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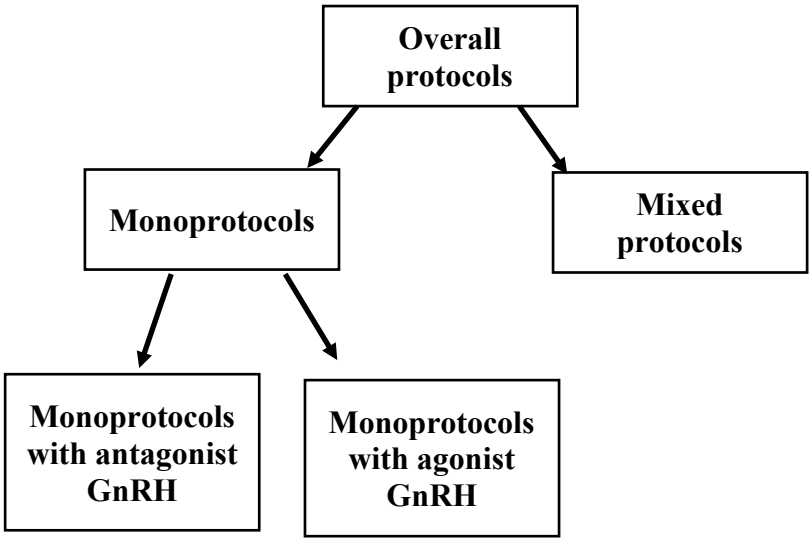
Official Title of the study:	An Observational Study "FOLLITROPIN" Comparing the Efficacy of Follitropin Alpha Biosimilar: The Real-world Data
Ethics approval and consent to participate:	Women with established causes of infertility and indications for the use of ART methods, according to the Order of 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.
Unique Protocol ID:	IVF-2020
NCT number:	ClinicalTrials.gov Identifier: NCT04854707 Date of registration: April 22, 2021, retrospectively registered.
General Manager/IVFarma LLC Mikhail Polzikov (PhD)	Study protocol approval: 10.01.2021

STUDY SUMMARY

Study title:	An Observational Study "FOLLITROPIN" Comparing the Efficacy of Follitropin Alpha Biosimilar: The Real-world Data
Study type:	Phase IV
Test product	*TN:* Primapur® INN: follitropin alpha *Dosage form*: solution for subcutaneous injection *Pharmaceutical form*: pre-filled disposable syringe containing follitropin alpha 66 μg (900 IU), 33 μg (450 IU), 22 μg (300 IU), *Manufacturer*: Zavod Medsintez LLC, Russia
Ethical and legal aspects:	This study conducted in strict accordance with the following international and Russian documents: 1. Principles of the World Medical Association Declaration of Helsinki (Fortaleza, Brazil, 2013). 2. Constitution of the Russian Federation. 3. Federal Law "On the fundamentals of protecting the health of citizens in the Russian Federation" dated November 21, 2011 No. 323-FZ, 2011. 4. Federal Law "On the Circulation of Medicines" No. 61-FZ dated 12 April 2010. 5. Federal Law "On personal data" No. 152-FZ dated July 27, 2006. 6. 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.
Study goals:	To investigate the efficacy of follitropin alpha biosimilar therapy (Primapur®) in nonselected real-world population.
Study objectives:	The efficacy and safety of biosimilar follitropin alpha have been demonstrated in randomized blinded prospective clinical trials of phases I and III. Unfortunately, there is a gap between the clinical trials and real clinical practice data. The real-world patient data helps to create an evidence-based background for successful implementation of medicine at everyday practice in a nonselected population. The ovarian stimulation (OS) protocols included: monotherapy protocols with using only follitropin alpha biosimilar (Primapur®); mixed protocols (recombinant and urinary-derived gonadotropins) and follitropin alpha biosimilar; short protocols with using antagonists of gonadotropin-releasing hormone (GnRH) and long protocols with

	GnRH agonists. The stimulation protocols were analyzed with Primapur® application for at least 5 days.
Study design:	Retrospective, observational (non-interventional), anonymized, cohort study
Number of patients	5500 patients
Study centers	35 in vitro fertilization (IVF) clinics in the Russian Federation
Study population:	Women aged 20-43 with established causes of infertility and indications for the use of assisted reproductive technologies (ART) and ovarian stimulation.
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. Infertility due to female and/or male factor. 3. Presence of ovaries accessible for aspiration of follicles. 4. Anatomical and functional capability of uterus to bear pregnancy.
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. Presence of pregnancy 3. Hypersensitivity to follitropin alpha and other gonadotropins or excipients. 4. Ovarian cysts (not associated with polycystic ovarian syndrome), uterine hemorrhage of unclear etiology 5. Premature ovarian failure 6. Presence of clinically significant systemic disease 7. Presence of chronic cardiovascular, hepatic, renal or pulmonary disease 8. Neoplasia 9. Narcomania, alcoholism
Dosage and duration of treatment; route of administration:	Drug: Follicle Stimulating Hormone/Luteinizing Hormone Overall ovarian stimulation protocols with follitropin alpha biosimilar for at least 5 days (100-300 IU) and other recombinant follitropins and menotropins, short (antagonists of GnRH) or long protocols (agonist of GnRH).
Concomitant therapy:	All patients received approved medication by physician, accordingly to National guidelines.

Efficacy evaluation criteria:	**Study endpoints per patient:** **Primary point:** • Total number of aspirated oocytes. • Incidence of clinical pregnancies (up to 6 weeks after the embryo(s) transfer). **Secondary points:** • Number of mature oocytes (MII stage). • Number of fertilized oocytes (zygotes with 2PN). • Total dose of a follitropin alpha biosimilar injected (IU).
Safety evaluation criteria:	• Incidence of serious adverse events e.g., severe ovarian hyperstimulation syndrome (%) with hospitalization. • Incidence of the adverse event, such as injection site pain (%).
Groups/arms to compare:	**1. Monoprotocols: follitropin alpha biosimilar only and antagonists/agonists of GnRH** (The ovarian stimulation (OS) protocols included monotherapy protocols with using follitropin alpha biosimilar only and antagonists/agonists of of gonadotropin-releasing hormone (GnRH): ganirelix, cetrorelix, triptorelin, buserelin). **2. Mixed protocols: recombinant and urinary-derived gonadotropins and antagonists/agonists of GnRH.** (The OS protocols included: mixed protocols (recombinant with addition of urinary-derived gonadotropins) and antagonists/agonists of GnRH (ganirelix, cetrorelix, triptorelin, buserelin), where follitropin alpha biosimilar used for at least 5 days during OS). **3. Monoprotocols: follitropin alpha biosimilar only and antagonists of GnRH** (The OS protocols included: monotherapy protocols with using only follitropin alpha biosimilar and antagonists of GnRH). **4. Monoprotocols: follitropin alpha biosimilar only and agonist of GnRH** (The OS protocol included: monotherapy protocols with using only follitropin alpha biosimilar and agonists of GnRH). **5. The overall protocols** (The OS protocols included: (1) Monoprotocols: follitropin alpha biosimilar only and antagonists/agonists of GnRH, (2) Mixed protocols: recombinant and urinary-derived gonadotropins and antagonists/agonists of GnRH).

	Flow chart: 
Outcome Measures:	Primary outcomes: 1. Number of Oocytes Retrieved 2. Percentage of Participants With Ongoing Clinical Pregnancy Per Embryo Transfer Secondary outcomes: 1. Number of Mature Oocytes 2. Number of Fertilized Oocytes **3.** Total Dose of Follitropin Alpha Biosimilar Protocol
Groups/Arms to compare	1. Mixed protocols: recombinant and urinary-derived gonadotropins and antagonists/agonists of GnRH **AND** Monoprotocols: follitropin alpha biosimilar only and antagonists/agonists of GnRH 2. Monoprotocols: follitropin alpha biosimilar only and antagonists of GnRH **AND** Monoprotocols: follitropin alpha biosimilar only and agonist of GnRH 3. Overall protocols – descriptive statistics for all in vitro fertilization protocols
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. **Applicable significance level** In this study, the indicators are considered statistically significant at the bilateral p-value level <0.05.