Non-Interventional Study Report

Title	A non-interventional register-based comparative effectiveness study of rhFSH-alfa reference product vs. highly purified human menopausal gonadotropin or rhFSH-alfa biosimilar products for ovarian stimulation in *in vitro* fertilization or intracytoplasmic sperm injection treatment in Denmark – The Nordic Follitropin Alfa Comparative Effectiveness (NORD-FACE) Study.
Study Number	MS700623_0049
Version identifier of the final study report	1.0
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EU PAS register number	EUPAS41175
Sponsor	Merck Healthcare KGaA an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 Darmstadt, Germany
Coordinating Investigator / Principal Investigator(s)	Mickael Arnaud
Active substance	G03GA05: Follitropin alfa G03GA02: Human menopausal gonadotropin
Medicinal product	Follitropin alfa, recombinant human follicle-stimulating hormone (rhFSH) Human menopausal gonadotropin
Research question and objectives.	The research question was whether, among women undergoing in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatment, recombinant human follicle-stimulating hormone (rhFSH)-alfa reference product is associated with better treatment results than highly purified human menopausal gonadotropin (HP-hMG) or

	rhFSH-alfa biosimilar products in terms of clinical effectiveness and safety outcomes.
Country(-ies) of study	Denmark
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Abstract

Title: A non-interventional register-based comparative effectiveness cohort study of rhFSH-alfa reference product vs. highly purified human menopausal gonadotropin or rhFSH-alfa biosimilar products for ovarian stimulation in in vitro fertilization or intracytoplasmic sperm injection treatment in Denmark – The Nordic Follitropin Alfa Comparative Effectiveness (NORD-FACE) Study.

Study Number: Merck study number: MS700623_0049 and EUPAS: EUPAS41175

Marketing Authorization Holder: Merck Healthcare KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany

Research Keywords: Biosimilar, Recombinant human follicle-stimulating hormone (rhFSH); Human menopausal gonadotropin (hMG), In Vitro Fertilization (IVF), Pregnancy

Rationale and background: Gonadotropins extracted from the urine of post-menopausal women were the first drugs used to stimulate folliculogenesis in the treatment of infertility and in assisted reproductive technology (ART). The last generation of gonadotropins is represented by recombinant human follicle stimulating hormone (rhFSH) products, including follitropin alfa. These rhFSH products are used for ovulation induction in anovulatory women and for stimulation of multifollicular development in women undergoing ovarian stimulation for ART.

Previous trials have yielded mixed results or lacked sufficient statistical power to enable comparisons among treatment groups for meaningful endpoints. Therefore, the use of real-world data was proposed as an efficient way to analyze long-term outcomes such as live birth rate (LBR) and cumulative live birth rate (CLBR).

With the long-term market use of rhFSH-alfa reference and urinary products, and the increased use of rhFSH-alfa biosimilar products within the real-world setting, it is important to assess whether there are differences in effectiveness and safety outcomes between products, with a beneficial effect of rhFSH-alfa reference product in terms of meaningful clinical outcomes.

Research Question and Objectives: The research question was whether, among women undergoing IVF or intracytoplasmic sperm injection (ICSI) treatment, rhFSH-alfa reference product is associated with better treatment results than highly purified human menopausal gonadotropin (HP-hMG) or rhFSH-alfa biosimilar products in terms of clinical effectiveness and safety outcomes.

Primary Objective: The primary objective of this study was to compare rhFSH-alfa reference product with HP-hMG or rhFSH-alfa biosimilar products in women undergoing IVF/ICSI for treatment of infertility relative to the following live birth outcomes: 1) LBR per initiated IVF/ICSI stimulation cycle 2) CLBR per initiated IVF/ICSI stimulation cycle and, 3) CLBR in up to five initiated IVF/ICSI stimulation cycles (termed multiple-cycle (MC)- CLBR).

Secondary Objectives: To compare rhFSH-alfa reference product with HP-hMG or rhFSH-alfa biosimilar products regarding the following outcomes: 1. a) Clinical pregnancy rate (CPR) and ongoing pregnancy rate (OPR) per initiated IVF/ICSI stimulation cycle, and b) Cumulative clinical pregnancy rate (CCPR) and cumulative ongoing pregnancy rate (COPR) per initiated IVF/ICSI stimulation cycle 2. Number of oocytes retrieved, embryos transferred, embryos cryopreserved, and utilizable embryos (defined as the sum of transferred and cryopreserved embryos) per initiated IVF/ICSI stimulation cycle and per oocyte retrieval cycle 3. Implantation rate 4. Time-to-live birth (TTLB) in up to five IVF/ICSI stimulation cycles 5. Rate of pregnancy loss for the first (and successive) IVF/ICSI stimulation cycle(s) 6. Rate of multiple pregnancy for the first (and successive) IVF/ICSI stimulation cycle(s) 7. Number of cancelled cycles for the first (and successive) IVF/ICSI stimulation cycle(s) 8. Number of ovarian hyperstimulation syndrome (OHSS) cases for the first (and successive) IVF/ICSI stimulation cycle(s). An additional secondary objective describes costs associated with the rhFSH-alfa reference product, HP-hMG and rhFSH-alfa biosimilar products individually and overall, across all products: 9. Costs associated with IVF/ICSI treatment (including drugs and other treatments), miscarriage/birth, and adverse events (i.e., OHSS).

Study Design: This was a non-interventional cohort study based on secondary data using population-based registers in Denmark.

Setting: The study comprised women who underwent IVF/ICSI treatment with fresh and frozen embryo transfer cycles (originated from the same stimulation cycle), receiving rhFSH-alfa reference product, HP-hMG or rhFSH-alfa biosimilar products for controlled ovarian stimulation (COS) during the overall study period from 2010 to 2018 in Denmark. The study period was 2010-2018 when the comparator group was HP-hMG, and 2014-2018 when the comparator was rhFSH-alfa biosimilar. The Swedish part of the study was not included in the analyses due to data access issues.

Inclusion/exclusion criteria: For inclusion of a stimulation cycle, the following inclusion criteria were required: 1. Initiated IVF/ICSI stimulation cycle with rhFSH-alfa reference product, HP-hMG or rhFSH-alfa biosimilar product monotherapy for COS during the study period 2. Aged 18 years or more at stimulation cycle index date 3. Female sex at stimulation cycle index date.

Stimulation cycles were not eligible if any of the following: 1. History of 5 or more IVF/ICSI stimulation cycles prior to the stimulation cycle index date. Ovarian stimulation for the purpose of oocyte donation, oocyte storage, embryo donation or oncological or other medically indicated embryo storage, or preimplantation genetic testing 3. Non-availability of individual-level data on IVF/ICSI treatment, dispensed drugs, and medical history for 36 months or more prior to and including the stimulation cycle index date 4. All embryos from the stimulation cycle are frozen and there is no linked frozen embryo transfer (FET) cycle initiated within 12 months of the stimulation cycle index date.

Variables and data sources: The study dataset was constructed from the following Danish data sources: Danish data sources included the Civil Registration System (CPR), the Danish In Vitro Fertilization Register (DIVF), the Danish National Patient Register (DNPR), the Danish Medical Birth Register (DMBR), the Danish Register of Medicinal Product

Statistics (RMPS), and the Danish Register of Laboratory Results for Research (RLRR). The study exposures are IVF/ICSI treatment using rhFSH-alfa reference product (follitropin alfa, ATC code G03GA05), HP-hMG (ATC code G03GA02) or rhFSH-alfa biosimilar product (ATC code G03GA05). The primary outcome of this study is live birth, measured as LBR, CLBR, MC-CLBR (primary objective) and TTLB (secondary objective 4). Secondary outcomes including clinical pregnancy, ongoing pregnancy, oocytes retrieved, embryos transferred, embryos cryopreserved, utilizable embryos, implantation, pregnancy loss, multiple pregnancy, cycle cancellation, OHSS, and treatment-associated costs were analyzed. Covariates included in this study were age, IVF/ICSI treatment characteristics, other clinical characteristics (comorbidities and medication), fertility-related medical history, and laboratory test history.

Statistical Analysis: Propensity Score (PS)-based methods are frequently used in non-interventional studies to control for confounding when estimating treatment effects. In this study, the PS weighting was implemented using IPTW approach. The main data analysis was conducted in two stages: (i) construction of the inverse probability of treatment weighted (IPTW) study cohorts by modeling the rhFSH-alfa reference product vs. HP-hMG treatment initiation and rhFSH-alfa reference product vs. rhFSH-alfa biosimilar product treatment initiation, (ii) estimating the effectiveness of rhFSH-alfa reference product on the (cumulative) live birth rates and other study outcomes using adjusted (IPTW-weighted) odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (95% CIs), comparing rhFSH-alfa reference product to the comparators, HP-hMG or rhFSH-alfa biosimilars. Covariates included in this study were age, IVF/ICSI treatment characteristics, other clinical characteristics (comorbidities and medication), fertility-related medical history, and laboratory test history.

Results: Two cohorts of patients were analyzed in the study i.e., rhFSH-alfa reference product and HP-hMG and, rhFSH-alfa reference product and rhFSH-alfa biosimilars.

The study cohort comparing rhFSH-alfa reference product and HP-hMG consisted of 11,987 women treated with rhFSH-alfa reference product during 18,125 cycles and 8,324 women treated with HP-hMG during 11,912 cycles for IVF or ICSI treatment between 2010- 2017. The mean age of women treated with rhFSH-alfa reference product and HP-hMG were 33.9 and 34.7 years, respectively. The study cohort comparing rhFSH-alfa reference product and rhFSH-alfa biosimilars consisted of 5,519 women treated with rhFSH-alfa reference product during 7,484 cycles and 790 women treated with rhFSH-alfa biosimilars during 921 cycles for IVF or ICSI treatment between 2014- 2017. The mean age of women treated with rhFSH-alfa reference product and rhFSH-alfa biosimilars were 33.9 and 33.6 years, respectively. After IPTW the sample was balanced relative to the available variables included in the PS. However, there was high level of missingness of several outcome variables (i.e., inability to link FET to originating OPU yielding difficulty in estimating cumulative outcomes, residual and unmeasured confounders) to inform the PS adjustments across patient cohorts, because a large sample of patients across cohorts had significant missing data variables.

Results for the comparison of rhFSH-alfa reference product and HP-hMG indicated that for the three primary outcomes, LBR, CLBR per initiated IVF/ICSI stimulation cycle, and MC-CLBR in up to five initiated IVF/ICSI stimulation cycles, showed a slightly higher odds of live birth in women treated with HP-hMG compared to women treated with rhFSH-alfa reference product.

The secondary outcome analyses of CPR, OPR, CCPR and COPR showed that women treated with HP-hMG had slightly higher odds of clinical and ongoing pregnancy compared to women treated with rhFSH-alfa reference product. Furthermore, for the TTLB outcome, a slightly higher hazard ratio for women treated with HP-hMG compared to those treated with rhFSH-alfa reference product. Results showed no difference detected in number of oocytes retrieved however, women treated with HP-hMG had a slightly lower number of embryos transferred, and a lower number of embryos cryopreserved and utilizable embryos per initiated stimulation cycle when compared to women treated with rhFSH-alfa reference product. The results also suggest that women treated with HP-hMG had a slightly higher implantation rate, a lower rate of pregnancy loss and cycle cancellation when compared to women treated with rhFSH-alfa reference product. Nevertheless, there were too few events to calculate plausible effect estimates for the outcome cycle cancellation rate. No difference was detected regarding multiple pregnancy rate and OHSS rate. Sensitivity analyses were consistent with the main analyses.

For the cohort study cohort comparing rhFSH-alfa reference product and rhFSH-alfa biosimilars, results showed that for the for the primary outcomes, there was no difference detected in women treated with rhFSH-alfa reference product compared to rhFSH-alfa biosimilar products regarding the odds of LBR, CLBR, and the first two cycles of MC-CLBR and also up to the second cycle. While for later cycles of MC-CLBR where rhFSH-alfa biosimilar products were associated with a slightly lower odds of live birth. Sensitivity analyses were consistent with the main analyses. Results of secondary outcome analyses showed no detectable difference in CPR, OPR, CCPR, and COPR. A higher number of oocytes retrieved, and a slightly lower number of embryos transferred was shown in women treated with rhFSH-alfa biosimilar when compared to women treated with rhFSH-alfa reference product. No difference between the treatments were detected in the number of embryos cryopreserved or utilizable embryos per initiated stimulation cycle, implantation rate, pregnancy loss, multiple pregnancy rate, TTLB or odds of OHSS. There were too few events to calculate effect estimates for the outcome cycle cancellation rate.

Discussion and Conclusion: This large study of women undergoing IVF or ICSI treatment in Denmark compared results of different gonadotropins products in terms of clinical effectiveness and safety outcomes. The study adds to the expanding literature of RWE studies of different gonadotropins used in ART and showcases some difficulties in drawing correct inference from databases with incomplete information.

A range of study of study limitations were observed for example, residual confounding and FET linkage deficiencies limiting the evaluation of cumulative outcomes. Nevertheless, there currently exists no direct link between a FET cycle and the stimulation cycle it originated from within the DIVF database. This was observed in the implausible number of linked FET cycles and births originating from them meaning that the cumulative outcomes including FET cycles should be interpreted with great caution. Additionally, the type of clinic, whether private or public, may have also been associated with the type of IVF or ICSI treatment and the quality of care provided and the failure to adjust for the type of clinic could have resulted in residual confounding. As well, another potentially important confounder such as type of clinic (public or private) were missing and, laboratory measurements of anti-Müllerian hormone also showed a large amount of missing data.

In conclusion, the study found that cycles treated with HP-hMG exhibited slightly higher rates of live birth compared to the rhFSH-alfa reference product, while no significant differences were observed between rhFSH-alfa biosimilar products and the reference product. The study adds to the expanding literature of RWE studies of different gonadotropins used in ART. It also showcases some difficulties in drawing correct inference from databases with incomplete information. This study was especially limited by the missing direct linkage between FET cycles and the originating stimulation cycles. In addition, residual confounding due to missing data on ovarian reserve biomarkers and important confounders such type of clinic (public or private) could have impacted the results.

Overall, the results from this study present significant limitations that challenge the reliability, applicability and generalisability of the findings to current real-word clinical practice and thus, not deemed plausible for primary publication in a peer-reviewed journal.