Post-Authorisation Safety Study Protocol Version 4.0 with Amendment 01

SOFIA: Safety of Ovaleap® (Follitropin alfa) in Infertile Women Undergoing Superovulation for Assisted Reproductive Technologies. A Multi-National, Comparative, Prospective, Non-Interventional, Observational Cohort Study

Phase 4

Study XM17-WH-50005

Version 4.0 with Amendment 01 Approval Date: 27th October 2016

Protocol Version 4.0 Approval by the EMA: 13th October 2016

Sponsor
Teva Branded Pharmaceutical Products R&D, Inc
41 Moores Road, Frazer, PA, USA

Confidentiality Statement

PASS Information

Title	SOFIA: Safety of Ovaleap® (Follitropin alfa) in Infertile Women Undergoing Superovulation for Assisted Reproductive Technologies. A Multi-National, Comparative, Prospective, Non-Interventional, Observational Cohort Study
Protocol Version Identifier	Version 4.0 with Amendment 01
Protocol Last Version Date	Version 4.0. (Signed by the Marketing Authorization Holder on 08 July 2016)
EU PAS Register Number	Study not yet registered
Active Substance	Recombinant human follicle stimulating hormone (r-hFSH)
Medicinal Product	Ovaleap® (follitropin alfa)
Product Reference	EU/1/13/871/001-003
Procedure Number	Not applicable
Marketing Authorisation Holder(s)	Teva B.V., Swensweg 5, 2031GA Haarlem, The Netherlands
Joint PASS	No
Research Question and Objectives	The primary objective is to assess the safety of Ovaleap compared to Gonal-f® in one treatment cycle with respect to the incidence rates of Ovarian Hyperstimulation Syndrome (OHSS) in infertile women undergoing superovulation for assisted reproductive technologies (ART). Secondary objectives are to examine the severity grade of OHSS (World Health Organization [WHO] Scientific Group classification [1973]) of Ovaleap compared to Gonal-f and to describe the adverse events/adverse drug reactions
Countries of Study	France, Germany, United Kingdom, Spain, Italy, Netherlands, Belgium
Authors	Nicole Lang Sigalit Kaplan Rachel Levy-Toledano

Marketing Authorisation Holder(s)	Teva B.V. Swensweg 5 2031GA Haarlem The Netherlands
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DOCUMENT APPROVAL FORM

Post-Authorisation Safety Study Protocol Version 4.0 with Amendment 01

Document Type:	Post-Authorisation Safety Study Protocol
Study No.:	XM17-WH-50005
Study Title:	SOFIA: Safety of Ovaleap® (Follitropin alfa) in Infertile Women Undergoing Superovulation for Assisted Reproductive Technologies. A Multi National, Comparative, Prospective, Non Interventional, Observational Cohort Study
Sponsor:	Teva . Branded Pharmaceutical Products R&D, Inc
Prepared By:	Nicole Lang, Sigalit Kaplan, Rachel Levy-Toledano

27/ Oct / 2016

Approved by: Eberhard Landsbeck, PhD Date

Head of German Pharmacovigilance Department
Local Safety Officer and Deputy EU QPPV for Teva Pharmaceuticals Europe BV.

28/OCT/2016

Approved by: Date

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INVESTIGATOR AGREEMENT

PASS Protocol Version 4.0 with Amendment 01

Study XM17-WH-50005 (Post-Authorization Safety Study)

SOFIA: Safety of Ovaleap® (Follitropin alfa) in Infertile Women Undergoing Superovulation for Assisted Reproductive Technologies. A Multi-National, Comparative, Prospective, Non-Interventional, Observational Cohort Study

Principal Investigator:_____

Title: _____

Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this observational study. I will conduct the study as outlined therein.

I agree to keep records on all patient information (ie, case report forms and informed consent forms) and all other information collected during the study.

Principal Investigator	**Signature**	**Date**

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AMH	Anti-Mullerian hormone
ART	Assisted reproductive technologies
CDMS	clinical data management system
CFR	Code of Federal Regulations (US)
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GnRH	gonadotropin-releasing hormone
GVP	Good Pharmacovigilance Practices
hCG	human chorionic gonadotropin
hMG	Human menopausal gonadotropin
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
IU	International Units
IVF	in vitro fertilization
LH	luteinizing hormone
LSO	local safety officer
MedDRA	Medical Dictionary for Regulatory Activities
OHSS	Ovarian Hyperstimulation Syndrome
PASS	Post-Authorisation Safety Study

Abbreviation	Term
PCOS	polycystic ovary syndrome
PSUR	Periodic Safety Update Report
r-hFSH	recombinant human follicle stimulating hormone
sc	subcutaneous
SOC	System Organ Class
SOP	standard operating procedure
SmPC	Summary of Product Characteristics
u-hFSH	urinary human follicle stimulating hormone
WHO	World Health Organization

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title of Study

SOFIA: Safety of Ovaleap®(Follitropin alfa) in Infertile women undergoing superovulation for Assisted reproductive technologies. Multi-national, comparative, prospective, non-interventional, observational cohort study.

Rationale and Background

The European Medicines Agency (EMA) has requested post-authorization data to examine the risk of Ovarian Hyperstimulation Syndrome (OHSS), a potentially serious adverse effect under treatment with recombinant human follicle stimulating hormone (r-hFSH), in Ovaleap® compared to Gonal-f®. An observational Post-Authorisation Safety Study (PASS) will therefore be performed.

Research Question and Objectives

Primary objective: The primary objective of the study is to assess the safety of Ovaleap compared to Gonal-f in one treatment cycle with respect to the incidence rates of OHSS in infertile women undergoing superovulation for assisted reproductive technologies (ART).

Secondary objectives: The secondary objectives of the study are:

- To examine the severity grade of OHSS (World Health Organization [WHO] Scientific Group classification [1973]) in Ovaleap compared to Gonal-f
- To assess adverse events/adverse drug reactions

Study Design

General design: This is a multi-national, comparative, prospective, non-interventional, observational cohort study.

The study population will comprise infertile women, who have not previously received treatment with any FSH (ie, r-hFSH, urinary-hFSH (u-hFSH)) or any product containing FSH activity (ie, human menopausal gonadotropin (hMG)), and who are undergoing ART and are administered Ovaleap or Gonal-f for ovarian stimulation.

After study entry, study participants will be observed for one treatment cycle only. They will be followed for the time of treatment with Ovaleap or Gonal-f and up to 30 days after the last dose administration.

Treatments will be individualized for each woman. After evaluation of patient eligibility, patients in each center will be observed following the routine clinical practice for superovulation. Data for study participants will be obtained from approximately 60 centers in countries of the European Union. The study intends to collect data from a similar number of patients using Ovaleap and using Gonal-f in each country.

Population

Selection of study population: Patients will enter into the study only if all inclusion criteria and none of the exclusion criteria are fulfilled.

Inclusion criteria: Patients may be included in the study if all of the following criteria are met:

a. Signed and dated written informed consent
b. Infertile female patients naïve to any FSH (r-hFSH, u-hFSH) and/or hMG treatment undergoing superovulation for ART and about to start first treatment with Ovaleap or Gonal-f for ovarian stimulation
c. A negative pregnancy test prior to treatment

Exclusion criteria: Patients will be excluded from participating in this study if they meet either of the following criteria:

a. Primary ovarian failure
b. Ovarian enlargement or cyst not due to polycystic ovarian syndrome
c. Neoplasm (eg, tumors of the ovary, breast, uterus, hypothalamus, or pituitary gland)
d. Prior history of OHSS
e. Prior history of any r-hFSH use (eg, Puregon, Ovaleap, Bemfola, Elonva and/or Gonal-f), u-hFSH (eg, Bravelle and/or Fostimon) and/or hMG (eg, Menopur)
f. Known allergy or hypersensitivity to recombinant follicle stimulating hormone (FSH) preparations or one of their excipients
g. Gynecologic bleeding (haemorrhages) of unknown aetiology
h. Any other contra-indications to receive r-hFSH

Variables

Primary endpoint: OHSS

Secondary endpoints:

- Severity grade of OHSS (WHO Scientific Group classification [1973])
- Adverse events/adverse drug reactions

Other variables:

- Demographic data and baseline characteristics
- Relevant medical history
- Relevant co-morbidities and risk factors
- Baseline condition
- Drug exposure (study drug and concomitant medication)
- Ovarian stimulation protocol used (i.e. GnRH agonist or GnRH antagonist protocol)
- Oocyte retrieval under the current treatment
- Biochemical pregnancy (human chorionic gonadotropin [hCG] test)

Data Sources

Data for this study will be obtained from various sources, including treating physicians and source documentation such as medical records.

Exposure to Ovaleap and Gonal-f, medical and gynecologic/obstetric history, comorbidities, concomitant medications, primary and secondary outcomes, potential confounding factors, and potential effect modifiers will be documented by treating physicians. Data will be recorded and summarized using a study-specific case report form.

The primary study outcome (OHSS) will be captured and validated via the patient's physician and medical records. Other secondary study endpoints will be captured based on physicians and/or medical records.

Study Size

It is planned to enroll 820 patients (410 patients per treatment arm) in this study. The sample size is based on the following approach for the comparison of the OHSS incidence in the two treatment arms, Ovaleap and Gonal-f. In the European Public Assessment Report for Gonal-f, the OHSS incidence is estimated as 3.6%. For the purpose of the sample size calculation, an OHSS incidence of 4% in both treatment arms is assumed, i.e. it is expected that the incidence of OHSS in patients treated with Ovaleap is not higher than in patients treated with Gonal-f. With 410 patients per treatment arm and assuming an OHSS incidence of 0.04 in both treatment arms, the upper limit of the observed one-sided 97.5% confidence interval (CI) for the difference in OHSS incidence (Ovaleap - Gonal-f) will be expected to be less than 0.04 with 80% power.

Data Analysis

Descriptive summary statistics (including number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables, and number and percentage of patients per category for categorical variables) will be provided for all variables.

The primary objective of the study is to compare the incidence rate of OHSS in both Ovaleap and Gonal-f groups. The incidence rate of OHSS in both groups (along with the 95% CI) and the difference in OHSS incidence (Ovaleap - Gonal-f) along with the two-sided 95% CI will be calculated. In addition, a logistic regression model will be constructed to estimate the effect of age, country, and other baseline variables on the OHSS rate.

Milestones

Milestone	Planned Date
Start of data collection	Q1 2017[1]
Study progress report	Q3 2018
End of data collection	Q3 2019
Interim report(s) of study results	Not applicable
Final report of study results	Q1 2020

[1] depending on the launch of Ovaleap in the respective countries.

5. AMENDMENTS AND UPDATES

Table 1: Amendments and Updates

Changes made to "Number 1" were implemented to Version 3.0. Changes made to "Number 2" were implemented to PASS Protocol Version 4.0. EMA has approved Versions 3 and 4. Changes made to Protocol Version 4 with Amendment 01 represented administrative changes.

Number	Date	Section of study protocol	Amendment or update	Reason
1	March 28, 2016	Section 6- Milestones	Update study timelines	Product Launch was delayed by one year and thus the study timelines were delayed by one year and updated accordingly
2	July 3, 2016	PASS Information; Section 3- Responsible Parties; Section 4- Abstract; Section 9- Research Methods; and Section 11- Management and Reporting of Adverse Events/Adverse Reactions Appendix 1- List of stand-alone documents	Change in MAH; Update responsible parties; update abstract to align with protocol; include additional country; update study inclusion/exclusion criteria, study variables; add summary table of data collection; refine analytic methods; add a list of special situations; and update questionnaire accordingly	Change in MAH was approved on 16 September 2014. Update responsible parties. Update abstract to align with protocol. Additional country was added to enhance recruitment. Inclusion criteria were refined to account for other potential drugs given for ovulation stimulation. Additional risk factors for OHSS (or means to reduce OHSS incidence or to prevent severe OHSS) not included previously were added. A summary table of data collection was added to provide a brief overview of how data elements have been organized and expected to be collected. Refine analytic methods. A list of special situations was added to provide a comprehensive list of event reporting. Questionnaire was updated accordingly.

Number	Date	Section of study protocol	Amendment or update	Reason
3	October 26, 2016	Title Page Investigator Approval Page	Changes were implemented to Version 4.0 with Amendment 01. Title page and investigator approval page have been added. The sponsor has changed from Teva B.V. to Teva Branded Pharmaceutical Products R&D, Inc.	Teva internal decision.

6. MILESTONES

Study milestones along with planned dates are presented in Table 2. The dates listed are subject to change depending on the timeline of protocol approval and the launch of Ovaleap in the respective countries.

The MAH has extended the original timelines proposed in the study synopsis and postponed the start of data collection to allow for varying launch dates of the product in various member states where the study will take place in. To retrieve the target number of patients required for the study during the time period provided, the study is planned to begin approximately one year following the product launch, i.e., Q1 2017. The countries that were tentatively selected to participate in the study are France, Germany, United Kingdom, Spain, Italy, Netherlands, and Belgium. The planned list of participating countries may be subject to modifications, according to changing launch dates and reimbursement policies. The study progress will depend on the prescribing rate of Ovaleap, which may differ by site and country. Therefore, the timeline may change accordingly.

The milestone section has been updated in the protocol and includes submission of a progress report as a milestone as shown below.

Table 2: Study Milestones

Milestone	Planned Date
Start of data collection	Q1 2017[1]
Study progress report	Q3 2018
End of data collection	Q3 2019
Interim report(s) of study results	Not applicable
Final report of study results	Q1 2020

[1] depending on the launch of Ovaleap in the respective countries.

7. RATIONALE AND BACKGROUND

Assisted reproductive technology (ART) treatments, such as in vitro fertilization (IVF), gamete intra-fallopian transfer and zygote intra-fallopian transfer, are performed yearly in thousands of women in Europe (Nyboe Andersen 2009). These treatments involve administration of recombinant human follicle stimulating hormones (r-hFSH), which stimulates multifollicular development.

Ovaleap® (follitropin alfa), an r-hFSH developed by Teva, is a biosimilar medicinal product to Gonal-f®, marketed by Merck Serono Europe Ltd. The product was approved on 27 September 2013 by the European Medicines Agency (EMA) for the following indications:

In adult women

- Anovulation (including polycystic ovarian syndrome [PCOS]) in women who have been unresponsive to treatment with clomifene citrate.
- Stimulation of multifollicular development in women undergoing superovulation for ART such as IVF, gamete intra-fallopian transfer and zygote intra-fallopian transfer.
- Ovaleap in association with a luteinizing hormone (LH) preparation is recommended for the stimulation of follicular development in women with severe LH and follicle stimulating hormone (FSH) deficiency. In clinical trials these patients were defined by an endogenous serum LH level <1.2 IU/L.

In adult men

- Ovaleap is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotropic hypogonadism with concomitant human chorionic gonadotropin therapy.

One of the serious adverse outcomes that may occur during ART is Ovarian Hyperstimulation Syndrome (OHSS) (Fiedler 2012). OHSS is an iatrogenic complication of the ovarian stimulation (Delvigne 2009). This condition may manifest in various degrees of severity, with mild and moderate OHSS resolving spontaneously and severe OHSS requiring hospitalization (Kissler 2007). OHSS is associated with several risk factors, including PCOS, long menstrual cycle length (Gizzo 2015), high antral follicular count and Anti-Mullerian hormone (AMH) serum level (Ocal 2011), high or rapidly increasing serum estradiol, increased number of developing follicles (Delvigne 2009), and potentially low body weight. In addition, it had been shown that when pituitary desensitization is obtained using GnRH agonist - in so-called GnRH agonist ovarian stimulation protocols - the incidence rate of OHSS is higher than in GnRH antagonist stimulation protocols (Olivennes 2002).

During clinical development, OHSS occurred in 11 patients (3.7%); 7 patients (4.6%) in the Ovaleap group and 4 patients (2.7%) in the Gonal-f group. By comparison, in the European Public Assessment Report (EPAR) for Gonal-f, the OHSS incidence is given as 3.6%. The discontinuation rate due to OHSS was, however, in favor of the Ovaleap group (1 case) vs. Gonal-f group (2 cases).

The EMA has requested a Post-Authorisation Safety Study (PASS) to compare the risk of OHSS in infertile women undergoing ART treatment with Ovaleap to those treated with Gonal-f. This proposed study has been designed in response to the EMA request.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Primary objective

The primary objective of the study is to assess the safety of Ovaleap compared to Gonal-f in one treatment cycle with respect to the incidence rates of OHSS in infertile women undergoing superovulation for ART.

8.2. Secondary Objectives

The secondary objectives of the study are:

- To examine the severity grade of OHSS (World Health Organization [WHO] Scientific Group classification [1973]) in Ovaleap compared to Gonal-f
- To assess adverse events/adverse drug reactions

9. RESEARCH METHODS

9.1. Study Design

This is a multi-national, comparative, prospective, non-interventional, observational cohort study.

9.2. Setting

The study population will comprise infertile women, who have not previously received treatment with any FSH (ie, r-hFSH, u-hFSH) and/or hMG, who are undergoing ART and are administered Ovaleap or Gonal-f for ovarian stimulation. A total of 820 patients will be recruited from approximately 60 centers specializing in ART from approximately 7 European countries. The countries that were tentatively selected to participate in the study are France, Germany, United Kingdom, Spain, Italy, Netherlands, and Belgium. The planned list of participating countries may be subject to modifications, according to changing launch dates and reimbursement policies that may differ by site and country. During the time period following the product launch and the beginning of the study, the types of clinical centres administering and prescribing Ovaleap or Gonal-f will be identified in the participating countries. Practices and treatments will vary by country and centres and will be considered in the selection of the centres. It is expected that many selected centres will specialized in one treatment regimen and thus minimizing the concern regarding potential change in prescribing behaviour. Efforts will be made to collect a balanced and representative sample of treatment and centres in each country.

Approximately 410 Ovaleap users and 410 Gonal-f users will be included by participating physicians. The study intends to collect data from a similar number of patients using Ovaleap and using Gonal-f in each country (and across countries). Patient will be equally distributed between treatment and across countries. These two groups will be compared to examine differences with regards to the outcome of interest.

Patients will be considered for enrolment in the study after the participating physician has determined the appropriateness of Ovaleap or Gonal-f use. The participating physician will first decide on the treatment regimen for his patient. Then, after the treatment is agreed upon, the physician will assess the patient eligibility by going through a check list to verify if the patient meets the inclusion/exclusion criteria. All eligible women are to be asked by their physician if they are willing to participate in the study. Physician will attempt to recruit Ovaleap and Gonal-f users in a 1:1 ratio so that the physician is to recruit the next new Ovaleap or Gonal-f user who is eligible but also willing to participate in the study. Therefore, the decision of the physician to treat the patient with one treatment regimen or another is separated from the decision of the patient to participate in the study. As this is a non-interventional study, participation in the study should be discussed between the physician and potential participant only after the treatment has been agreed upon. The physician is to explain the nature of the study, its purpose and associated procedures, and the expected duration of follow-up for each woman prior to her entry into the study. Each woman is to have opportunity to ask questions and is to be informed that she is entitled to withdraw from the study for any reason at any time. Information about the study and

the participant's rights will be provided on an informed consent and data privacy form and must be signed by all study participants.

Since the representativeness of the enrolled sample is unknown, a register for eligible patients (both enrolled and not enrolled) treated with Ovaleap and Gonal-f will be established. The register will include the following items: the proposed enrolment date, clinical practice type, age, reason for not participating (a list will be provided in the study report and any progress reports). This register will provide some insight on participation rates and potential selection bias.

According to the SmPC, patients are to self-administer daily subcutaneous (sc) injections of Ovaleap or Gonal-f, with the first dose given in the center under medical supervision. Patients are to be dosed at the physicians' discretion, up to a maximum of 450 IU sc daily for up to 20 days per cycle. Treatments will be individualized for each woman.

Eligible patients consented to participate in the study will be followed for one treatment cycle only (of up to 20 days) as part of their routine medical care. Once entered into the study, a participant may switch or discontinue therapy at any time. However, subjects will continue to be followed until end of follow-up or end of enrollment. Follow-up time will begin with the date of treatment initiation with Ovaleap or Gonal-f and end upon study completion (up to 30 days after the last dose administration), subject disenrollment from the study, or death. Since patient follow-up is relatively short, starting from drug initiation through one treatment cycle of up to 20 days, and a 30-day follow up period for a total follow-up of up to 50 days, loss to follow-up is expected to be low.

Necessary information on relevant clinical characteristics and outcomes will be captured. The study will use standardized, comprehensive, reliable data collected during these treatments in a routine clinical practice setting. Regular, active contacts with the study participants will provide information on changes in health status and adverse event reporting. Additional follow-up procedures will be used to validate self-reported events.

9.2.1. Inclusion Criteria

Patients may be included in the study only if they meet all of the following criteria:

a. Signed and dated written informed consent
b. Infertile female patients naïve to any FSH (r-hFSH, u-hFSH) or hMG treatment undergoing superovulation for ART and about to start first treatment with Ovaleap or Gonal-f for ovarian stimulation
c. A negative pregnancy test prior to treatment

9.2.2. Exclusion Criteria

Patients will be excluded from participating in this study if they meet any of the following criteria:

a. Primary ovarian failure
b. Ovarian enlargement or cyst not due to polycystic ovarian syndrome
c. Neoplasm (e.g. tumors of the ovary, breast, uterus, hypothalamus, or pituitary gland)
d. Prior history of OHSS.

e. Prior history of any r-hFSH use (eg, Puregon, Ovaleap, Bemfola, Elonva and/or Gonal-f), u-hFSH (eg, Bravelle and/or Fostimon) and/or hMG (eg, Menopur)
f. Known allergy or hypersensitivity to recombinant FSH preparations or one of their excipients
g. Gynecologic bleeding (haemorrhages) of unknown aetiology
h. Any other contra-indications to receive r-hFSH

Patients with reproductive system neoplasms will be excluded as there have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple treatment regimens for infertility treatment (van Leeuwen 2011, Fischerova 2012, Tworoger 2007, Harris 1992). It is not yet established whether or not treatment with gonadotropins increases the risk of these tumors in infertile women (SmPC of Gonal-f, 04 July 2011). Reproductive system neoplasms are considered important potential risks for the use of r-hFSH treatments, including Ovaleap and Gonal-f. Thus, women with these known preexisting conditions are excluded to remove any effect of these conditions on the treatment effectiveness and the study outcome.

Moreover, patients with a history of OHSS after ovulation induction by gonadotropins may have some form of PCOS (Aboulghar 1998). Repeated induction of ovulation in these women may carry a high risk of development of OHSS once more. Thus, women with prior history of OHSS are excluded.

9.3. Variables

9.3.1. Primary Outcome (s)

The primary outcome of interest is OHSS. Identification of OHSS will be based on patient symptoms and will be validated by physician's diagnosis and medical records.

9.3.2. Secondary outcome (s)

Several secondary outcomes will be collected and examined to investigate the severity and potential complications of OHSS.

The severity of OHSS will be classified according to the WHO Scientific Group (1973), as follows:

- Grade I (mild) - characterized by ovarian enlargement (5 to 7 cm). Abdominal discomfort of various degrees may be present.
- Grade II (moderate) - characterized by distinct ovarian cysts (ovary size 8 to 10 cm), accompanied by abdominal pain and tension, nausea, vomiting, diarrhea.
- Grade III (severe) - characterized by enlarged cystic ovaries (ovary size >10 cm), accompanied by ascites and occasionally hydrothorax. Abdominal tension and pain may be severe. Pronounced hydrothorax together with an abdominal cavity filled with cysts and fluid elevating the diaphragm, may cause severe breathing difficulties. Large quantities of fluid inside the cysts and in the peritoneal and pleural cavities cause haemoconcentration and increased blood viscosity. In rare cases, the syndrome may further be complicated by the occurrence of thromboembolic phenomena.

The relevant data to justify grading selection must be recorded in the medical records. In case OHSS was recorded, the physician will be asked to record any hospitalisation recorded in the patient's medical record that occurred as a result of the OHSS.

Another secondary outcome is the occurrence of adverse events, including serious adverse events/adverse drug reactions (refer to Section 11 for details).

9.3.3. Exposure (s)

The primary exposure variable is administration of Ovaleap. Women participating in this study will be divided into two exposure groups: Ovaleap and Gonal-f (active control or comparator). Detailed information on the study drug administration will be collected including dates of administration, dose, and duration of treatment. In addition, data will be collected on the use of gonadotropin-releasing hormone (GnRH) antagonist or GnRH agonist for pituitary desensitization and prevention of endogenous luteinizing hormone (LH) surge, on the use of human chorionic gonadotropin (hCG) or GnRH agonists (type, dose, time of administration) for oocyte maturation, on the luteal phase support and on concomitant medications (indication, route of administration, dose, frequency, start and stop dates).

9.3.4. Other Variables

Other variables, including potential confounders and effect modifiers collected in this study prior to treatment administration are:

- Demographic data and baseline characteristics, including:
  - Year of birth, age, race, weight, menstrual cycle length, and country, centre/site
  - Illicit drug use, alcohol, and smoking
- Relevant medical history, including:

  Pre-existing medical conditions and co-morbidities: Allergies/Hypersensitivities, cardiovascular conditions, diabetes, hypertension, and PCOS

  Reproductive history: prior pregnancies, prior miscarriages, infertility duration, and last menstrual cycle.

Other variables collected around the time of IVF treatment administration cycle are:

- Prior to FSH treatment:
  Small antral follicle count, and basal serum level of AMH as high number of antral follicles and high basal serum level of AMH have been associated with a higher risk of OHSS (Ocal 2011, Salmassi 2015, La Marca 2007).
- During FSH treatment:
  Type of ovarian stimulation protocol used (eg, GnRH agonist or GnRH antagonist protocol) as OHSS incidence varies with the ovarian protocol used (Olivennes 2002).
- Post- FSH treatment:

  Number of follicles and serum estradiol (E2)-level prior to oocyte maturation triggering; type of oocyte maturation triggering (ie, hCG or GnRH agonist) since triggering oocyte maturation with GnRH agonist in GnRH antagonist stimulation

protocol has been found to reduce the risk of OHSS (Fusi 2015); oocyte retrieval under the current treatment (whether or not oocyte retrieval was performed, number of oocytes retrieved); embryo transfer following oocytes fertilization (whether or not embryo transfer was performed, number of embryos transferred) since withholding embryo transfer may decrease severity of OHSS (Absalan 2013).

Other variables collected post-IVF treatment cycle are:

Biochemical pregnancy, results from sonographic pregnancy test (if available), and luteal support

Table 3 below summarizes the information to be collected during the routine visits expected during IVF cycles.

Table 3: Information to be collected during the routine visits for IVF cycles

	Enrolment **Start of downregulation or start of FSH treatment**	**Visit 1** **Day of oocyte retrieval**	**Visit 2** **Investigation on pregnancy (4 – 6 weeks after visit 1)**	**Pregnancy Follow up form** **In pregnant patients (after delivery, up to 10- 11 months after visit 1)**
Patient information and consent	x			
Inclusion/exclusion criteria	x			
Demographic data	x			
Medical history	x			
Reproductive history including:	x			
Menstrual Cycle Length (days)	x			
AMH level[a]	x			
Antral follicular count[a]	x			
Ovarian stimulation protocol (agonist or antagonist)		x		
Study drug used (Ovaleap or Gonal-f)		x		
Study dose administered		x		
Number of follicles prior to ovulation triggering		x		
Estradiol level prior to ovulation triggering		x		
Ovulation triggering: Product and dose		x		
Number of Oocytes retrieved (date and number)		x		
Estradiol level around time of retrieval[a]		x		
Embryo transfer (date and number)			x	
Luteal phase support: product, dose and route of administration			x	

	Enrolment **Start of downregulation or start of FSH treatment**	**Visit 1** **Day of oocyte retrieval**	**Visit 2** **Investigation on pregnancy (4 – 6 weeks after visit 1)**	**Pregnancy Follow up form** **In pregnant patients (after delivery, up to 10- 11 months after visit 1)**
Biochemical pregnancy (beta-hCG)			x	
Clinical pregnancy (assessed by ultrasound)			x	
Concomitant medication	x	x[b]	x[c]	x
Adverse events		x	x	x[d]
OHSS (following IVF cycle)		x	x	

[a] If available
[b] Including GnRH agonist, GnRH antagonist and product used for oocyte maturation triggering (eg, hCG or GnRH agonist)
[c] Including name, dose and date of administration of product used during the luteal phase support
[d] Including abortions or ectopic pregnancies if not reported at Visit 2

9.4. Data Sources

Data for this study will be obtained from various sources, including treating physicians and source documentation such as medical records.

Exposure to Ovaleap and Gonal-f, medical and gynecologic/obstetric history, comorbidities, concomitant medications, primary and secondary outcomes, potential confounding factors, and potential effect modifiers will be documented by the treating physicians. Data will be recorded and summarized using a study-specific case report form (CRF).

The primary study outcome (OHSS) will be captured and validated via the patient's physician and medical records. Other secondary study endpoints will be captured based on physicians and/or medical records.

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed onto the CRF. Data may not be recorded directly onto the CRF and considered as source data unless the center obtains written documentation from the sponsor, before the beginning of the study, indicating which data are permitted to be recorded directly onto the CRF. The CRFs are filed in the sponsor's central file.

Data collection will be accomplished by contacting the relevant physicians and by reviewing relevant source documents.

9.5. Study Size

The primary endpoint of the statistical analysis is the difference in incidence rates of OHSS between Overleap and Gonal-f. In the EPAR for Gonal-f, the OHSS incidence is given as 3.6%. For the purpose of the sample size calculation, an OHSS incidence of 4% in both treatment arms is assumed, i.e. it is expected that the incidence of OHSS in patients treated with Overleap is not higher than in patients treated with Gonal-f.

With 410 patients per treatment arm and assuming an OHSS incidence of 0.04 in both treatment arms, the upper limit of the observed one-sided 97.5% confidence interval (CI) for the difference in OHSS incidence (Overleap - Gonal-f) will be expected to be less than 0.04 with 80% power.

In addition, with a sample size of 410 (per treatment) and an observed incidence rate of 0.04, the expected half-width of the two-sided 95% CI for the OHSS incidence rates of Overleap and Gonal‑f will extend by ± 0.019 from the observed incidence rate (large sample approximation).

9.6. Data Management

Data relevant for this study will be collected from the patient's medical records and summarized in a study-specific CRF. Adverse events/adverse drug reactions, concomitant medications, and medical history data will be encoded with the latest version of Medical Dictionary for Regulatory Activities (MedDRA). All prior and ongoing therapy and medications will be encoded according to the World Health Organization (WHO) drug dictionary (WHO Drug) and Anatomical Therapeutic Chemical (ATC) Classification System, as appropriate.

9.6.1. Data Collection

Data will be transcribed from the patient's medical records into CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21 CFR part 11. The CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture data from this study. Before using the CDMS, all users will receive training on the system and any study-specific training. After they are trained, users will be provided with individual system access rights.

CRFs must be completed for each patient who provided informed consent according to the data source. Patient identity should not be discernible from the data transcribed to the CRF.

9.6.2. Data Quality Assurance

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality assurance, will comply with international regulatory guidelines, including International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality assurance, will be described in a data-management plan.

CRFs received will be processed and reviewed for completeness, consistency, and the presence of mandatory values. Applicable terms will be coded according to the coding conventions for this study. Logical checks will be implemented to ensure data quality and accuracy. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS. Discrepancies found will be queried.

Data corrections in the CDMS will be made using the CDMS update function. The system requires a reason for each change and keeps a complete audit trail of the data values, dates and times of modifications, and authorized electronic approvals of the changes.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate.

9.6.3. Archiving of Case Report Forms and Source Documents

The sponsor will be responsible for the processing and quality control of the data. Data management and filing will be carried out as described in the sponsor's standard operating procedures (SOPs) for clinical studies.

If data management and filing of documents for this study are delegated to a contract organization (CRO), these functions will be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management and filing activities. The original CRFs will be archived by the sponsor.

9.7. Data Analysis

9.7.1. General Considerations

The statistical analysis will be performed with SAS®. Descriptive statistics will be prepared for all variables documented in the CRF. For continuous variables, at a minimum, the number of non-missing observations, mean, standard deviation, median, minimum and maximum will be presented. For categorical variables, at a minimum, the number and percentage of patients falling into each category will be presented. All tables will be presented by treatment group and country. Further stratification by baseline variables and other potential confounding variables may be performed and will be described in the statistical analysis plan.

9.7.2. Analysis of the Primary Safety Endpoint

The primary endpoint of the study is the incidence of OHSS; 95% CIs will be calculated for the rates in each treatment group. The difference in the rates between the treatment groups (Ovaleap and Gonal-f) and the 95% CI will be calculated, for the entire population and by country. In addition, the effect of potential confounding variables on the OHSS rate will be explored using logistic regression. The following variables were selected among variables listed in section 9.3.4 to be included in the model as clinically most relevant with expected low correlation among each other: age, body mass index (BMI), country (countries may be pooled together in case of low enrollment), and PCOS.

Stratified odds ratio and their 95% CI along with forest plots will be performed to scrutinize the homogeneity of findings across selected variables. Assumptions for normal approximation will be investigated; exact methods will be used if they do not hold.

An analysis will be performed using stepwise logistic regression to derive adjusted odds ratio and corresponding 95% CI between treatments. The odds ratio will be modeled to include treatment and selected confounding variables. In the model building process the variables will be entered in a forward fashion if p-value < 0.25 (entry criterion) and retained if p-value < 0.3 (leave criterion) until all variables from the list above will be investigated (Bursac 2008). This final model will then be used to estimate the adjusted odds ratio between treatments and its 95% CI.

9.7.3. Analysis of the Secondary Safety Endpoints

The severity of OHSS will be summarized by means of a frequency table, stratified by treatment and country.

Adverse events will be displayed by MedDRA System Organ Class (SOC) and preferred term, and treatment group. Separate tables will be prepared for all adverse events, drug-related adverse events, serious adverse events, drug-related serious adverse events, severe adverse events, drug-related severe adverse events, adverse events leading to discontinuation and drug-related adverse events leading to discontinuation. In addition an overview table will be prepared, displaying number and percent of patients, and number of events for:

- any adverse events
- drug-related adverse events

- serious adverse events
- drug-related serious adverse events
- severe adverse events
- drug-related severe adverse events
- adverse events leading to discontinuation
- drug-related adverse events leading to discontinuation

9.7.4. Handling of Missing Data

Imputation of missing values is not foreseen.

9.8. Quality Control

To ensure compliance with GCP guidelines, checks will be in place to ensure that patients have signed the informed consent form.

Data will be transcribed directly from the patient's medical records into CRFs that are specifically designed for this study.

All records related to the study (ie, medical records, CRFs, correspondence, patient identification lists, signed informed consent forms, and other essential documents) must be retained until the sponsor notifies the center, in writing, that records may be destroyed.

The sponsor will be responsible for the processing and quality control of the data. Data management and filing will be carried out as described in the sponsor's SOPs for clinical studies.

If data management and filing of documents for this study are delegated to a CRO, these functions will be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management and filing activities. The original CRFs will be archived by the sponsor.

9.9. Limitations of the Research Methods

This observational study follows up patients treated with r-hFSH, Ovaleap and Gonal-f in routine clinical practice in order to estimate the incidence of OHSS in those two groups. The study is designed to collect comprehensive data from both exposed Ovaleap and unexposed patients (active controls on Gonal-f). The use of a parallel-cohort design allows for a study internal comparison.

Given the observational nature of the study, different biases could be introduced. Recruitment for this study largely depends on the initial contact of patients or health care providers and their consent to participate. Potential selection bias with regards to the selection of the participating study centers or individuals who consent to participate or who complete the study cannot be ruled out. Nonparticipation bias, which is characteristic of survey study design, may be expected and may influence the representativeness of the sample selected. This selection bias may affect the generalizability of the findings.

All efforts will be made to recruit a representative set of medical sites within each country. Since Ovaleap is a new product and low recruitment may be caused by limited use of a new drug, the study will start one year after the product launch to allow physicians to adopt the use of the drug. Once medical sites have been selected, several strategies will be used to increase participation in the survey, including telephone reminders to non-respondents physicians and various options for contacting potential study participants. An attempt will be made to have a ratio of 1:1 for Ovaleap and Gonal-f users within each country and overall. In order to assess the representativeness of the sample and the size and direction of the potential selection bias (due to nonparticipation), a register for eligible patients (both enrolled and not enrolled) treated with Ovaleap and Gonal-f will be established and the characteristics of enrolled and not enrolled patients within the same country will be compared. This register will provide an insight on participation rates and potential selection bias. Additional bias could result from the timing of the treatment initiation (lead time bias), due to difference in the time of the recruitment for both test drug and active comparator. To address this potential bias and to ensure that recruitment from one treatment cohort does not exceed recruitment of the other group within the country and a ratio of 1:1 will be kept as far as possible.

Due to the nature of the individualized treatment of IVF, clinical decisions of physicians, prescribing drugs based on factors like age, prior treatment, medical and obstetric history of the woman, presence of comorbidities, and channeling patients to specific treatment may result in systematic differences between the Ovaleap and Gonal-f cohorts. These cohort differences could potentially introduce bias and confound the association between treatment and the risk of OHSS. These potential biases are addressed in the study design as well as in the analysis phase. To minimize confounding by indication and depletion of susceptible bias (patients that can tolerate a given drug are more likely to continue its use), this study will include only women naïve to FSH (eg, r-hFSH, u-hFSH) and/or hMG treatment. In addition, the collection of the baseline information in the CRF will help to identify potential confounding factors. During the data analysis stage, every effort should be undertaken to control for potential confounding factors and reduce biases in the statistical models used. This can be attempted by use of stratified analysis and/or the implementation of multivariate statistical models.

9.10. Other Aspects

The study protocol was prepared using ENCePP Checklist Revision 2 for Study Protocols adopted by the ENCePP Steering Group in January 2013 (ENCePP, 2013) and will be registered in the ENCePP study registry, EU PAS Register (ENCePP, 2010). A final study report will be written using the appropriate STROBE checklist (STROBE, 2007). A completed and signed copy of the ENCePP Checklist for Study protocols is included in Appendix 2.

10. PROTECTION OF HUMAN SUBJECTS

The study will be conducted in a manner that is consistent with all relevant European and national guidelines and regulations for conducting studies with human subjects.

The study will be conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE) (2007), Good Pharmacovigilance Practices (GVP) and in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (ENCePP, 2012) as well as the ENCePP Code of Conduct (2014).

The study is a post-authorisation safety study (PASS) and will comply with the definition of the non-interventional (observational) study provided in Article 2(c) of Directive 2001/20/EC (European Commission, 2008) and the 2012 Guideline on Good Pharmacovigilance Practice (GVP): Module VIII – Post-Authorisation Safety Studies (EMA, 2012a, module VIII). The study will comply with the nature of non-interventional (observational) studies referred to in the ICH harmonised tripartite guideline Pharmacovigilance Planning E2E (ICH, 2004).

10.1. Health Authorities and Independent Ethics Committees/Institutional Review Boards

Review of the study protocol will be obtained at the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) in the appropriate geographies as required by local law. Regional regulatory approval within certain European member states will be obtained as required by national regulations. All relevant data protection laws in the participating continents and countries will be followed.

10.2. Informed Consent

This study is non-interventional and by definition, no additional procedures will be performed on the patient in addition to the normal clinical practice of the treating physician. Informed consent will be obtained from all patients for their clinical data to be recorded anonymously. Patients will also be informed of their right to withdraw their consent at any time during the study.

The physician, or a qualified person designated by the physician, should fully inform the patient of all pertinent aspects of the study. All written and/or oral information about the study will be provided in a language as nontechnical as practical and understood by the patient. The patient should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study.

Written informed consent will be obtained from each patient participating in the study. The patient’s willingness to participate in the study will be documented in a consent form, which will be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The physician will keep the original consent forms, and a copy will be given to the patient. It will also be explained to the patients that the patient is free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

10.3. Patient Confidentiality

The privacy of patients, including their identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification code (eg, initials and identification number). All data will be collected, maintained, and analyzed on a de-identified patient-level dataset. Personal medical information may be reviewed for the purpose of patient safety and/or verifying data in the source and transcribed onto the CRF. This review may be conducted by properly authorized persons on behalf of the sponsor, the quality assurance unit, and/or regulatory authorities. Personal medical information will always be treated as confidential.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment.

In this study, any serious adverse event occurring after the patient has signed the informed consent form should be recorded and reported as a serious adverse event. Any non-serious adverse event that was considered by the physician to have a reasonable possibility of being related to Ovaleap or Gonal-f should be reported as a non-serious adverse drug reaction.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of the study, or significant worsening of any concurrent disease, whether or not considered related to the study drug. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during the study will not be considered adverse events.

An adverse event can include any of the following:

- concurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of pre-existing conditions (Note: A condition recorded as pre-existing that is intermittently symptomatic [eg, headache] and that occurs during the study is an adverse event.)
- drug interactions
- events occurring during diagnostic procedures
- laboratory or diagnostic test abnormalities that are associated with clinical signs and symptoms or a serious adverse event, or require medical treatment or further diagnostic work-up, or are considered by the physician to be clinically significant

11.2. Definition of an Adverse Drug Reaction

An adverse drug reaction is a response to a medicinal product which is noxious and unintended.

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

11.3. Recording and Reporting Adverse Events/Adverse Drug Reactions

For adverse event/adverse drug reaction recording, the study period is defined for each patient as that time period from signature of the informed consent form through the end of the follow-up period. For this study, the follow-up period is defined as 30 days after the last administration of Ovaleap or Gonal-f.

Serious and non-serious adverse events, including special situations, that occur during the study period which are recorded in the patient's medical records or source documentation must be transcribed onto the CRF, regardless of the severity of the event. For serious adverse events, and non-serious adverse drug reactions, the Adverse Event/Adverse Drug Reaction Form must be completed and reported to the local safety officer (LSO).

The clinical course of each adverse event will be monitored at suitable intervals per standard clinical practice until resolved or stabilized or returned to baseline, or until the patient is referred to the care of a different health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made.

The onset and end dates and times, duration, action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded in the patient's medical records or source documentation and be transcribed onto the CRF.

The relationship of each adverse event to study drug treatment and study procedures, and the severity and seriousness of each adverse event, as judged by the physician, must be recorded as described below.

Only special situations leading to either an SAE or related AE have to be reported to MAH Pharmacovigilance.

Special situations:

- **Breastfeeding** - Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk.
- **Lack of therapeutic efficacy**
- **Abuse** - Intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
- **Medication error** - any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient or consumer.
- **Misuse** -

  – Intentional and inappropriate use of medicinal product not in accordance with the authorised product information.

  – Misuse for illegal purposes is misuse with the additional connotation of an intention of misusing the medicinal product to cause an effect in another person. This includes, amongst others: the sale, to other people, of medicines for recreational purposes and use of a medicinal product to facilitate assault.

- **Off-label use** Intentional use of medicinal product for a medical purpose not in accordance with the authorised product information.
- **Overdose** - Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information.
- **Occupational exposure to a medicinal product** - An exposure to a medicinal product as a result of one's professional or non-professional occupation.
- **Unexpected benefits of drug**

All special situations (even if not accompanied by any AE) should be summarized in the interim safety analysis and final study report, where applicable.

11.4. Severity of an Adverse Event

A distinction should be drawn between serious and severe adverse events/adverse drug reactions. "Severe" is one of three categories defining the intensity of an adverse event/adverse drug reaction. A severe adverse event/adverse drug reaction does not necessarily need to be considered serious and a serious adverse event/adverse drug reaction does not need to be severe.

Regardless of the classification of an adverse event/adverse drug reaction as serious or non-serious (see Section 11.6.1), its severity must be assessed according to medical criteria alone.

The severity of each adverse event must be recorded as one of the choices on the following scale:

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

11.5. Relationship of an Adverse Event to the Study Drug

The relationship of an adverse event to the study drug is characterized as follows:

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the study drug. • It could readily have been produced by the patient's clinical state, environmental, or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the study drug. • It does not reappear or worsen when the drug is re-administered.

Term	Definition	Clarification
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the study drug administration cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the drug. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet a drug relationship clearly exists. • It follows a known pattern of response to the study drug.

11.6. Serious Adverse Events

11.6.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- death
- a life-threatening adverse event (ie, the patient was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event. Hospitalizations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study will not be considered serious adverse events.
- persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

11.7. Protocol-Defined Adverse Events for Expedited Reporting

No protocol-defined adverse events for expedited reporting were identified for this study

11.7.1. Reporting Serious Adverse Events and Non-Serious Adverse Drug Reactions

To satisfy regulatory requirements, all serious adverse events regardless of judged relationship to treatment with Ovaleap or Gonal f, and non-serious adverse drug reactions that occur during the study period (including the 30-day protocol-defined follow-up period), must be reported to the sponsor by the physician. The event must be reported within 24 hours of when the physician learns about it or, if the event occurs on a weekend or national holiday, on the next working day. Completing the Adverse Event/Adverse Drug Reaction Form and reporting the event must not be delayed, even if not all the information is available. The physician does not need to actively monitor patients for adverse events once the study has ended. Serious adverse events occurring to a patient after the treatment of that patient has ended should be reported to the sponsor if the physician becomes aware of them.

The Adverse Event/Adverse Drug Reaction Form should be sent to the LSO or other designated personnel; the LSO will forward the report to the sponsor's Global Patient Safety & Pharmacovigilance Department.

The following information should be provided to record the event accurately and completely:

- study number
- physician and center identification
- patient number
- patient initials
- onset date and description of adverse event
- physician's assessment of the relationship of the adverse event to the study drug (no reasonable possibility, reasonable possibility)
- age of patient
- date of first dose of study drug
- date and amount of last administered dose of study drug
- action taken
- outcome, if known
- severity
- concomitant therapy (including doses, routes, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data

- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death:
  - cause of death (whether or not the death was related to study drug)
  - autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the physician and the sponsor to assess the nature of the event and the relationship of the event to the study drug, study procedures, and to underlying disease.

Additional information (follow-up) about any serious adverse event or non-serious adverse drug reaction unavailable at the initial reporting should be forwarded by the physician within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's Global Patient Safety & Pharmacovigilance Department will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/XML file to the LSO/CRO for local submission to the regulatory authorities, IEC/IRBs and investigators, according to regulations.

11.7.2. Pregnancy

All pregnancies that occur during the study are to be reported immediately to the Pharmacovigilance Department LSO using the pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event (see Section 11.7.1).

All patients who become pregnant will be monitored to the completion or termination of the pregnancy. If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including spontaneous or voluntary termination, details of birth, and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy does not continue to term, one of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event.
- For an elective abortion due to developmental anomalies, report as a serious adverse event.
- For an elective abortion not due to developmental anomalies, report on the pregnancy form.

11.8. Withdrawal Due to an Adverse Event

Any patient who experiences an adverse event may be withdrawn from the study or from study treatment at any time at the discretion of the physician. If a patient is withdrawn wholly or in part because of an adverse event, the CRF will be completed at that time.

If a patient is withdrawn from the study for multiple reasons that include adverse events, details recorded in the CRF should indicate that the withdrawal was related to an adverse event.

11.9. Medical Emergencies

Medical emergencies must be reported to the individual identified in the clinical study personnel contact information section of this protocol.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Reporting and Publication of Results

The study will be registered in the ENCePP Electronic Register of Studies.

Common study protocol, study status, and report(s) will be included in regulatory communications in line with the risk management plan, Periodic Safety Update Report (PSUR), and other regulatory milestones and requirements.

Study results will be considered for publication and will follow the International Committee of Medical Journal Editors (ICMJE 2013) guidelines. In addition, communication in appropriate scientific meetings will be considered.

When reporting results of this study, the appropriate STROBE checklist (STROBE 2007) will be followed.

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APPENDIX 1. LIST OF STAND-ALONE DOCUMENTS

Not applicable.

APPENDIX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

APPENDIX 3. ADDITIONAL INFORMATION

STUDY QUESTIONNAIRE - OVALEAP® (FOLLITROPIN ALFA).