % CI (unless otherwise specified).

Unless otherwise specified, in the plan of statistical analysis, statistical test will be bilateral with 5% confidence level.

Anamnesis and ARs will be coded using MedDRA classifier.

This section briefly describes the planned analysis. A complete analysis will be described in the plan of statistical analysis.

#### **9.1.1 Demographic data, baseline data and follow-up data**

Demographic characteristics, characteristics of baseline level and follow-up, such as anamnesis (classified according to MedDRA) and concomitant drugs will be described by treatment groups for ITT population and then for safety, if they are different (see section 9.7).

#### **9.1.2 Analysis of main efficacy parameters**

Main efficacy parameter in the given study is achieving clinical efficacy of the drug defined as:

- Frequency of reducing number of adhesions after repeated MRI by 3 or more (in female patients with 10 and less adhesions at the baseline) or by 30% and more (in patients with >10 adhesions at the baseline)) in comparison to baseline MRI data

Considering that the given analysis will be performed in the confirmation form of superiority over placebo hypothesis (superiority testing), unilateral statistical criteria will be used, and the level of significance will be established at 5%. For differences between each dose of the drug Seroguard and the placebo, a bilateral 95% binominal accurate confidence interval will be calculated for percentage difference. Superiority will be confirmed, if the lower limit of the confidence interval will exceed 0.05 (5%).

#### **9.1.3 Analysis of secondary efficacy endpoints**

For evaluation of the following additional efficacy parameters:

- Frequency of hyperechoic linear lesions in post-surgical period based on results of transvaginal ultrasound investigation
- Change in frequency of detecting limited displaceability in comparison to baseline (absolute change and in % of baseline value)
- Change in frequency of detecting hyperechoic linear lesions based on repeated transvaginal ultrasound investigation in comparison to baseline
- Frequency of detecting complete absence of USI – signs of adhesion process in the pelvis in post-surgical period (defined as absence of limited displaceability of pelvic organs and absence of hyperechoic linear lesions)

Respective relative (%) and absolute (number of observations) frequencies as well as accurate 95% binominal CIs will be calculated for each group. For evaluation of difference between each dose

of the drug Seroguard and the placebo, Fisher's exact test will be used as well as accurate 95% CI will be calculated for differences in percentages between the groups.

#### **9.1.4 Safety analysis**

Descriptive part of safety analysis by primary endpoint will include evaluation of frequencies and bilateral 95% CI for the following primary endpoint parameters:

- AR – common frequency and frequency in separate groups (as per ICD-10)
- SAR - common frequency and frequency in separate groups (as per ICD-10)
- Frequency of clinically significant changes in results of physical examination – in general, for the study and by visits
- Frequency of clinically significant changes in parameters of laboratory investigations – in general, for the study and by visits
- Frequency of clinically significant changes in parameters of BP and heart rate – in general, for the study and by visits
- Frequency of clinically significant changes in ECG parameters – in general, for the study and by visits

Comparison of frequencies between main and control groups will be performed using Fisher's exact test (bilateral variant).

Analysis of the specified safety parameters will be performed for ITT and safety population (if it is different from ITT).

## **9.2 Planned number of the study subjects**

In the studies of the drug Adept® (Innoventica plc), maximally close to the test drug by mechanism of action, a primary endpoint was used. It was determined as a decrease in number of adhesions during second look diagnostic laparoscopy by 3 or more (in patients with 10 or less adhesions at the baseline) or by 30% and more (in patients with >10 adhesions at the baseline)) is 45%.

Performance of second look laparoscopy under the present study is unacceptable from the ethical point of view, MRI will be used for evaluation of the primary end point. As per the publication (21), MRI data highly correlate with laparoscopy picture (both pre-surgical and post-surgical studies during repeated laparoscopies). The exclusions are the thinnest adhesions that may not be seen on MRI which may be compensated by use of high-field MRI. Hence, MRI allows to visualize adhesions qualitatively and quantitatively and to obtain data with the same degree of detalization as during laparoscopic investigation before and after the surgery.

Thus, calculation of sample size will be based on efficacy of similar drugs studied based on laparoscopic data, however, MRI control will be used in the study, first of all due to ethical considerations and due to strong correlation between MRI data and laparoscopy data.

Accordingly, as per the above studies of the drug Adept® (20), efficacy related to achieving the primary end point (clinical efficacy determined as a decrease in number of adhesions during second look diagnostic laparoscopy by 3 and more (in female patients with 10 or less adhesions at



the baseline) or by 30% and more (in patients with > 10 adhesions at the baseline)) is 45%. In the control group (placebo) based on literature review and meta-analysis (31) achieving clinical efficacy is recorded in not more than 10% cases.

Using these baseline data, the following assumptions were introduced (as per the method specified in (32)):

- The study will be conducted as a *superiority trial*, i.e. at least one dosage of Seroguard must be more efficient than the placebo, whereby the *superiority margin* will be 5% and more (definition of endpoint and superiority margin from the main study of Adept® was used). Comparison with placebo will be performed for each dosage of the drug separately. Comparison of dosages by efficacy between them is not planned and will be a subject of investigation in the Phase III of clinical studies of the drug
- Expected rates of achieving the primary endpoint in the groups with different dosages will be considered initially equal
- First type error ( $\alpha$ ) = 5 % (0.05) for *superiority* hypothesis
- Second type error ( $\beta$ ) = 20 % (0.2), that corresponds to 80 % power.
- Expected withdrawal from the study will make 15% at screening and 10% after randomization

Null and alternative hypotheses for the *superiority testing* stage are worded as follows:

1. Null hypothesis ( $H_0$ ) holds that the difference in the rate of the primary endpoint achievement for one of the dosages of the drug Seroguard and the placebo will not exceed 5% in favor of the drug

$$H_0: p_1 - p_0 \leq 0.05$$

2. Alternative hypothesis ( $H_A$ ) holds that the difference in the rate of the primary endpoint achievement of one of the dosages of the drug Seroguard and the placebo will exceed 5% in favor of the drug

$$H_A: p_1 - p_0 > 0.05$$

Where  $p_0$  and  $p_1$  are the rates of the primary endpoint achievement in the groups of the placebo and Seroguard (of any dosage), respectively.

For the purpose of calculation of the sample size in each group in this case, the formula is applied which is given in (33)

$$n = (p_1 \times (1 - p_0) + p_0 \times (1 - p_0)) \times \left( \frac{z_{1-\alpha} + z_{1-\beta}}{p_1 - p_0 - \delta} \right)^2$$

where

$n$  is the size of one group;

$z$  is the value of the normal distribution function with the given  $\alpha$  and  $\beta$  levels;

$\delta$  is superiority margin - 5%;

$p_1$  is the expected percentage in the active drug group (one of the dosages) – 45%

$p_0$  is the expected percentage in the placebo group – 5%

Applying the above data into this formula, we obtain the minimum number of patients in the placebo group without considering withdrawal: 24 completed cases which corresponds to 26 randomizations and 30 screenings.

Thus, the total number to be enrolled in the study is:

- 1) Placebo group, 1.5 mL/kg – up to 30 screened female patients that corresponds to 26 randomizations and 24 completed cases
- 2) Placebo group, 2.4 mL/kg – up to 30 screened female patients that corresponds to 26 randomizations and 24 completed cases
- 3) Seroguard group, 1.5 mL/kg – up to 30 screened female patients that corresponds to 26 randomizations and 24 completed cases
- 4) Seroguard group, 2.4 mL/kg – up to 30 screened female patients that corresponds to 26 randomizations and 24 completed cases

Thus, total of 120 female patients are to be screened and at least 104 female patients are to be randomized for the study.

### **9.3 A significance level used**

In all the tests, a 5% significance level will be used, whereby a primary endpoint will be analyzed using unilateral test, and bilateral statistical tests will be used for analysis of secondary endpoints.

### **9.4 Study termination criteria**

Study termination criteria are described in section 4.6.

### **9.5 Procedures for accounting absent, unevaluable and doubtful data**

At monitoring visit in the clinical site, monitoring officers authorized by the Sponsor will perform analysis of CRFs of the study subjects to check for absence of the required data. In case of absence of data in CRF and presence of respective information in the primary documentation, questions to the Investigators and assignments for elimination of non-conformities will be sent.

When checking database of the study results, a statistician authorized by the Sponsor and the Principal Investigator will perform analysis with respect to doubtful, omitted and unevaluable data by results of which the questions to the Investigators will be sent.

When applicable, the Investigators will eliminate the revealed errors in the CRF and inform the Principal Investigator and authorized representatives of the Sponsor on it. If the errors found in data will be impossible to be corrected after completion of female patient participation in the study, during statistical analysis of data, an analysis of sensitivity of the resulting parameters to presence

of doubtful data will be performed. Information on omitted, doubtful and unevaluable analysis of data will be provided in the final report on the clinical study.

## **9.6 Procedures of reporting on any deviations from the primary statistical plan**

Decision on change in statistical plan reflected under the present protocol is made by the Sponsor. All the changes in the primary statistical plan along with their justification are provided in the final report on the clinical study.

## **9.7 Selection of the study subjects for the analysis**

### **9.7.1 Intent-to-treat population (ITT)**

ITT set, also known as full analysis set, comprises all the randomized patients administered the study drug regardless of the degree of compliance with the protocol during the study. This set of data is main for the analysis; it will be used for evaluation of all the planned parameters.

### **9.7.2 Per protocol population**

All the planned parameters will be analyzed (in addition to analysis as per ITT) using set of data of the study subjects, selected by the per protocol principle (PP). The given population will not be analyzed, if it is more than 90% and less than 50% from ITT population. A subject will be excluded from PP set in the following cases:

- Significant violation of inclusion and non-inclusion criteria.
- Use of forbidden concomitant therapy.
- Any other significant violation of the protocol accepted as significantly violating main evaluation of efficacy in the specific subject of the study.

### **9.7.3 Safety population**

Safety set is identical to that of ITT. However, compared to the treatment administered, subjects are analyzed depending on the real treatment (in case when it is different from treatment which was administered by randomization). All the types of safety analysis will be based on using set of data for evaluation of safety.

All the decisions concerning determination of the databases analyzed will be summarizing the results of the database shutdown.

## **10 Direct access to primary data/documentation**

Primary data is all the information which is contained in the original records and attested copies concerning the clinical data, observations and other activities within the study and which is necessary for reconstruction and evaluation of the study. The Investigator provides possibility of

the study monitoring, audit (-s), inspection by Ethics Committee and regulatory bodies, represents a direct access to the primary data/records.

Primary data should be kept for the maximum period of time allowed by the local rules. For each included subject, the Investigator will specify a fact of participation in the present study in the primary records as well as will record at least the following information: individual identification code, personal data on female patients (full names, addresses), dates of the drug administration, vital signs, any ARs, dates of the study completion and main reasons of treatment discontinuation (if applicable).

The Investigator is responsible for provision of direct access to primary data and documentation for the study monitor of the Sponsor and/or its authorized representatives (CRO), auditor of competent authorities, representatives of an insurance company, ethics committees.

## **11 Quality control and quality assurance**

### **11.1 Study monitoring**

Regular visits of the study monitor by order of the Sponsor and according to Standard Operating Procedures (SOP) before beginning, during and after the study contribute to successful performance of the study and serve as a guarantee of accurate data collection, early detection of possible errors, documenting the process of the clinical study and provision of protecting the rights of the study subjects, conformity of the study performance to requirements of an international legislation and the legislation of the Russian Federation.

Routine monitoring of the study includes:

- Confirmation of adequate performance and documenting the process of obtaining informed consent as well as screening and inclusion of subjects into the study.
- Verification of data in CRF and primary medical documentation of the study subjects.
- Confirmation of documentation and early reporting the data on AR during the study.
- Confirmation of compliance with the requirements to performance of diagnostic and therapeutic procedures of the study protocol by the staff of the clinical site.
- Confirmation of documenting supplies, storage, distribution and disposal of the test drug/the placebo and the study materials.
- Confirmation of the competence of the study site staff, independent laboratory required for conducting the study.
- Confirmation of conformity of diagnostic and laboratory equipment to the requirements of safe and adequate use during the study.
- Confirmation of cooperation of the Investigator with local ethics committee on issues of the study safety and entering amendments to the study protocol agreed with the Sponsor.

Provision of the study result quality control is performed by the Sponsor's employees/Sponsor's authorized representative (for example, CRO), performing management of the study electronic

database who reveal non-conformities, erroneously entered data and omitted data. In case of questions or required clarification, a special form is sent to the Investigator by e-mail/fax, its inquiry should be satisfied in written form within 7 days after its delivery.

According to the legislation requirements, the Sponsor or authorized governmental bodies have a right to perform check (audit) of equipment and material procurement of the study and the study documentation. The Investigator should provide access to documentation and all the required information to persons authorized to perform audit or inspection.

## **11.2 Amendments to the protocol, deviations and violations of the protocol**

Signatures of Investigators on the approval page mean written confirmation of consent to perform the study as per the given protocol. During the clinical study, changes and additions may be entered into the study materials. Such changes and additions are considered as amendments.

Amendment to the protocol is a written description of changes or official clarification of the clinical study protocol text. Amendments may be essential and not essential. Any amendment to the protocol, before coming into force, should be adequately approved according to the in-house SOPs of the Sponsor company, then it should be approved by regulatory bodies, NEC and signed by the Investigator.

In the Decree of the Ministry of Health of the RF No 775 dated 31.08.2010 “On approval of review procedure of entering the required changes in the protocol of the clinical study of the drug for medical use”, a list of significant/insignificant amendments and the order of providing materials on them for inspection is determined.

Amendments to materials of the clinical study are significant, if they may influence on purposes, forms of organization, methodology of conducting, statistical methods of handling the results of the clinical study and measures to provide safety of female patients participating in it.

Amendments to materials of the clinical study are insignificant, if they do not influence on purposes, forms of organization, methodology of conducting, statistical methods of handling the results of the clinical study and measures to provide safety of female patients participating in it.

In case of required entering changes into the present protocol, the Sponsor of the study submits a message on required entering changes into the clinical study protocol to the MoH of the RF. Taking decision on entering changes or on refusal from entering changes is performed by the MoH of the RF after an inspection of the submitted updated materials. Amendments to the protocol should be kept along with initial revision of the protocol. Amendment No and effective date should be recorded on the title page of the protocol.

All the protocol deviations in the study should be recorded during monitoring of the clinical study and reported to the Sponsor company.

## **12 Ethics**

### **12.1 General provisions**

The present study will be conducted as per the World Medical Association Declaration of Helsinki “Ethical principles for medical research involving human subjects” dated 1964 as amended; National standard of the Russian Federation “Good Clinical Practice” GOST R52379-2005 dated 25.09.2005, the Federal Law of the Russian Federation dated April, 12 2010 No 61-Φ3 “On drug circulation” (as amended), as well as regulatory documents of the International Conference on Harmonization - Good Clinical Practice (ICH GCP).

### **12.2 Procedure of obtaining informed consent**

Written information and oral explanation of purposes, objectives and methods of conducting the study as well as of the expected benefit and possible risk related to participation in the study are provided to female patients before inclusion into the study. Besides, female patients should be informed on voluntary nature of participation in the study and on the fact that the subject has a right to refuse from participation in the study at any time, and that this refusal will not affect the quality of medical service provided to her. In case of the study discontinuation, a subject is not obliged to inform on the reasons, motivated her to discontinue participation in the study, however, the Investigator should try to clarify these reasons without disturbing the rights of the female patient. Consent of the female patient should be obtained before any study procedures.

Handling of data collected during the study is performed in compliance with confidentiality of subject's data. The study subjects should be informed on purposes of planned computer handling of data and on conditions of publishing these data (for example, for presentation in medical conferences, in magazine articles and other open sources), provided only in summary, not allowing to make their identification.

Female patients should be notified that authorized representatives of health authorities and of the Sponsor will have access to their confidential medical information in order to perform monitoring, inspection and audit. However, a strict confidentiality of all the information allowing to identify a study subject and non-disclosure of such information should be guaranteed to subjects.

Informed consent form (patient information sheet) is to be completed in two copies, signed and dated by a female patient and Investigator by their own hands. The first copy of signed forms of Informed consent is kept by Investigator in Investigator's file, a second copy is provided to the study subject.

### **12.3 Confidentiality and identification of the study subjects**

Confidentiality of records allowing to identify the study subjects will be provided adhering to the rights to privacy and protection of confidentiality according to the regulatory requirements. Records identifying personality of patient will be confidential and may be disclosed only to the

extent to which it is allowed by the legislation. In publication of the study results, confidentiality of the study subject data will be kept.

## **12.4 Enrollment of the study subjects from vulnerable and special groups**

Inclusion/non-inclusion criteria consider participation in the study of fertile women, if they provide consent to use effective contraception methods throughout the study.

## **13 Data management and record keeping**

In the clinical site, all the records and documents related to the clinical study kept in the Investigator's File, including CRFs, informed consent forms, logs, registers of female patients as well as primary medical documentation of the study subjects are kept for 15 years after the study completion. The Sponsor of the study provides storage of all the materials of the clinical study throughout the life cycle of the study drug. Archival data may be stored as photocopies or on optical/electronic data storage devices. The Principal Investigator must immediately inform the Sponsor on facts of disposal, change of storage place of the clinical study archival materials.

After each planned visit by the study subjects and completion of CRF by the Investigator, verification of CRF and the primary documentation will be performed by authorized monitors of the Sponsor. If CRFs are completed accurately and precisely in accordance with the data of the primary documentation, the study monitor withdraws original pages of CRFs and sends them to the Sponsor, whereby copies of CRF pages are left in the site. If at the stage of evaluating data in CRF, a manager on control of data and/or biostatistician will have questions on data, all the clarifications and changes in CRF data will be documented by preparing forms of clarifying queries (data queries). Responses completed, signed and dated by the Investigator to clarifying queries are checked by the monitor and in case of recognizing the response as sufficient, originals of completed forms will be withdrawn from the site, whereby the copies of the completed forms of clarifying queries will be left in the site.

The Investigator must provide information confirming possible timely enrollment of the study subjects when complying with the criteria under the protocol.

The study must be performed according to the protocol, Sponsor's Standard Operating Procedures. If necessary, entering changes in the protocol are agreed by the Investigator and the Sponsor and provided as an amendment to the protocol approved by ethics committee.

Completion of main documentation of the clinical study – primary medical documentation and CRF – is obligatory for all the subjects of the study.

The Investigator is responsible for complete and precise completion of CRF. All the data recorded in CRF should be reflected in the primary medical documentation of the study subject in print format or in written records made by the Investigator or other authorized person of the clinical site.

All planned data on participation of a female patient in the study are recorded in CRF according to the primary documentation. CRF should also contain data on completed participation by female

patient in the study. CRF should be completed within 5 days after visit of the study subject in the clinical site. CRF should be completed in a legible handwriting with black ink. The mistakes made in the text should not be corrected over the record or erased slightly, or deleted using correction fluid. Instead of this, an error is crossed out with a straight line, a corrected text or digit is written above it as well as signature, date and initials of the Investigator. For all the omitted data, explanations in CRF should be provided, which will be realized by presence of a special tag field ("tick"), confirming omission of data. If required, on the page of comments in CRF with reference to respective page, explanations of data omission reasons will be provided. CRFs should be signed by Co-Investigator and Principal Investigator. The signatures confirm that the information contained in the CRF is true.

All the information on the study and the collected data are strictly confidential. The Investigator has a right to report information on the study to persons not directly participating in the study performance, only after permission of the Sponsor.

A final report consisting of statistical and clinical report is prepared after database shutdown and completion of statistical handling of the study results.

The final report is signed by the Principal Investigator of the clinical site, who confirms the results and inferences of the study by affixing a seal of his (her) institution.

## **14 Finance and insurance**

Finance of the present study is performed by the Sponsor company through CRO. Before the study beginning, respective agreement will be concluded between CRO and each study site.

The Sponsor of the study provides insurance of life and health of female patients – subjects of the clinical study. Female patients will be paid for damage in case of threatening to life or health due to administration of the test drug/placebo according to the current legislation.

## **15 Publications**

### **15.1 General provision**

Information contained in the present document is a property of the Sponsor and its presentation to third parties is permitted only after written approval of the Sponsor. A right to access to the given information is provided only to investigators and employees of the study site participating in the study, members of NEC and employees of healthcare authorities, authorized to control the clinical study. Information on the study in the volume required for making decision on providing consent for participation is provided to female patients who may participate in the present study.



## **15.2 Issues of publication and use of the study results**

The study Sponsor has exclusive rights for the present study results. No data of the present study may be presented or published without written approval of the Sponsor.

## 16 Literature

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## 17 Annexures

### 17.1 Serious adverse reaction report form

<b>Site ID:</b>	<b>Protocol ID:</b>
<b>Principal Investigator/Coordinator:</b>	Office phone No:
<b>Information on patient:</b>	ID: _____ Randomization ID: _____ Gender: M / F Birth date: ____ / ____ / ____ Previous participation in the clinical studies: yes / no
<b>Information on the drug:</b>	Name _____ Dose _____ Route of administration _____ Date of administration: ____ / ____ / ____ Time of administration: _____ hour _____ min
<b>Brief description of adverse reaction:</b>	
<b>Report: primary / secondary</b> _____	
<b>SAR start date and time:</b>	Date: ____ / ____ / ____ Time: _____ hour _____ min
<b>SAR end date and time:</b>	Date: ____ / ____ / ____ Time: _____ hour _____ min
<b>Is SAR unexpected:</b>	Yes / No
<b>Criteria of AR seriousness:</b> <input type="checkbox"/> death <input type="checkbox"/> life-threatening <input type="checkbox"/> hospitalization or its prolongation <input type="checkbox"/> persistent or significant disability/incapacity <input type="checkbox"/> congenital anomaly/birth defect <input type="checkbox"/> important from medical point of view	<b>Causal relation of SAR to administration of the study drugs:</b> <input type="checkbox"/> definite <input type="checkbox"/> doubtful <input type="checkbox"/> probable <input type="checkbox"/> conditional <input type="checkbox"/> possible <input type="checkbox"/> unrelated <input type="checkbox"/> unclassified
	<b>Severity</b> <input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
<b>Actions taken</b> <input type="checkbox"/> withdrawal of patient from the study <input type="checkbox"/> hospitalization <input type="checkbox"/> drug or non-drug therapy for relief of SAR <input type="checkbox"/> no <input type="checkbox"/> other	<b>SAR outcome:</b> <input type="checkbox"/> recovered/resolved <input type="checkbox"/> recovering/resolving <input type="checkbox"/> recovered/resolved with sequelae <input type="checkbox"/> not recovered/not resolved <input type="checkbox"/> fatal <input type="checkbox"/> unknown <input type="checkbox"/> other
<b>Additional information:</b>	
<b>Signature of the Investigator:</b>	<b>Date:</b>