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Official Title of the study:	**Multicentre randomized comparative parallel group Phase III clinical study of efficacy and safety of Primapur® (follitropin alfa), a solution for subcutaneous administration, and GONAL-F® (follitropin alfa), a solution for subcutaneous administration, for the controlled superovulation induction in programs of assist reproductive technologies.**
Ethics approval and consent to participate:	**The study protocol and informed consent were approved by the Russian Ministry of Health (RCT 754 dated 26.10.16) and the independent interdisciplinary ethics committee for ethical review of clinical studies (protocol №17 dated 28.10.2016).**
Unique Protocol ID:	**FSG-03-01**
NCT number:	**NCT03088137. Date of registration: March, 2nd, 2017, retrospectively registered.**
General Manager/IVFarma LLC Mikhail Polzikov (PhD)	**04.10.2016**

STUDY SUMMARY

Study title:	Multicentre randomized comparative parallel group Phase III clinical study of efficacy and safety of Primapur® (follitropin alfa), a solution for subcutaneous administration, and GONAL-F® (follitropin alfa), a solution for subcutaneous administration, for the controlled superovulation induction in programs of assist reproductive technologies.
Study type:	Phase III therapeutic equivalence study
Test product	*TN:* Primapur® INN: follitropin alfa *Dosage form*: solution for subcutaneous injection *Pharmaceutical form*: pre-filled disposable syringe containing follitropin alfa 66 μg (900 IU), *Manufacturer*: Medsintez Plant OOO, Russia
Reference product	*TN:* GONAL-F® INN: follitropin alfa *Dosage form*: solution for subcutaneous injection *Pharmaceutical form*: pre-filled disposable syringe containing follitropin alfa 66 μg (900 IU), *Manufacturer:* Merck Serono S.p.A, Italy
Ethical and legal aspects:	This study will be conducted in strict accordance with the clinical study protocol and the following international and Russian documents: 1. Principles of the World Medical Association Declaration of Helsinki (Fortaleza, Brazil, 2013). 2. ICH Harmonised Tripartite Guideline (ICH E6). 3. Constitution of the Russian Federation. 4. Federal Law “On the fundamentals of protecting the health of citizens in the Russian Federation” dated November 21, 2011 No. 323-FZ, 2011. 5. Federal Law “On the Circulation of Medicines” No. 61-FZ dated 12 April 2010. 6. National standard of the Russian Federation GOST R52379-2005 “Good Clinical Practice”. 7. Decree of the Government of the Russian Federation “On approval of typical rules for the compulsory insurance of life and health of the patient involved in clinical study of medicinal product for medical use” N 714 dated September 13, 2010. 8. Order of the Ministry of Health and Social Development of the Russian Federation "On the ethics council" No. 986n dated November 29, 2012. 9. Federal Law "On personal data" No. 152-FZ dated July 27, 2006.

	10. Order of the Ministry of Health of the Russian Federation "On the use of assisted reproductive technologies, contraindications and limitations to their use" No. 107 n dated August 30, 2012. 11. Federal State Budgetary Institution "Scientific Center for Expertise of Medical Products" of the Ministry of Health of Russia - Guidance on the examination of medicines, Volume 1, 2013. 12. Federal State Budgetary Institution "Scientific Center for Expertise of Medical Products" of the Ministry of Health of Russia - Guidance on the examination of medicines, Volume 4, 2014. 13. Guidance on the examination of medicines. Volume 3. - M .: POLYGRAPH-PLUS, 2014 - P. 344
Study goals:	Confirm the biosimilarity of Primapur® (follitropin alfa), a solution for subcutaneous administration, and reference GONAL-F® (follitropin alfa), a solution for subcutaneous administration, for the controlled superovulation induction in programs of assist reproductive technologies. Final goal: Authorization of Primapur® (follitropin alfa), a solution for subcutaneous administration for clinical use in in programs of assist reproductive technologies in the territory of the Russian Federation.
Study objectives:	1. Comparative assessment of efficacy of Primapur® (follitropin alfa), a solution for subcutaneous administration, and GONAL-F® (follitropin alfa). 2. Comparative assessment of safety of Primapur® (follitropin alfa), a solution for subcutaneous administration, and GONAL-F® (follitropin alfa).
Study design:	multicenter randomized embryologically blinded parallel group comparative therapeutic equivalence study of Primapur®, a solution for subcutaneous administration, and GONAL-f®, a solution for subcutaneous administration.
Planned number of patients	110 female patients randomized into two equal groups of 55 subjects receiving study referenced drugs.
Study centers	3 specialized medical centers in the Russian Federation
Study population:	Women aged 20-35 with established causes of infertility (tubal factor, male factor (oligoasthenoteratozoospermia) and indications for the use of assist reproductive technologies (ART).
Inclusion criteria:	1. Women with established causes of infertility and indications for the use of ART methods, according to the Order of the Ministry of Health of the Russian Federation "On the use of assisted reproductive technologies, contraindications and limitations to their use" No. 107 n dated August 30, 2012. 2. Causes of infertility: Tubal factor and/or male factor (oligoasthenoteratozoospermia). 3. Female patients aged 20 to ≤35 with an independent regular menstrual cycle (duration: 21 to 35 days); 4. First or second attempt of IVF/ICSI.

	5. $18 \leq BMI \leq 30$ kg/m^2; 6. Basal level of FSH 10< IU/L (cycle day 2-5); 7. Estradiol level (E2) on the 2nd day of the menstrual cycle (<50 pg/mL (<180 pmol/L)); 8. AMH level (≥1.0 ng/mL); 9. AFC ≥4 and ≤15 in both ovaries; 10. Anatomical and functional capability of uterus to bear pregnancy (with no pathology of the endometrium). Presence of two ovaries accessible for aspiration of follicles; 11. Medical history of the analysis for blood group and Rh factor determination . 12. Medical history of the mammologist's conclusion no more than 3 months before the female patient was included in the clinical study. 13. Study results received no more than 1 year before the female patient was included in the clinical study; Ultrasound of the mammary glands; TORCH infection; fluorography; colposcopy. 14. Negative smear for oncocytology (PAP test) for 6 months before randomization. 15. Results of the following investigations no more than 6 months before the patient was included in the clinical study: Determination of chlamydia, mycoplasma, ureaplasma, HPV 16/18, HSV types 1 and 2, CMV. 16. Negative test results no more than 3 months before the patient was included in the clinical study: RW, anti-HIV, anti-HBcor, HBSAg, anti-HCV, HSV antigen. 17. ECG results no more than 1 month before inclusion of the patient in the study. 18. Results of the analysis of the husband (partner) no more than 3 months before the patient was included in the clinical study: RW, anti-HIV, anti-HBcor, HBSAg, anti-HCV, HSV antigen, swab flora, HSV 1 and 2 types, CMV, chlamydia, mycoplasma, ureaplasma. 19. Medical history of the husband (partner) analysis: blood type and Rh factor determination. 20. Conclusion of the therapist consultation confirming the indication to planning of pregnancy by methods of ART and the absence of contraindications to pregnancy. 21. A signed informed consent form that confirms in writing the patient's consent to participate in this clinical study and the patient's willingness to comply with all physician recommendations and protocol limitations for the time of participation in the clinical study; 22. The husband's (partner's) consent for the implementation of the procedures provided for by the protocol (spiromogram analysis).
Exclusion criteria:	1. Women with established contraindications to the use of ART methods, according to the Order of the Ministry of Health of the Russian Federation "On the use of assisted reproductive technologies,

	contraindications and limitations to their use" No. 107 n dated August 30, 2012. 2. Pregnancy. 3. Hypersensitivity to follitropin alpha or excipients. 4. Ovarian cysts (not associated with polycystic ovarian syndrome), uterine hemorrhage of unclear etiology; 5. Medical history of 2 or more cycles of IVF/ICSI without clinical pregnancy. 6. Medical history of severe ovarian hyperstimulation syndrome (OHS). 7. Polycystic ovarian syndrome (POS); 8. Ovarian endometriosis; endometriosis of hydrosalpinks; ultrasound signs of varian endometriomas. 9. Uterine cavity pathology: polyps, endomestudy hyperplasia, uterine cavity synechia. 10. Medical history of poor ovarian response or excessive ovarian response (≥25 oocytes retrieved) to stimulation with a human rFSH dose of at least 150 IU in a short protocol with the use of GnRH antagonists (less than 4 eggs obtained in the previous program). 11. Primary ovarian failure. 12. Ectopic pregnancy for 3 months before enrollment. 13. Acute diseases of the genitourinary system. 14. Suspicion of a tumor of the hypothalamus or pituitary gland based on the blood hormone test results (ACTH, estradiol, testosterone, STH, LH, FSH, Prolactin, TSH). 15. Male infertility: Severe oligoasthenoteratozoospermia (sperm concentration - less than 2 million/mL, mobility less - than 10% progressively and non-progressively motile sperm; normal sperm morphology of less than 1%); azoospermia: indications for TESA/MESA/PESA; donor sperm program. 16. Smoking (≥10 cigarettes per day). 17. Planned PGD program 18. History pf abuse of narcotics and alcoholism. 19. The patient's unwillingness to follow the procedures prescribed by the CT protocol and/or her husband's unwillingness to follow the procedures provided for in the protocol.
Exclusion criteria:	1. The patient's refusal participate in the study at any stage. 2. Development of one of the exclusion criteria. 3. Development of severe OHS. 4. Ineffective stimulation of FSH (no pool of growing follicles) on Day 5 or Day 8 of stimulation. 5. Necessity of cryopreservation of embryos due to cancellation/postponement of embryo transfer according to the indications. 6. Development of AEs/adverse reactions that cause an unacceptable risk to the patient's health if the patient continues to participate in the study

	and requires the withdrawal of the therapy and/or the concomitant therapy. 7. The patient's major violation of the medical investigator's recommendations under the protocol and deviation from the study procedures. 8. Occurrence of concomitant somatic diseases/symptoms or aggravation of chronic diseases not associated with taking medications (at the discretion of the medical investigator), requiring changes in therapy and observation procedures that are incompatible with the clinical study protocol.
Dosage and duration of treatment; route of administration:	QD, starting from Day 2 of Day 3 of menstrual cycle, 150 IU of study/reference drug per day, according to the protocol controlled superovulation induction, with the use of GnRH antagonist, providing the ability to adjust the dose of study drug on Day 5 or Day 8 of stimulation as a result of transvaginal ultrasound of ovaries. The duration of stimulation is no more than 15 days.
Concomitant therapy:	All patients included in the clinical study protocol under the ART program will be stimulated according to the short protocol with the use of GnRH antagonist (Orgalutran®, Tsetrotid®) since the lead follicle reaches the more than 14 mm (day 5 or day 6 of stimulation), including the day after triggering of ovulation (hCG or alternative indications of GnRH antagonist); will receive anesthesia in a step of puncture of follicles, oocytes fertilization by IVF/ICSI, transfer of up to 2 embryos (on days 2,3,4,5 of embryo development in vitro). Concomitant medication. Approved medication: - GnRH antagonists (Organlutran®, Cetrotide®). - hCG. - Human rLH. - GnRH agonist as an inducer of ovulation in patients at risk of developing OHS. - Folic acid at a dosage of 400-800 mg/day, including in combination with vitamin B12. - Iron preparations for iron deficiency anemia. - Natural micronized progesterone, dydrogesterone. - Blood-thinning drugs (antiaggregants and anticoagulants: Kleksan, Fraxiparine, Zibor, Curantil, Cardiomagnyl, Thrombo ACC, Sulodexide). Prohibited medication: Any other products containing FSH, including urinary gonadotropins (menotropins, urofollitropins); aromatase inhibitors; clomiphene citrate; contraceptives; hCG and hLH products luteal phase support.

	During the study, all patients also may receive introduction of drugs relieving adverse symptoms, treatment of opportunistic diseases in case of aggravation of such diseases, at the investigator's discretion, if they are not included in the list of protocol-banned medicines and will not affect changes in therapy and observation procedures that are incompatible with the clinical study protocol.
Study visit procedures:	The total duration of the study for each patient is no more than 16 weeks (about 4 months), divided into study stages: **Screening period** (of initial survey) lasting no more than 4 weeks, **Therapy period** (study drug/reference drug) lasting not more than 15 days (2 weeks and 1 day), **Follow-up period** (not more than 3 weeks prior to the confirmation of biochemical pregnancy and not more than 10 weeks prior to the confirmation of clinical pregnancy).
<u>Screening period.</u> **4 weeks.**	**Visit 1. Screening (Day -28 to Day 1).** At this visit, the use of the results of routine studies and analysis is permissible, if the term of their implementation is within the 4-week screening period and the conclusion/outcome includes the listed parameters. Exceptions are laboratory clinical blood and urine tests (complete blood count, biochemical blood test, common urine analysis) which must be performed in one laboratory at all stages of the clinical study. All screening procedures should be performed prior to randomization of the patient. 1. The patient's informed consent. 2. Initial observation by obstetrician-gynecologist (reproductologist): ✓ History taking (medical history, life history, gynecological history, family history), registration of concurrent conditions and concomitant therapy. ✓ Gynecological examination. ✓ Physical examination ✓ Measurement of vital parameters, particularly HR, BP, RR, body temperature. ✓ Registration of patient complaints. 3. Instrumental examinations: ✓ Ultrasound of the pelvic organs, including transvaginal ultrasound of the uterus and ovaries; assessment of the state of the endometrium and the presence/absence of signs of pregnancy; ✓ Transvaginal ultrasound of ovaries for the absence of cysts and endomestudy pathology (*performed strictly according to the schedule on Day 1, before the procedure of randomization of the patient).*

	4. Laboratory testing: ✓ Complete blood count. ✓ Biochemical blood test. ✓ Blood sampling for the analysis of anti-FSH antibodies* (point "0"). ✓ General urine analysis. ✓ Blood hormones: AMH; on Day 2-5 of the menstrual cycle: FSH, LH, estradiol, prolactin, bound testosterone, cortisol, TSH, ACTH, STH. ✓ Coagulogram. ✓ Smear on the flora. 5. Husband (partner) inspection: ✓ Laboratory tests - spermogram.
<u>Period of PI/PR therapy.</u> Up to 15 days (2 weeks and 1 day).	**Visit 2. Randomization. Day 1. Beginning of the stimulation protocol (2-3 day of the menstrual cycle)** 1. Selection criteria check. *Decision of randomization into a clinical study or registration of a screening failure.* 2. Carrying out randomization, using IWRS, distribution into groups: *group FSG031* of Primap®, a study drug, or *group FSG032* of GONAL-f®, a reference drug. 3. Inspection: ✓ Registration of patient complaints. ✓ Registration of changes in concurrent conditions and concomitant therapy. ✓ Physical examination ✓ Measurement of vital parameters, particularly HR, BP, RR, body temperature. ✓ Prescription of the stimulation protocol. 4. Introduction of the 1st dose of PI/PR. 5. Registration of adverse events/reactions after the first dose of PI/PR. **Visit 3. Day 5-8 of stimulation.** The 3rd visit procedures are aimed at a primary evaluation of the therapy efficacy. The patient may be invited to conduct the procedure once (on the 5th day) or several times (additionally on the 6th, 7th, 8th days of the therapy) at the investigator's discretion, depending on the results of the required diagnostic procedures. 3 visit procedures: 1. Instrumental examinations: ✓ Transvaginal ultrasound of ovaries. Follicle count and determination of follicle diameter in both ovaries. 2. Inspection: ✓ PI/PR dose adjustment (in the absence of follicles more than 10 mm on 5-8 days of stimulation).

	✓ Registration of patient complaints, concurrent conditions and concomitant therapy. ✓ Physical examination ✓ Measurement of vital parameters, particularly HR, BP, RR, body temperature. 3. *Exclusion of the patient from the study in case of failed stimulation (with no response to FSH administration on day 5-8 of stimulation).* 4. Initiation of GnRH antagonist administration (when the lead follicle is about 14 mm); 5. Registration of adverse events/reactions. **Additional visit for GnRH antagonist administration (if required).** If the size of the follicles according to the results of ultrasound is not sufficient for the initiation of GnRH antagonist introduction (the lead follicle is not determined) at Visit 3 (Day 5-8), the patient will be invited later on the day planned by the investigator for an additional visit to begin the introduction of GnRH antagonist. Visit procedures: 1. Transvaginal ultrasound (with the definition of the lead follicle). 2. Inspection: ✓ Registration of patient complaints, concurrent conditions and concomitant therapy. ✓ Physical examination ✓ Measurement of vital parameters, particularly HR, BP, RR, body temperature. 3. Initiation of GnRH antagonist administration. 4. Registration of adverse events/reactions. **Visit 4. Completion of stimulation. Introduction of the ovulation inducer. Next day after the completion of the PI/PR therapy (Day ≤ 16 from Visit 2).** 1. Instrumental examinations. ✓ Ultrasound. Count of follicles ≥ 16 mm (number of 20 or more follicles is an indication for the introduction of the GnRH agonist, an alternative induction ovulation). 2. Laboratory testing: ✓ Biochemical blood test. ✓ Complete blood count. ✓ General urine analysis. 3. Inspection: ✓ Registration of patient complaints. ✓ Registration of changes in concurrent conditions and concomitant therapy. ✓ Physical examination

	✓ Measurement of vital parameters, particularly HR, BP, RR, body temperature. 4. Introduction of an ovulation inducer (hCG or GnRH agonist according to the indications). 5. Registration of adverse events/reactions. Items 1, 2, 3 of the visit are conducted before the introduction of the ovulation inducer.
<u>Follow-up period.</u> **10 weeks.**	**Visit 5. Puncture of follicles. IVF/ICSI. No more than 37 hours from the introduction of the ovulation inducer (Visit 4).** 1. Examination before follicle puncture: ✓ Registration of patient complaints. ✓ Registration of changes in concurrent conditions and concomitant therapy. ✓ Physical examination ✓ Measurement of vital parameters. *2. <u>Blinding of the studied therapy at the stage of oocyte counting performed by the embryologist (by coding the data on the study drugs in the patient's electronic medical record viewed by the embryologist).</u>* 3. Puncture of follicles: ✓ Ultrasound. Follicle count before anesthesia and follicle puncture. ✓ USG-guided puncture of follicles under general anesthesia. ✓ Obtained oocyte counting performed by the embryologist. 4. Carryinh out of IVF/ICSI. ✓ Determination of the number of mature/immature oocytes. 5. Registration of adverse events/reactions. 6. *Exclusion of the patient from the study if cryopreservation of embryos is required according to the indications.* **Visits 6 and 7: Transfer of the embryo(s)/blastocyst(s) into the uterine cavity. Up to 5 days after Visit 5.** 1. Inspection: ✓ Registration of patient complaints. ✓ Registration of changes in concurrent conditions and concomitant therapy. ✓ Physical examination ✓ Measurement of vital parameters, particularly HR, BP, RR, body temperature. *2.* USG-guided transfer of embryos/blastocysts (1 or 2, but not more than 2). 3. Registration of adverse events. *4. Exclusion of the patient from the study if cryopreservation of embryos is required according to the indications.*

	Telephone contact. Day 7 from embryo/blastocyst transfer. 1. Registration of patient complaints, changes in concurrent conditions and concomitant therapy. State assessment. 2. Registration of adverse events. **Visit 8: Confirmation of biochemical pregnancy/early study termination. Day 12-17 from embryo/blastocyst transfer.** 1. Laboratory testing: ✓ hCG blood test. 2. Inspection: ✓ Registration of patient complaints. ✓ Registration of changes in concurrent conditions and concomitant therapy. ✓ Physical examination ✓ Measurement of vital parameters. 3. Registration of adverse events. *4. Early study termination in patients with hCG <25 mU/mL.* In case of early study termination, the patient should complete study termination procedures. **Additional visit for biochemical pregnancy confirmation (if required).** If there is a border value of hCG (5-25 mU/mL) at Visit 8, the patient can be invited for blood resampling for hCG counting within 12-17 days from the transfer. Visit procedures: 1. Transvaginal ultrasound (control of biochemical pregnancy, fetal egg determination or fetus palpitation). 2. Laboratory testing: ✓ hCG blood test. 3. Inspection: ✓ Registration of patient complaints. ✓ Registration of changes in concurrent conditions and concomitant therapy. ✓ Physical examination ✓ Measurement of vital parameters, particularly HR, BP, RR, body temperature. 4. Registration of adverse events. **Additional visit to confirm the intra-uterine pregnancy (if required).** In the event that the result of the hCG level obtained at Visit 8 causes suspicion of extrauterine pregnancy, the physician will conduct an additional examination (visit) of the patient in the period of 35 to 42 days after hCG administration to confirm the intra-uterine pregnancy, which will include: 1. Transvaginal ultrasound (confirmation of biochemical pregnancy, fetal egg determination or fetus palpitation). 2. Laboratory testing:

	✓ hCG blood test. 3. Inspection: ✓ Registration of patient complaints. ✓ Registration of changes in concurrent conditions and concomitant therapy. ✓ Physical examination ✓ Measurement of vital parameters, particularly HR, BP, RR, body temperature. 4. Registration of adverse events. **Visit 9: Study termination visit. Week 10 from embryo/blastocyst transfer.** 1. Instrumental examinations. ✓ Ultrasound. Confirmation/exclusion of clinical (progressive) pregnancy; fetal egg count. 2. Laboratory testing: ✓ Biochemical blood test. ✓ Complete blood count. ✓ General urine analysis. ✓ Additionally: Blood sampling for determining the titer of anti-FSH antibodies*. 3. Inspection: ✓ Registration of patient complaints. ✓ Registration of changes in concurrent conditions and concomitant therapy. ✓ Physical examination ✓ Measurement of vital parameters. 4. Registration of adverse events.
Unscheduled visit.	At any stage of the study, an additional visit to the center can be made at the investigator's discretion if a patient has a complaint requiring a reproductologist's intervention for the purpose of individually monitoring the superovulation induction course and monitoring the pregnancy course in order to reduce the risk of developing any adversed reaction and to monitor the therapy efficacy. Additional visits may include, but not be limited to, the following procedures (depending on the indications): 1. Instrumental examinations: ✓ Transvaginal ultrasound of ovaries. 2. FSH dose adjustment. 3. Physical examination. 4. Measurement of vital parameters. 5. Registration of patient complaints. 6. Complete blood count. 7. Biochemical blood test. 8. Coagulogram. 9. General urine analysis.

	10. Blood test for hormones and other clinically relevant markers.
***The presence of anti-FSH antibodies** will be determined centrally at the laboratory of Exacte Labs LLC and/or an additional research laboratory on a contractual basis (if required). The study results will be attached to the initial documentation of the investigation site. Immunogenicity will be evaluated using the following methods: enzyme immunoassay and surface plasmon resonance for positive samples.	
Efficacy evaluation criteria:	**Study endpoints per patient:** **Primary point:** • Total number of aspirated oocytes. **Secondary points:** • Number of follicles ≥ 16 mm on the day of administration of hCG. • Number of mature oocytes (MII stage). • Number of fertilized oocytes. • Number of patients with embryo transfer (days 2-3). • Number of patients with blastocyst transfer (days 4-5). • Total dose of a human rFSH product injected (IU). • Number of days of stimulation. • Percentage of patients who needed a FSH dose adjustment on the 5th-8th day of stimulation. • Number of patients who abandoned the IVF/ICSI program in the process of stimulation. • Number of non-responders to stimulation. • Incidence of biochemical pregnancies. • Incidence of clinical pregnancies (up to 10 weeks after the embryo(s) transfer).
Safety evaluation criteria:	• Incidence of serious adverse events such as severe ovarian hyperstimulation syndrome (%). • Incidence of detection of autoantibodies to the studied FSH products (%); titer of autoantibodies to anti-FSH, study/reference product, in case of a change in the level of the end point "1" in comparison with the point "0". • Incidence of the adverse reaction of ectopic pregnancy (%). • Incidence of the adverse reaction of multiple pregnancies (%). • Incidence of other adverse reactions and serious adverse reactions (%) and their severity at all stages of the patient's participation in the clinical study. • Incidence of topic and constitutional adverse reactions associated with the use of PI/PR (according to the Instructions for Medical Use, and unforeseen reactions) (%). • Incidence of clinically significant changes in laboratory parameters (%). • Incidence of clinically significant changes in the data of physical examinations and indicators of HR, BP, RR, body temperature (%).

	• Acceptability of the treatment, which will be estimated by the proportion of patients excluded from the study due to AEs/adverse reactions.
Statistical processing of data:	**Description of methods of statistical data processing** The quantitative data obtained during the study will be tested for normal distribution, using the Shapiro-Wilk test and, if necessary, the F-test of equality of variances. For variables corresponding to the normal distribution, mean values and standard deviation of the mean will be calculated; Quantitative data not corresponding to the normal distribution will be described using the median and interquartile interval. Qualitative variables will be described using absolute and relative frequencies (percentages). In order to compare two groups of normally distributed quantitative data, the Student's t-test will be used; if quantitative data distribution differs from normal values, the Mann-Whitney U test will be used. For intergroup comparisons by qualitative characteristics, the Fisher's exact test will be used; correction of p-value in the case of multiple hypotheses will be realized through the Bonferroni adjustment. **Applicable significance level** In this study, the indicators are considered statistically significant at the bilateral p-value level <0.05. **Therapeutic equivalence criteria.** The conclusion about the therapeutic equivalence of the two drugs will be made if the difference between the mean values of the total number of oocytes obtained when applying both drugs lies within the limits of the equivalence threshold (± 3.4 oocytes). **Procedures for accounting of missing, not-analyzable and uncertain data.** CRF information will be entered into the computer database, and data will be electronically and visually verified for completeness, and allowable ranges will be checked. All errors detected during the quality control process will be corrected. In the presence of deviating data ("outliers"), the correctness of their measurement and introduction into the database will be rechecked. Data will be analyzed twice: with and without "outliers". If the results are stable to the "outliers", a calculation that includes all available values of the variable will be used. If there is the influence of "outliers" on the initial result, the results obtained both taking into account the deviating data and without deviating data will be presented and commented on.

Calculation of sample size	For the present study, calculation of sample size is based on data on the number of oocytes obtained from clinical studies of GONAL-F® (follitropin alfa) and its biosimilars (*Rettenbacher M. et al. Reprod Biomed Online. 2015;30(5):504-13; Strowitzki T. et al. Reprod Biol Endocrinol. 2016;14:1.; Moon SY et al. J Obstet Gynaecol Res. 2007;33(3):305-15).* Based on the results of these studies, it is assumed that the total number of oocytes obtained for study and reference product of follitropin alfa is 12.0 ± 5.9 and 10.9 ± 6.5, respectively. To suppress the release of endogenous LH, ART programs use either GnRH antagonist or GnRH agonist, together with the use of follitropin. According to meta-analyzes (*van Wely M. et al. Cochrane Database Syst Rev. 2011;(2):CD005354; Al-Inany HG et al. Cochrane Database Syst Rev. 2016; 4: CD001750)*, the use of GnRH agonists and antagonists in ART programs leads to the same number of live births; and the use of GnRH antagonist statistically significantly reduces the risk of serious adverse events, compared with the use of GnRH agonist; however, the number of oocytes obtained may differ slightly in the protocols with the use of GnRH antagonists, which is explained by the difference in growth of a size-synchronized pool of follicles. In accordance with this, the following hypotheses have been formulated: H0 (zero hypothesis): $\mu A - \mu B \leq -d, \mu A - \mu B \geq +d$ H1 (alternative hypothesis): $-d < \mu A - \mu B < +d$ where μA and μB are the selective average number of oocytes of study drug and reference drug (GONAL-F®). The required number of patients in equal parallel groups was calculated according to the following formula (*Julious, SA. Statist. Med. 2004; 23:1921–1986*): $1-\beta = \text{Probt}(-t_{1-\alpha,n_A(r+1)-2}, n_A(r+1)-2, \tau_2) - \text{Probt}(t_{1-\alpha,n_A(r+1)-2}, n_A(r+1)-2, \tau_1)$ where τ_1 and τ_2 are the uncertainty parameters calculated by the following formulas: $\tau_1 = \frac{((\mu_A - \mu_B) + d)\sqrt{rn_A}}{\sqrt{(r+1)\sigma^2}} \quad \tau_2 = \frac{((\mu_A - \mu_B) - d)\sqrt{rn_A}}{\sqrt{(r+1)\sigma^2}}$ Thus, to provide a study power of at least 80% at a significance level α0.05, a standard deviation of the number of oocytes obtained equal to σ=6 and an equivalence threshold value d = 3.4 oocytes, the required sample size is 55 subjects per each group (n_A) and only 110 subjects in total; taking into account 27% drop out, the number of screened patients is recommended to be increased to 140.