FINAL STUDY REPORT FOR XM17-WH-50005

POST-AUTHORISATION SAFETY STUDY

STUDY 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
Version identifier of the final study report	Version 1.0
Date of last version of the final study report	Not applicable
EU PAS register number	EUPAS17328
Active substance (ATC code)	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	Theramex Ireland Limited, 3rd Floor, Kilmore House, Park Lane, Spencer Dock, Dublin, Ireland, DO1 YE64
Joint PASS	No
Research question and objectives	The primary objective was 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). The secondary objectives were 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	Belgium, France, Germany, Italy, Spain, United Kingdom
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MARKETING AUTHORISATION HOLDER

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1 ABSTRACT

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

Date: 31 Jul 2020

Author: Xin Zhan, Principal Medical Writer, Pharmaceutical Research Associates, Inc.

Keywords: Ovaleap, Gonal-f, Ovarian Hyperstimulation Syndrome, recombinant follicle stimulating hormone therapy, safety

Rationale and Background:

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

Research Question and Objectives:

Primary objective:

- 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:

- 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 (AEs)/adverse drug reactions (ADRs)

Study Design:

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

The study population comprised infertile women, who had not previously received treatment with any FSH (i.e., r-hFSH, urinary-hFSH [u-hFSH]) or any product containing FSH activity (i.e., human menopausal gonadotropin [hMG]), and who were undergoing ART and administered Ovaleap or Gonal-f for ovarian stimulation.

Setting:

A total of 820 patients were to be recruited with 410 patients each in the Ovaleap and Gonal-f arms by 31 July 2019 (scheduled end of patient recruitment) from 56 centres specializing in ART from 6 European countries: Belgium, France, Germany, Italy, Spain, and the United Kingdom. One centre was closed due to non-compliance and the sponsor decided to exclude all data collected from this centre. As of 31 July 2019, the Gonal-f arm's sample size had not been reached. However, a review of available data at that time suggested that it was unlikely that further recruitment to the Gonal-f arm would alter study conclusion. Based on the data available at that time and analysis thereof, a submission was made to the Pharmacovigilance Risk

Assessment Committee, requesting cessation of further Gonal-f patients recruitment, and adherence to original timescales. This request was approved on 20 September 2019.
Subjects and Study Size, Including Dropouts: 833 patients were enrolled and 817 included in the full analysis set, including 408 in the Ovaleap arm and 409 in the Gonal-f arm. Inclusion Criteria: 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 the first treatment with Ovaleap or Gonal-f for ovarian stimulation c. A negative pregnancy test prior to treatment
Variables and Data Sources Primary variable: OHSS Secondary variables: • Severity grade of OHSS (WHO Scientific Group classification [1973]) • AEs/ADRs Other variables: • Demographic data and baseline characteristics • Relevant medical history • Relevant comorbidities and risk factors • Baseline condition • Drug exposure (study drug and concomitant medications) • Ovarian stimulation protocol used (i.e., gonadotropin-releasing hormone [GnRH] agonist or GnRH antagonist protocol) • Oocyte retrieval under the current treatment • Biochemical pregnancy (human chorionic gonadotropin test) Data for this study were obtained from various sources, including treating physicians and source documentation such as medical records.
Results: Overall, 21 out of 408 patients in the Ovaleap arm and 13 out of 409 patients in the Gonal-f arm experienced OHSS during the study. The OHSS incidence rate was 5.1% (95% CI: 3.4%, 7.7%) in the Ovaleap arm and 3.2% (95% CI: 1.9%, 5.4%) in the Gonal-f arm. The rate difference between the Ovaleap and Gonal-f arms was 2.0% (95% CI: -0.8%, 4.9%) and no statistically significant difference (p=0.1589) was observed between the two treatment groups. The univariate logistic regression analysis supported this result and neither Ovaleap nor Gonal-f treatment was favoured in terms of OHSS incidence. In addition, the univariate analysis also identified potential confounders which may be associated with the incidence of OHSS, after adjusting for treatment effect (p<0.05). The majority of patients experienced mild OHSS (14 out of 21 patients in the Ovaleap arm and 8 out of 13 patients in the Gonal-f arm). Moderate OHSS was observed in 5 patients (1%) in the Ovaleap arm and 4 patients (<1%) in the Gonal-f arm, and severe OHSS was observed in

2 patients (<1%) in the Ovaleap arm and 1 patient (<1%) in the Gonal-f arm. The safety profiles were generally comparable between the two treatment groups.
Discussion: No statistically significant difference in OHSS incidence was observed between Ovaleap and Gonal-f arms. The univariate logistic regression analysis supported this result. The potential confounders including country, PCOS, embryo transfer, antral follicle count, basal serum level of AMH, pregnancy, FSH dose reduction, and FSH treatment duration had a statistically significant association with OHSS incidence at the univariate level. The safety results of AEs/ADRs besides OHSS demonstrated comparable safety profiles between Ovaleap and Gonal-f.
Marketing Authorisation Holder: Theramex Ireland Limited 3rd Floor, Kilmore House, Park Lane, Spencer Dock Dublin, Ireland, DO1 YE64
Names and Affiliations of Principal Investigators (coordinating investigators per region): Belgium: Anne Delbaere, CUB Hospital Erasmue, Anderlecht France: Paul Barriere, Centre Hospitalier Universitaire, Nantes Germany: Stefan Dieterle, Kinderwunschzentrum Dortmund, Dortmund Italy: Enrico Papaleo, Ospedale San Raffaele, Milano Spain: Gemma Castillon, Clínica IVI Barcelona, Barcelona United Kingdom: David Ogutu, Herts & Essex Fertility Centre, Hertfordshire

2 LIST OF ABBREVIATIONS

Table 1 List of Abbreviations

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AMH	anti-Mullerian hormone
ART	assisted reproductive technology(ies)
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CI	confidence interval
CRF	case report form (refers to any media used to collect study data [i.e., paper or electronic])
CRO	contract research organization
CTMS	clinical trial management system
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FAS	full analysis set
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
hCG	human chorionic gonadotropin
hMG	human menopausal gonadotropin
IU	International Units
IVF	in vitro fertilisation
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
OHSS	Ovarian Hyperstimulation Syndrome
OR	odds ratio
PASS	Post-Authorisation Safety Study

Abbreviation	Definition
PCOS	polycystic ovary syndrome
PT	preferred term
r-hFSH	recombinant human follicle stimulating hormone
SAE	serious adverse event
SAP	statistical analysis plan
s/c	subcutaneous
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SmPC	Summary of Product Characteristics
u-hFSH	urinary human follicle stimulating hormone
WHO	World Health Organization
WHODrug	World Health Organization drug dictionary

3 INVESTIGATORS

The coordinating investigators per region are listed below:

Country	Investigator Name and Affiliation
Belgium	Anne Delbaere, CUB Hospital Erasmue, Anderlecht
France	Paul Barriere, Centre Hospitalier Universitaire, Nantes
Germany	Stefan Dieterle, Kinderwunschzentrum Dortmund, Dortmund
Italy	Enrico Papaleo, Ospedale San Raffaele, Milano
Spain	Gemma Castillon, Clínica IVI Barcelona, Barcelona
United Kingdom	David Ogutu, Herts & Essex Fertility Centre, Hertfordshire

A list of all investigators is available upon request (Annex 1).

4 OTHER RESPONSIBLE PARTIES

Role/Responsibility	Name and Address of Organisation
Marketing Authorisation Holder	Theramex Ireland Limited 3rd Floor, Kilmore House, Park Lane, Spencer Dock Dublin, Ireland, DO1 YE64
Clinical Research Organisation: Development of materials, recruitment, training and management of sites, electronic data capture, data management and analysis	Pharmaceutical Research Associates, Inc. 4130 ParkLake Avenue, Suite 400 Raleigh, NC 27612, USA

5 MILESTONES

Milestone	Planned Date	Actual Date	Comments
Start of data collection	Q1 2017	27 January 2017	First patient in
Study progress report	Q3 2018	05 September 2018	Submitted to EMA by Teva
End of data collection	Q3 2019	30 September 2019	Collection of pregnancy outcome data is ongoing. Current data cut-off contains data up to 28 October, 2019.

Milestone	Planned Date	Actual Date	Comments
Interim report	Not applicable	-	-
Registration in the EU PAS register	Not applicable	19 January 2017	-
Final report of study results	Q1 2020	31 July 2020	-

6 RATIONALE AND BACKGROUND

Assisted reproductive technology (ART) treatments, such as in vitro fertilisation (IVF), gamete intrafallopian transfer and zygote intrafallopian transfer, are performed yearly in thousands of women in Europe.[1] 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 and acquired by Theramex, 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 ovary 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 intrafallopian transfer and zygote intrafallopian 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).[2] OHSS is an iatrogenic complication of ovarian stimulation.[3] This condition may manifest in various degrees of severity, with mild and

moderate OHSS resolving spontaneously and severe OHSS requiring hospitalization.[4] OHSS is associated with several risk factors, including PCOS, long menstrual cycle length[5], high antral follicular count and anti-Mullerian hormone (AMH) serum level[6], high or rapidly increasing serum oestradiol, increased number of developing follicles[3], and potentially low body weight. In addition, it had been shown that when pituitary desensitization is obtained using gonadotropin-releasing hormone (GnRH) agonist - in so-called GnRH agonist ovarian stimulation protocol - the incidence rate of OHSS is higher than in GnRH antagonist stimulation protocol.[7]

During clinical development, OHSS was reported in 11 patients (3.7%); 7 patients (4.6%) in the Ovaleap group and 4 patients (2.7%) in the Gonal-f group, of which severe OHSS was reported in 1 case in each group.[8] One case of OHSS was reported in the follow-up study (n=147), which included up to two additional treatment cycles in patients who did not become pregnant in the Phase 3 Main Study.[9] By comparison, in the European Public Assessment Report (EPAR) for Gonal-f, the OHSS incidence was given as 3.6%.[10] The discontinuation rate due to OHSS was, however, in favour of the Ovaleap group (1 case) versus 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 study was designed in response to the EMA request.

7 RESEARCH QUESTION AND OBJECTIVES

7.1 Primary Objective

The primary objective of the study was 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.

7.2 Secondary Objectives

The secondary objectives of the study were:

- 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 (AEs)/adverse drug reactions (ADRs)

8 AMENDMENTS AND UPDATES TO THE PROTOCOL

Table 2 Protocol Amendments and Updates

Changes made to “Number 1” were implemented to PASS Protocol version 3.0. Changes made to “Number 2” were implemented to PASS Protocol version 4.0. EMA has approved Protocol versions 3 and 4. Changes made to Protocol version 4 with Amendment 01

represented administrative changes. Numbers 4 and 5 represented 2 letters of clarification documenting non-substantial changes to Protocol version 4 with Amendment 01.

Number	Date	Section of study protocol	Amendment or update	Reason
1	30 March 2016	Section 6 – Milestones	Updated study timelines	Product launch was delayed by one year and thus the study timelines were delayed by one year and updated accordingly
2	03 July 2016	PASS Information; Section 3 – Responsible Parties; Section 4 – Abstract; Section 9 – Research Methods; Section 11 – Management and Reporting of Adverse Events/Adverse Reactions; Appendix 1 – List of Stand-alone Documents	Change in MAH; updated responsible parties; updated abstract to align with protocol; included additional country; updated study inclusion/exclusion criteria, study variables; added summary table of data collection; refined analytic methods; added a list of special situations; and updated questionnaire accordingly	Change in MAH was approved on 16 September 2014; updated responsible parties; updated abstract to align with protocol; an 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 had been organized and expected to be collected; refined 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	26 October 2016	Title Page; Investigator Approval Page	Changes were implemented to version 4.0 with Amendment 01; title page and investigator approval page were added; the sponsor was changed from Teva B.V. to Teva Branded Pharmaceutical Products R&D, Inc.	Teva's internal decision
4	09 May 2018	Section 3 – Responsible Parties; Section 11.7.1 – Reporting Serious Adverse Events and Non-serious Adverse Drug Reactions; Section 9.3.4 – Other Variables, and Table 3	Updated MAH contact person and the sponsor's QPPV; updated the sponsor's safety officer; deleted the sponsor's global medical affair project leader; updated the process for reporting adverse reactions for Gonal-f; added the collection of additional variables at the time of the diagnosis of OHSS	Administrative changes; reflected the current process that the sponsor's Global Patient Safety & Pharmacovigilance Deportment followed; the additional data collected were used as data check to confirm the accuracy and validity of the diagnosis of OHSS and the severity grade of OHSS classification
5	15 November 2019	Section 9.2.1 – Inclusion Criteria; Appendix 3	Changed the sponsorship from Teva to Theramex; Clarified that standard-of-care procedures and testing utilized by each respective centre was acceptable for confirmation of negative pregnancy test relative to Inclusion Criterion c, "A negative pregnancy test prior to treatment"; clarified the definition of female infertility	This observational-only study allowed centres to utilize their respective standard-of-care for procedures and testing; the definition of female infertility was clarified as it pertained to population eligibility for this study

Abbreviations: MAH=Marketing Authorisation Holder; OHSS=Ovarian Hyperstimulation Syndrome; PASS=Post-Authorisation Safety Study; QPPV=qualified person for pharmacovigilance.

All versions of the protocol and the 2 letters of clarification are available upon request (Annex 1).

9 RESEARCH METHODS

9.1 Study Design

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

The study population comprised infertile women, who had not previously received treatment with any FSH (i.e., r-hFSH, urinary-hFSH [u-hFSH]) or any product containing FSH activity (i.e., human menopausal gonadotropin [hMG]), and who were undergoing ART and were administered with Ovaleap or Gonal-f for ovarian stimulation.

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

Treatments were individualized for each woman. After evaluation of patient eligibility, patients in each centre were observed following the routine clinical practice for superovulation. Data for study participants were obtained from 56 centres in countries of the European Union. The study intended to collect data from a similar number of patients using Ovaleap and using Gonal-f in each country.

9.2 Setting

A total of 820 patients were to be recruited with 410 patients each in the Ovaleap and Gonal-f arms by 31 July 2019 (scheduled end of patient recruitment) from 56 centres specializing in ART from 6 European countries: Belgium, France, Germany, Italy, Spain, and the United Kingdom. One centre was closed due to non-compliance and the sponsor decided to exclude all data collected from this centre. As of 31 July 2019, the Gonal-f arm's sample size had not been reached. However, a review of available data at that time suggested that it was unlikely that further recruitment to the Gonal-f arm would alter study conclusion. Based on the data available at that time and analysis thereof, a submission was made to the Pharmacovigilance Risk Assessment Committee, requesting cessation of further Gonal-f patients recruitment, and adherence to original timescales. This request was approved on 20 September 2019.

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 were identified in the participating countries. Practices and treatments varied by country and by centre and these variations were considered in the selection of the centres. It was expected that many selected centres were specialized in one treatment regimen and thus minimizing the concern regarding potential change in prescribing behaviour. Efforts were made to collect a balanced and representative sample of treatments and centres in each country.

Approximately 410 Ovaleap users and 410 Gonal-f users were included by participating physicians. Patients were equally distributed between treatments in each country. These two groups were compared to examine differences with regards to the outcome of interest.

Patients were considered for enrolment in the study after the participating physicians had determined the appropriateness of Ovaleap or Gonal-f use. The participating physician first decided on the treatment regimen for his/her patient. After the treatment was agreed upon, the physician assessed the patient eligibility by going through a checklist to verify if the patient met the inclusion/exclusion criteria. All eligible women were asked by their physician if they were willing to participate in the study. Physicians attempted to recruit Ovaleap and Gonal-f users in a 1:1 ratio so that the physician was to recruit the next new Ovaleap or Gonal-f user who was eligible and also willing to participate in the study. Therefore, the decision of the physician to treat the patient with one treatment regimen or another was separated from the decision of the patient to participate in the study. As this was a non-interventional study, participation in the study should be discussed between the physician and potential participant only after the treatment had been agreed upon. The physician was 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 had an opportunity to ask questions and was informed that she was entitled to withdraw from the study for any reason at any time. Information about the study and the participant's rights was provided on an informed consent and data privacy form, which was signed by all study participants.

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

According to the Summary of Product Characteristics (SmPC), patients self-administered daily subcutaneous (s/c) injections of Ovaleap or Gonal-f, with the first dose given in the centre under medical supervision. Patients were dosed at the physicians' discretion, up to a maximum of 450 IU s/c daily for up to 20 days per cycle. Treatments were individualized for each woman.

Eligible patients who consented to participate in the study were 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 should continue to be followed until end of follow-up or end of pregnancy. Follow-up time began with the date of treatment initiation with Ovaleap or Gonal-f and ended upon study completion (up to 30 days after the last dose administration), subject disenrollment from the study, or death. Since patient follow-up was 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 was expected to be low.

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

9.3 Subjects

Patients entered into the study only if all inclusion criteria and none of the exclusion criteria were fulfilled.

9.3.1 Inclusion Criteria

Patients may have been included in the study if all of the following criteria were 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 the first treatment with Ovaleap or Gonal-f for ovarian stimulation
c. A negative pregnancy test prior to treatment

9.3.2 Exclusion Criteria

Patients were excluded from participating in this study if they met either of the following criteria:

a. Primary ovarian failure
b. Ovarian enlargement or cyst not due to polycystic ovarian syndrome
c. Neoplasm (eg, tumours 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. Gynaecologic bleeding (haemorrhages) of unknown aetiology
h. Any other contraindications to receive r-hFSH

Patients with reproductive system neoplasms were excluded as there had been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who had undergone multiple treatment regimens for infertility treatment.[11,12,13,14] It was not yet established whether or not treatment with gonadotropins increased the risk of these tumours in infertile women (SmPC of Gonal-f, 04 July 2011). Reproductive system neoplasms were considered important potential risks for the use of r-hFSH treatments, including Ovaleap and Gonal-f. Thus, women with these known pre-existing conditions were 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.[15] 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 were excluded.

9.4 Variables

9.4.1 Primary Variable

The primary variable was OHSS. Identification of OHSS was based on patient symptoms and was validated by physician's diagnosis and medical records.

9.4.2 Secondary Variables

The secondary variables were collected and examined to investigate the severity and potential complications of OHSS.

The severity of OHSS was 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, diarrhoea.

- 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 caused 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 was asked to record any hospitalisation in the patient's medical record that occurred as a result of the OHSS.

Another secondary variable was the occurrence of AEs, including serious adverse events (SAEs)/ADRs (refer to Section 11 of the protocol for details).

9.4.3 Exposure

The primary exposure variable was administration of Ovaleap. Women participating in this study were divided into two exposure groups: Ovaleap and Gonal-f (active control and comparator). Detailed information on the study drug administration was collected

including dates of administration, dose, and duration of treatment. In addition, data were collected on the use of GnRH antagonist or GnRH agonist for pituitary desensitization and prevention of endogenous 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).

9.4.4 Other Variables

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

- 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 were:

- 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.[6,16,17]

- During FSH treatment:

  Type of ovarian stimulation protocol used (eg, GnRH agonist or GnRH antagonist protocol) as OHSS incidence can vary with the ovarian protocol used.[7]

- Post-FSH treatment:

  Number of follicles and serum oestradiol level prior to oocyte maturation triggering; type of oocyte maturation triggering (i.e., hCG or GnRH agonist) since triggering oocyte maturation with GnRH agonist in GnRH antagonist stimulation protocol had been found to reduce the risk of OHSS[18]; 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.[19]

Other variables collected post-IVF treatment cycle were:

- Biochemical (urinary hCG) pregnancy results, results from sonographic pregnancy test (if available), and luteal support.

9.5 Data Sources and Measurement

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

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

The primary study variable (OHSS) was captured and validated via the patient's physician and medical records. Other secondary study variables were 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 were transcribed into the CRF. Data may not be recorded directly into the CRF and considered as source data unless the centre obtained written documentation from the sponsor, before the beginning of the study, indicating which data were permitted to be recorded directly into the CRF. The CRFs were filed in the sponsor's central file.

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

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	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		
Oestradiol level prior to ovulation triggering		x		
Ovulation triggering: product and dose		x		
Oocytes retrieved (date and number)		x		
Oestradiol level around time of retrieval[a]		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)**
Embryo transfer (date and number)			x	
Luteal phase support: product, dose and route of administration			x	
Biochemical pregnancy (beta-hCG)			x	
Clinical pregnancy (assessed by ultrasound)			x	
Concomitant medications	x	x[b]	x[c]	x
Adverse events		x	x	x[d]
OHSS (following IVF cycle)		x	x	

Abbreviations: AMH=anti-Mullerian hormone; FSH=follicle stimulating hormone; GnRH=gonadotropin-releasing hormone; hCG=human chorionic gonadotropin; IVF=in vitro fertilisation; OHSS=Ovarian Hyperstimulation Syndrome.
[a] If available
[b] Included GnRH agonist, GnRH antagonist and product used for oocyte maturation triggering (eg, hCG or GnRH agonist)
[c] Included name, dose and date of administration of product used during the luteal phase support
[d] Included abortions or ectopic pregnancies if not reported at Visit 2

9.6 Bias

This observational study followed 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 was designed to collect comprehensive data from both exposed Ovaleap and unexposed patients (active controls on Gonal-f). The use of a parallel-cohort design allowed for a study internal comparison.

Given the observational nature of the study, different biases could have been introduced. Recruitment for this study largely depended on the initial contact of patients or healthcare providers and their consent to participate. Potential selection bias with regard to the selection of the participating study centres or individuals who consented to participate or who completed the study cannot be ruled out. Non-participation bias, which was characteristic of survey study design, may have been expected and influenced the representativeness of the sample selected. This selection bias may have affected the generalizability of the findings.

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

Systematic differences between the Ovaleap and Gonal-f cohorts may have resulted from 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 channelling patients to specific treatment. These cohort differences could have potentially introduced bias and confounded the association between treatment and the risk of OHSS. These potential biases were 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 were more likely to continue its use), this study included 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

helped to identify potential confounding factors. During the data analysis stage, every effort was undertaken to control for potential confounding factors and reduce biases in the statistical models used. This was attempted by use of stratified analysis and/or the implementation of multivariate statistical models.

9.7 Study Size

The primary variable of the statistical analysis was the difference in incidence rates of OHSS between Ovaleap and Gonal-f. In the EPAR for Gonal-f, the OHSS incidence was given as 3.6%.[10] For the purpose of the sample size calculation, an OHSS incidence of 4% in both treatment arms was assumed, i.e., it was expected that the incidence of OHSS in patients treated with Ovaleap was 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) was 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 Ovaleap and Gonal-f was extended by ± 0.019 from the observed incidence rate (large sample approximation).

9.8 Data Transformation

Data relevant for this study were collected from the patient's medical records and summarised in a study-specific CRF. AEs/ADRs, concomitant medications, and medical history data were encoded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA, version 19.1). All prior and ongoing therapy and medications were encoded according to the World Health Organization drug dictionary (WHODrug) and Anatomical Therapeutic Chemical (ATC) Classification System, as appropriate.

9.8.1 Data Collection

Data were transcribed from the patient's medical records into CRFs that were specifically designed for this study. The data collected in the CRFs were captured in a clinical trial management system (CTMS) that met the technical requirements described in 21 Code of Federal Regulations Part 11. The CTMS was fully validated to ensure that it met the scientific, regulatory, and logistical requirements of the study before it was used to capture data from this study. Before using the CTMS, all users received training on the system and any study-specific training. After they were trained, users were 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.

9.8.2 Data Quality Assurance

Data management was responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality assurance, complied with international regulatory guidelines, including International Council for Harmonisation 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, were described in a data management plan.

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

Data corrections in the CTMS were made using the CTMS update function. The system required a reason for each change and kept 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 CTMS and all other study data were locked to further additions or corrections. Locking the study data represented the acknowledgement that all data had been captured and confirmed as accurate.

9.8.3 Analysis Sets

The Patient Register included all patients who registered to participate in the study. The enrolled population included all registered patients who satisfied the eligibility criteria and enrolled into the study. The full analysis set (FAS) included all enrolled patients who received at least one dose of Ovaleap or Gonal-f. Subjects that received additional FSH products while being treated with Ovaleap or Gonal-f were excluded from the FAS. A patient that switched between the two treatments prior to receiving the first dose (eg, if the proposed treatment was Gonal-f but the patient was eventually administered Ovaleap and vice versa) was analysed according to the treatment received. A patient that switched from Gonal-f to Ovaleap and vice versa after receiving one or more doses of their initial treatment was analysed according to the treatment initially received. Further sensitivity analyses were considered to handle such patients.

All analyses were performed based on the FAS, unless otherwise specified.

9.9 Statistical Methods

9.9.1 General Considerations

The statistical analysis was performed with SAS®. Descriptive statistics were prepared for all variables documented in the CRF. For continuous variables, the number of non-missing observations, mean, standard deviation (SD), median, minimum, and maximum were

presented. For categorical variables, the number and percentage of patients with non-missing data in each category and the number of patients with missing data were presented. The default denominator for percentages calculation were the FAS, unless specified otherwise. The missing category (for missing data points) were excluded from the denominator for percentage calculations. All tables were presented by treatment group and country. All listings were ordered by treatment and then by country, patient number and date of assessment (where relevant).

9.9.2 Patient Disposition

Patient disposition was summarised by treatment group and overall and by country, treatment group and overall, and listed by patient based on all patients in the register.

Patients were classified as having completed the treatment of FSH if they had oocyte maturation triggering performed and study completion was assessed by whether the patient (pregnant and non-pregnant) completed the first part of the study (attended Visit 2) or discontinued earlier.

9.9.3 Demographics and Baseline Characteristics

Baseline characteristics referred to the data collected before the first dose administration of Ovaleap or Gonal-f (Day 1), including demographic data, relevant medical history, reproductive history, small antral follicle count and basal serum level of AMH.

Demographic data and baseline characteristics were collected before the first dose administration of Ovaleap or Gonal-f and were summarised by treatment group and overall, and by country/centre, treatment group and overall based on the FAS as follows: age, ethnic origin, height, weight, body mass index (BMI), current smoker, alcohol consumption, and illicit drug use.

Individual listing of all demographics and baseline characteristics were provided.

9.9.4 Medical History and Comorbidities

Relevant medical history and comorbidities were collected before the first dose administration of Ovaleap or Gonal-f. These data included specific conditions included in the CRF (allergies/hypersensitivities, cardiovascular conditions, diabetes, hypertension, and PCOS) and any other relevant medical history reported by the investigator. All medical history was coded using MedDRA, version 19.1. The incidences of medical history abnormalities and comorbidities were summarised using descriptive statistics by system organ class (SOC) and preferred term (PT). Patients were counted only once in each PT and SOC category. Summaries were presented by treatment group and overall, and by country, treatment group and overall based on the FAS.

Individual listing of all medical history information recorded in the CRFs was provided, including date of medical history assessment, verbatim term, MedDRA PT and SOC category, start date, and stop date (if relevant) or ongoing.

9.9.5 Reproductive History

Reproductive history was collected before the first dose administration of Ovaleap or Gonal-f and was summarised by treatment group and overall, and by country, treatment group and overall based on the FAS as follows: number and percentage of patients with former or no former pregnancies, infertility duration for women diagnosed with infertility, mean menstrual cycle length, days since last menstrual cycle, antral follicular count – right and left ovary, and basal serum level of AMH.

Individual listing with reproductive history details was provided.

9.9.6 Analysis of the Primary Variable

The primary variable of the study was the incidence of OHSS. The primary analysis, based on the FAS, estimated the incidence rate of OHSS (with 95% CIs) based on the percentage of patients who experienced OHSS following IVF treatment (from Day 1 of Ovaleap or Gonal-f treatment up to 30 days after the last dose administered for this cycle) in each treatment group and the difference in incidence rates between the two treatment groups (Ovaleap – Gonal-f) (with 95% CIs). The Newcombe-Wilson method was used to estimate two-sided 95% CIs for the incidence rate and rate differences.[20] The chi-squared test or Fisher's exact test was used to estimate p-values for the difference in incidence rates between the two treatments.

The effect of potential confounders on the differences in the OHSS rate observed between treatments was explored using univariate and multivariate logistic regressions. The univariate models included treatment alone or in combination with each selected confounding variable. Confounders and stratification factors (as listed further below) that were missing for 70% or more patients were not considered. In addition, at least 20 patients were required in each subpopulation. The multivariate models included treatment in combination with multiple potential confounders selected as described below. The estimate of interest was the adjusted odds ratio (OR) for the treatment effect and corresponding 95% CI.

Potential confounders, including but not limited to those listed in Section 9.3.4 of the study protocol, were candidates for inclusion in the logistic regression model. The following were selected based on their clinical relevance to OHSS and low expected correlations among each other:

- Age (years; <30, 30 to <34, ≥34). Note: Highest risk of OHSS was among the youngest age group; therefore, the oldest group was used as the reference for analyses

- BMI (kg/m^2; <18.5, 18.5 to <25 [reference], ≥25)
- Country (countries may be pooled together in case of low enrolment; see below)
- PCOS (No [reference] versus Yes). Note: Since this risk factor was also linked to menstrual cycle length (as PCOS patients generally had >35 days menstrual cycle), antral follicle count, and basal serum level of AMH, the correlation with these variables were examined

Additional variables that may have been considered (also subject to their correlation to other variables) included:

- Menstrual cycle length (<21 days, ≥22 days and ≤35 days [reference], >35 days)
- Antral follicle count (right and left) (<12 [reference], ≥12)
- Basal serum level of AMH (<3.5 [reference], ≥3.5 ng/mL)
- Ovarian stimulation protocol (GnRH agonist vs GnRH antagonist [reference]). Note: Incidence of OHSS was expected to be lower in the GnRH antagonist protocol
- Total FSH dose received in this cycle (IU)
- FSH treatment duration (days)
- Type of oocyte maturation triggering (hCG versus GnRH agonist [reference])
- Centre (centres may be pooled together in case of low enrolment; see below)

Other variables may have been considered as stratification factors in multivariate models included:

- FSH dose reduction compared to the first dose (Yes versus No [reference])
- FSH dose missed in the 4 days preceding oocyte retrieval (Yes versus No [reference]; only patients with oocyte retrieval were included in this analysis, [i.e., patients who completed the treatment])
- Embryo transfer (Yes versus No [reference])
- Number of embryos transferred (1 [reference] versus >1). Note: Lower risk of OHSS with 1 embryo transferred

- Medications used in the luteal phase support (hCG versus other [reference]). Note: There was no luteal phase support if embryo transfer was "No"; therefore, patients with no embryo transfer performed were excluded from this analysis

- Pregnancy (Yes versus No [reference])

Selection of variables to be included in the final logistic model was based on forward stepwise logistic regression. Patients with missing data (including "unknown" category) in at least one of the candidate variables were excluded from the analysis prior to the stepwise regression analysis. For simplicity in interpretation only main level effects (i.e., treatment group and selected confounding variables, with no interactions) were explored in stepwise multiple regression. In the model building process the significance level to determine which candidate variables can enter the model in a forward fashion (1 at a time, in the order described above) was <0.25 (entry criterion), and the significance level to determine which variables can leave the model (leave criterion) was 0.3 (i.e., retained in the model if the significance level was <0.3) until all variables from the list above were investigated.[21]

This final model was then used to estimate the adjusted OR between treatments and its 95% CI. The robustness of the final model selected by forward stepwise regression was explored by altering the order in which variables were added to the model using backward stepwise logistic regression (starting with all candidate variables and deleting variables whose loss did not affect significantly the model fit). If a difference was found between the final models selected by forward stepwise and the backward stepwise regression, the model with the lower log-likelihood was chosen as the final model.

Univariate and multivariate adjustments were estimated. The following outputs were produced:

- Univariate associations summary table, presenting each potential confounder with corresponding OR, 95% CI, and p-value for the association between the confounder and OHSS incidence, and the OR, 95% CI, and p-value for the treatment effect on OHSS incidence (based on the univariate model adjusted for the potential confounder).

- Multivariate associations summary table corresponding to the final model selected via multiple stepwise regressions above. The table included the ORs, 95% CIs, and p-values corresponding to treatment and all other confounding variables present in the selected final model.

Incidence of OHSS was descriptively summarised by treatment group for each potential confounder, as number of patients (n) with events and corresponding percentage within sub-categories defined for the confounder (eg, within the age groups defined for the confounder age).

Pairwise correlations between all potential confounders examined were presented. The chi-squared test was used for associations between categorical variables. Analysis of variance or Spearman's rank correlation was used for examining the relationship between continuous and categorical variables depending on the number of categories, and Pearson's rho correlation was used for correlation between continuous variables.

ORs and their 95% CIs for interaction between treatment groups and each confounding variable along with forest plots were provided to explore the homogeneity of findings (i.e., homogeneity of the effect of covariates on treatment difference in OHSS rates across selected confounding covariates) by including the effect of interaction term between treatment and each covariate in the logistic regression models.

For each candidate confounding variable (among all variables listed as potential confounders in the previous section) a regression model was fitted that included treatment as a main effect, an additional factor representing the confounding variable of interest (excluding observations with missing data for this variable) and the interaction between this factor and treatment. The statistic of interest was the ORs and corresponding 95% CIs for the interaction terms. These ORs and 95% CIs were summarised for each interacting factor. A forest plot was also provided.

Pooling of countries/centres with few events

To avoid convergence problems in the logistic models (in case there were very few or 0 events [i.e., no patients with OHSS] per country), countries that had <2 OHSS events in either treatment group were pooled together. Pooling was done by first ordering the countries by increasing number of events per treatment group (based on the treatment group with the fewest events) and merging the first country (if it had fewer than 2 OHSS events in a treatment group) with the next country in the list, until there were at least 2 events per treatment group. The same approach was used for pooling centres.

9.9.7 Analysis of the Secondary Variables

9.9.7.1 Severity of OHSS

The number and percentage of patients in each category of OHSS severity grade (I, II or III) were descriptively summarised by country and treatment group based on the FAS for the overall study population (i.e., over all countries) and for each country. A p-value testing the statistical significance of any differences in the distribution of OHSS severity grade between the two treatment groups for the overall study population and for each country was provided for descriptive purposes (i.e., confined to the study population) based on the chi-squared test or Fisher's exact test as appropriate.

9.9.7.2 Adverse Events/Adverse Drug Reactions

Information on AEs was transcribed from the patients' medical records to the study CRFs. To evaluate the primary and secondary variables, the study period for recording AEs/ADRs was defined as the time between informed consent to 30 days after the last administration of Ovaleap or Gonal-f. In the event there were few such AEs continued to be captured in the study CRFs for patients who tested positive for pregnancy at Visit 2, the results were reported in a listing rather than a summary table.

All AEs were coded using MedDRA, version 19.1. The incidences of AEs were summarised as the number and percentage of patients who experienced the event and the number of AEs, categorized by SOC and PT. Patients were counted only once in each SOC or PT category, based on the event with the maximum severity or maximum treatment relation to Ovaleap or Gonal-f.

An AE listing was provided including start and end date or ongoing; duration in hours if AE terminated within 24 hours; whether the AE was serious; severity of the AE; action taken regarding Ovaleap or Gonal-f, dechallenge-rechallenge, and results (if yes, outcome, relation to Ovaleap or Gonal-f, whether the patient discontinued the study due to this AE, whether concomitant or additional treatment was given, and whether the event was OHSS).

For SAEs, the following additional details (to those provided for all AEs) were provided regarding whether the SAE resulted in persistent or significant disability/incapacity, was associated with congenital anomaly or birth defect, resulted in death, required or prolonged hospitalization, was life-threatening, and whether it was otherwise medically important (if not covered by other criteria).

An additional listing provided the additional details for OHSS collected in the CRF for any OHSS events diagnosed during the study, including the date of OHSS diagnosis, time (days) of diagnosis since the start of treatment, severity of OHSS (WHO Scientific Group classification, 1973), verbatim for the symptoms the patient manifested that led to the severity grading of OHSS, and whether the patient was hospitalized due to OHSS.

An overall summary table was provided, displaying the number (n) and percentage of patients; the number of events (m) by AE category, treatment group, and overall by country; and AE category, treatment group, and overall. In addition, separate summary tables were provided for any AEs, drug-related AEs, SAEs, drug-related SAEs, severe AEs, drug-related severe AEs, AEs leading to study discontinuation, and drug-related AEs leading to discontinuation.

AEs with missing relationship to Ovaleap or Gonal-f were assumed to be drug related. AEs missing the flag indicating serious were excluded from the summary of SAEs.

9.9.7.3 Deaths

If applicable, a listing of death details for fatal AEs was to be provided including date of death, cause of death, SOC, PT, whether the death was considered to be related to Ovaleap or Gonal-f (Yes, No), whether autopsy was conducted (Yes, No), and autopsy findings.

9.9.8 Exposure to Ovaleap and Gonal-f

Exposure information was summarised by treatment group over all countries, and by country and treatment group using descriptive summary statistics.

The summary of exposure included duration of treatment (days), patients who remained on the same FSH product for the duration of this treatment cycle, number of days on initial treatment, number of days with missed doses, patients who missed a dose in the 4 days preceding oocyte maturation triggering, patients who missed a dose in the 2 days preceding oocyte retrieval, patients who had their dose decreased (compared to first dose), patients who had their dose increased (compared to first dose), and the total dosage (IU) patient received up to the end of the treatment.

Treatment completion/discontinuation was summarised over all countries, by treatment group and overall; and by country, treatment group, and overall; giving the number and percentage of patients who completed or prematurely discontinued the ovarian stimulation treatment and reason for discontinuation of the FSH treatment (if applicable). If the reason was other, the reason was presented in the listings only.

Individual listing with details of Ovaleap and Gonal-f administration per patient per day was provided, and included the start and stop dates of Ovaleap or Gonal-f treatment, day of Ovaleap or Gonal-f treatment dosing, whether the dose was administered, dose administered, cumulative dose, whether dose was reduced or increased compared to the first dose, and, if the dose was missed: the day of dosing relative to the date of oocyte maturation triggering (if performed), and the day of dosing relative to the date of oocyte retrieval (if performed).

A further individual listing was provided summarizing details per patient of Ovaleap and Gonal-f administration in the current cycle, and included duration of exposure, whether the patient remained on the same FSH treatment, date of treatment switch (if applicable), whether the patient completed the treatment, date of completion or date of discontinuation (as appropriate), and reasons for discontinuation (if applicable).

9.9.9 Ovulation Triggering and Oocytes Retrieval

Descriptive statistics of ovulation triggering details during FSH treatment and oocytes retrieved following treatment by treatment group and overall were summarised and included:

- Prior to ovulation triggering
  - Number of follicles prior to ovulation triggering in current cycle
  - Most recent serum oestradiol-level (pg/mL) prior to ovulation triggering (if available)
  - Date of most recent oestradiol-level measurement
- Oocyte maturation triggering under the current treatment
  - Was the oocyte maturation triggering performed? (Yes, No)
  - If No, reason not performed: cycle cancellation due to insufficient response to FSH treatment, cycle cancellation due to overresponse to FSH treatment (to prevent OHSS), cycle cancellation due to OHSS, other
  - Type of medication used for oocyte maturation triggering (hCG, GnRH agonist) (details of medications were described under concomitant medications)
- Oocyte retrieval under the current treatment
  - Oocyte retrieval performed? (Yes, No)
  - If yes, number of oocytes retrieved
  - Date of retrieval
  - Oestradiol-level (pg/mL) around the time of oocyte retrieval

9.9.10 Embryo Transfer and Pregnancy Investigation

Embryo transfer and pregnancy investigation following IVF treatment were summarised by treatment group and overall using descriptive summary statistics, and individual listings were provided for embryo transfer following oocytes fertilisation and pregnancy investigation.

To assess the effect of embryo transfer practice (fresh embryo transfer, freeze all, no embryo obtained to be transferred, other) on OHSS incidence rate differences between the treatment groups, the number and percentage of patients who experienced OHSS were summarised by embryo transfer practice and treatment group, based on the FAS.

Depending on sample size per embryo practice per treatment group (i.e., number of patients with OHSS per embryo practice within treatment group), subgroup analysis might be carried out to test differences between treatments in patients with OHSS risk for each category of embryo practice. Treatment differences in OHSS were not reported for categories with fewer than 20 patients per embryo practice within treatment group.

Furthermore, should there be an indication of the effect of embryo transfer practice on OHSS risk between treatments, the frequency for each embryo transfer practice (fresh embryo transfer, freeze all, no embryo obtained to be transferred, and other) might be included in the univariate logistic regression analysis of the primary variable as a predictor of OHSS risk.

9.9.11 Concomitant Medications

Concomitant medications were transcribed into the CRF from the patient's medical records and included all medications up to the end of follow-up (up to 30 days following the last day of treatment administration). All concomitant medications were coded using the latest version of the WHODrug to provide the therapeutic class category and PT. In summary tables, patients were counted only once in each therapeutic class and only once in each PT category.

All concomitant medication details were listed, including the verbatim term and WHODrug for the medication name, therapeutic class, start and stop date (or ongoing where applicable) with corresponding study days, route (where applicable), frequency (where applicable), dose, dose unit, and indication (where applicable).

Separate summaries and listings were provided for ovarian stimulation protocol medications, medications used for oocyte maturation triggering and luteal phase support, and all other concomitant medications.

9.9.12 Patient Register and Enrolment

Prior to enrolment, a patient register was kept from each country that included patients whose proposed treatment was Ovaleap or Gonal-f. To assess the representativeness of the study sample and the size and direction of potential selection bias (due to non-participations), treatment groups (based on their proposed treatment), clinical practice, and patient characteristics were compared between patients who were interested in participating in the study and those who declined, for each country. A summary of the differences in a patient's willingness to participate was provided comparing patients in the register from each country who expressed an interest to participate versus those who declined: practice type (public hospital or private clinic), age group (18 to <30 years, 30 to <34 years, and ≥34 years), proposed treatment (Ovaleap or Gonal-f), and reason for not participating (lack of interest in the study, lack of time, other-specify) (if applicable).

Furthermore, differences between proposed treatment groups were evaluated among patients who were interested in participating in the study but did not eventually enrol with respect to their reason for non-enrolment.

The number and proportion of patients by reason for non-enrolment (death, AE, withdrawal by subject, inclusion criteria not met, exclusion criteria met, lost to follow-up, other-specify) were summarised overall within each country.

Listings were provided for the patient register and enrolment details.

9.9.13 Handling Withdrawals, Treatment Switching, and Missing Data

After commencing treatment, it was rare for a patient to switch to another treatment during the same cycle. Nonetheless, patients who switched or discontinued therapy at any time after entering the study and receiving the first dose of Ovaleap or Gonal-f remained in the study until end of follow-up or disenrollment (date of study completion/discontinuation entered in the CRF "End of Study" form). If cases of patients switching treatment occurred in the study their handling in the analyses was decided upon data review and the statistical analysis plan (SAP) accordingly, prior to the first database freeze.

Patients who switched were identified by a negative response to the CRF question "Did the patient remain on the same FSH product for the duration of this treatment cycle?" The FSH treatment that the patient switched to was recorded under concomitant medications.

Analysis was based on the observed data and no imputation for missing data was performed.

9.9.14 Study Protocol Deviations

For the purposes of this study a protocol deviation was defined as any unplanned instance(s) of protocol noncompliance. Protocol deviations were monitored during the study and recorded in the CTMS (not transferred to the eCRF). Protocol deviation classification (eg, violation of inclusion/exclusion criteria, violation of minimum follow-up) was performed after review of the available data and prior to the first database freeze. Data from patients with any protocol deviations during the study were summarised by treatment group and overall and for each deviation category using descriptive summary statistics. A supportive individual listing of protocol deviations was provided.

9.9.15 Amendments to the Statistical Analysis Plan

The SAP1 (SAP version 1.0) was finalized and issued on 16 October 2017 and amended twice.

The following changes were incorporated in SAP version 1.1 on 26 October 2018:

- Updated the statistical methods for pooling of centres and replacing centre with country as a confounder in the logistic regression models

The following changes were incorporated in SAP version 1.2 on 16 January 2019:

- Deleted coding to International Non-proprietary Names and maintained only WHO Drug coding

- Updated reporting of incidence rates using all centres within each country

- Eliminated certain summaries by centre
- Deleted verification of homoscedasticity assumptions for the logistic regression models

9.10 Quality Control

To ensure compliance with GCP guidelines, checks were in place to ensure that patients had signed the informed consent form.

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

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

The sponsor was responsible for the processing and quality control of the data. Data management and filing were carried out as described in the sponsor and contract research organization's (CRO) standard operating procedures (SOPs) for non-interventional observational studies (only CRO's SOPs were followed after Teva transferred the sponsorship to Theramex). These SOPs were reviewed by the sponsor before the start of data management and filing activities. The original CRFs were archived by the sponsor.

10 RESULTS

10.1 Participants

10.1.1 Patient Disposition

The patient disposition is presented in in-text Table 4 and post-text Summary 15.1.2 (by country) for all enrolled patients. A patient disposition flow diagram is shown in in-text Figure 1. Individual patient disposition data are included in Listing 16.2.1.3.

A total of 1147 patients were registered to participate in the study, and 833 patients satisfied the eligibility criteria and were enrolled in the study, including 419 and 414 patients that were planned to receive Ovaleap and Gonal-f treatments, respectively, upon the time of enrolment. During the study, 7 patients (2%) each in the Ovaleap and Gonal-f arms did not receive the treatment and 2 patients (<1%) in the Ovaleap arm received additional FSH treatment; they were not included in the FAS. In addition, 7 patients in the Ovaleap arm switched treatment to Gonal-f and 5 patients in the Gonal-f arm switched treatment to Ovaleap prior to receiving the first dose. Therefore, a total of 817 patients were included in the FAS, including 408 patients (97%) in the Ovaleap arm and 409 patients (99%) in the Gonal-f arm. A total of 772 patients (93%) completed FSH treatments, including 382 patients (91%) in the Ovaleap arm and 390 patients (94%) in the Gonal-f arm; 40 patients (5%) discontinued FSH treatment but completed study, including 23 patients (5%) in the Ovaleap arm and 17 patients (4%) in the Gonal-f arm. A total of 800 patients (96%) completed the study, including 403 patients (96%) in the Ovaleap arm and 397 patients (96%) in the Gonal-f arm; 17 patients (2%) discontinued the study, 5 (1%) from the Ovaleap arm and 12 (3%) from the Gonal-f arm. The reasons for study discontinuation included other (3 patients [<1%] in the Ovaleap arm due to insufficient ovarian response and 10 patients [2%] in the Gonal-f arm due to the sponsor's decision to stop data collection, patient did not return to site after Visit 2, or care error [receiving the wrong FSH treatment]) and lost to follow-up (2 patients [<1%] each in the Ovaleap and Gonal-f arms). The mean (SD) duration of study was 61.1 (57.88) days in the Ovaleap arm and 53.0 (39.63) days in the Gonal-f arm.

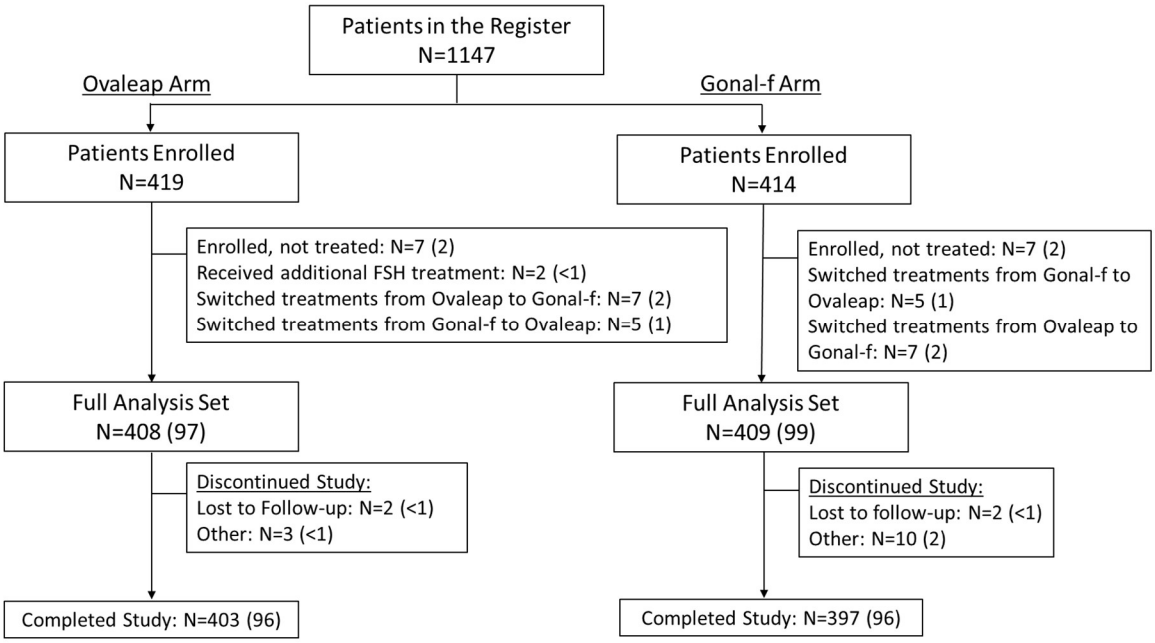
The enrolled and FAS patient numbers between the Ovaleap and Gonal-f arms were also at a ratio of close to 1:1 in each country.

Table 4 Patient Disposition by Treatment Group (All Enrolled Patients)

Characteristic	Ovaleap	Gonal-f	Total
Patients in the register			1147
Patients enrolled	419	414	833
Enrolled, not treated[a], n (%)	7 (2)	7 (2)	14 (2)
Full Analysis Set[b], n (%)	408 (97)	409 (99)	817 (98)
Completed FSH treatment[c], n (%)	382 (91)	390 (94)	772 (93)
Discontinued FSH treatment but completed study, n (%)	23 (5)	17 (4)	40 (5)
Completed study, n (%)	403 (96)	397 (96)	800 (96)
Discontinued study, n (%)	5 (1)	12 (3)	17 (2)
Lost to follow-up	2 (<1)	2 (<1)	4 (<1)
Other	3 (<1)	10 (2)	13 (2)
Death	0	0	0
Withdrawal by subject	0	0	0
Time on study (days)			
n	410	409	819
Mean	61.1	53.0	57.1
..SD	57.88	39.63	49.75
..Median	45.0	44.0	44.0
..Min, max	6, 556	7, 466	6, 556

FSH=follicle stimulating hormone; max=maximum; min=minimum; n=number of patients; SD=standard deviation.
Note: Time on study was calculated as date of completion/discontinuation (if patient completed/discontinued) or date of last contact (if lost to follow-up) - date of first administration of study drug + 1.
The denominator used for calculating the percentage was all enrolled patients.
Please refer to the source listing 16.2.1.3 for free text where Other specified.
a. Included patients who enrolled but did not receive at least one dose of Ovaleap or Gonal-f.
b. The full analysis set included all enrolled patients who received at least one dose of Ovaleap or Gonal-f. Two subjects receiving Ovaleap had additional FSH and were excluded from the full analysis set. Seven patients switched treatments from Ovaleap to Gonal-f and 5 patients switched treatments from Gonal-f to Ovaleap, prior to receiving the first dose.
c. Referred to completion up to Visit 2, irrespective of whether pregnancy follow-up was completed by patients found to be pregnant at Visit 2.
Source: Summary 15.1.1

Figure 1 Patient Disposition Flow Diagram by Treatment Group (All Enrolled Patients)



FSH=follicle stimulating hormone; N=number of patients.
The denominator used for calculating the percentage in parentheses was all enrolled patients.
Please refer to the source listing 16.2.1.3 for free text where Other specified.
Source: Summary 15.1.1

Individual patient participation and enrolment status are presented in Listing 16.2.1.1 and Listing 16.2.1.2. Comparison of patient participation status and reasons for non-enrolment in each country are summarised in post-text Summary 15.11.1 and post-text Summary 15.11.2.

10.1.2 Protocol Deviations

Protocol deviations by treatment group are summarised in in-text Table 5. Individual protocol deviation data is presented in Listing 16.2.2.1.

A total of 107 patients (13%) were reported to have protocol deviations during the study, including 55 patients (13%) in the Ovaleap arm and 52 patients (13%) in the Gonal-f arm. The two most common protocol deviation categories in both arms were assessment safety (failure or delay of safety/pregnancy assessment or reporting) (34 patients [8%] in the Ovaleap arm and 33 patients [8%] in the Gonal-f arm) and informed consent (23 patients [5%] in the Ovaleap arm and 24 patients [6%] in the Gonal-f arm). Overall, the numbers of patients with protocol deviations and categories of protocol deviations were comparable between the two treatment groups.

Table 5 Protocol Deviations (All Enrolled Patients)

Category Deviation	Ovaleap (N=419) [n (%)]	Gonal-f (N=414) [n (%)]	Total (N=833) [n (%)]
Any protocol deviation	55 (13)	52 (13)	107 (13)
Deviation			
Exclusion Criteria	0	1 (<1)	1 (<1)
Study Drug	1 (<1)	0	1 (<1)
Assessment Safety	34 (8)	33 (8)	67 (8)
Informed Consent	23 (5)	24 (6)	47 (6)
Other	2 (<1)	2 (<1)	4 (<1)

N=number of patients in treatment group; n=number of patients in treatment group within each sub-category.
Note: For each category and deviation, subjects were included only once, even if they experienced multiple events in a category or deviation. The denominator used for calculating the percentage was the N in the column header.
Please refer to the source listing 16.2.2.1 for free text where Other specified.
Source: Summary 15.2.1

10.2 Descriptive Data

10.2.1 Demographics and Baseline Characteristics

The patient demographics and baseline characteristics are summarised in in-text Table 6 (by treatment group) and post-text Summary 15.3.2 (by country, centre, and treatment group). Individual demographics and baseline characteristics are presented in Listing 16.2.4.1.

In the FAS, the mean (SD) age was 33.5 (4.67) years in the Ovaleap arm and 34.3 (4.55) years in the Gonal-f arm. Approximately half (382 patients, 47%) of the patients were >34 years old, 288 patients (35%) were aged between 30 and 34 years, and 147 patients (18%) were aged between 18 and 30 years. Overall, 59% of patients in the Ovaleap arm and 48% of patients in the Gonal-f arm were <35 years old. The majority (691 patients, 85%) of patients were Caucasian, followed by Asian (27 patients, 3%) and Black (23 patients, 3%). The mean (SD) weight, height, and BMI between the Ovaleap and Gonal-f arms were 65.1 (12.29) kg and 66.0 (13.14) kg, 165.0 (6.68) cm and 165.2 (6.54) cm, and 23.9 (4.15) kg/m^2 and 24.1 (4.39) kg/m^2, respectively. The majority (497 patients, 61%) of patients had BMI ranges of 18.5 to 25 kg/m^2. Most of the patients were not current smokers (661 patients, 81%) and had no alcohol consumption (689 patients, 84%) or illicit drug use (736 patients, 90%).

The patient demographics and baseline characteristics were well balanced between the two treatment groups both overall and in each country.

Table 6 Demographics and Baseline Characteristics by Treatment Group (Full Analysis Set)

Variable Statistic	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Age (years)			
n	408	409	817
Mean	33.5	34.3	33.9
SD	4.67	4.55	4.63
Median	34.0	35.0	34.0
Min, max	20, 44	19, 45	19, 45
Age - group (years), n (%)			
18 - <30	85 (21)	62 (15)	147 (18)
30 – 34	154 (38)	134 (33)	288 (35)
>34	169 (41)	213 (52)	382 (47)
Ethnic Origin, n (%)			
Caucasian	339 (83)	352 (86)	691 (85)
Black	14 (3)	9 (2)	23 (3)
Asian	16 (4)	11 (3)	27 (3)
Hispanic	5 (1)	4 (<1)	9 (1)
Other	8 (2)	13 (3)	21 (3)
Not reported	26 (6)	20 (5)	46 (6)
Weight (kg)			
n	408	408	816
Mean	65.11	65.99	65.55
SD	12.290	13.136	12.720
Median	63.00	63.00	63.00
Min, max	40.0, 116.0	40.0, 120.0	40.0, 120.0
Height (cm)			
n	407	407	814
Mean	165.0	165.2	165.1
SD	6.68	6.54	6.61
Median	165.0	165.0	165.0
Min, max	141, 186	142, 183	141, 186
BMI (kg/m^2)			
n	407	407	814
Mean	23.911	24.114	24.012
SD	4.1540	4.3941	4.2743
Median	23.110	23.050	23.060
Min, max	15.82, 39.21	16.42, 38.46	15.82, 39.21
BMI - group (kg/m^2)			
<18.5	18 (4)	25 (6)	43 (5)

Variable Statistic	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
18.5 to <25	257 (63)	240 (59)	497 (61)
25 and over	132 (32)	142 (35)	274 (34)
Missing	1 (<1)	2 (<1)	3 (<1)
Current smoker, n (%)			
Yes	76 (19)	73 (18)	149 (18)
No	330 (81)	331 (81)	661 (81)
Unknown	2 (<1)	5 (1)	7 (<1)
Alcohol consumption, n (%)			
Yes	43 (11)	30 (7)	73 (9)
No	340 (83)	349 (85)	689 (84)
Unknown	25 (6)	30 (7)	55 (7)
Illicit drug use, n (%)			
Yes	2 (<1)	2 (<1)	4 (<1)
No	371 (91)	365 (89)	736 (90)
Unknown	35 (9)	42 (10)	77 (9)

BMI=body mass index; max=maximum; min=minimum; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category; SD=standard deviation.
The denominator used for calculating the percentage was the N in the column headers.
Source: Summary 15.3.1

10.2.2 Medical History

The relevant medical history is summarised in post-text Summary 15.4.1 (by treatment group) and post-text Summary 15.4.2 (by country and treatment group). The medical history SOCs with percentages ≥10% by treatment group are presented in in-text Table 7. Individual medical history data is presented in Listing 16.2.4.2.

A total of 333 patients (41%) were reported to have a past medical history of at least one medical condition, including 180 patients (44%) in the Ovaleap arm and 153 patients (37%) in the Gonal-f arm.

The most common medical history SOC in the Ovaleap and Gonal-f arms was immune system disorders (60 patients [15%] versus 56 patients [14%]), followed by reproductive system and breast disorders (44 patients [11%] versus 41 patients [10%]), and endocrine disorders (41 patients [10%] versus 39 patients [10%]). The numbers and percentages of these medical history SOCs were similar between the two treatment groups.

The most common medical history PT in the Ovaleap and Gonal-f arms was drug hypersensitivity (allergy to different drugs in different drug classes) (33 patients [8%] versus 31 patients [8%]), followed by hypothyroidism (32 patients [8%] versus 29 patients [7%]), polycystic ovaries (22 patients [5%] versus 11 patients [3%]), seasonal

allergy (15 patients [4%] versus 17 patients [4%]), endometriosis (14 patients [3%] versus 13 patients [3%]), and fallopian tube obstruction (6 patients [1%] versus 7 patients [2%]). The numbers and percentages of all these medical history PTs were also similar between the two treatment groups. All other medical history PTs were reported in ≤1% of patients in the FAS.

Table 7 Relevant Medical History System Organ Classes with Percentages ≥10% by Treatment Group (Full Analysis Set)

System organ class MedDRA 19.1 preferred term, n (%)	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Patients with a past medical history of at least one medical condition	180 (44)	153 (37)	333 (41)
Endocrine disorders	41 (10)	39 (10)	80 (10)
Anovulatory cycle	0	1 (<1)	1 (<1)
Autoimmune thyroiditis	4 (<1)	2 (<1)	6 (<1)
Basedow's disease	1 (<1)	1 (<1)	2 (<1)
Hyperandrogenism	1 (<1)	0	1 (<1)
Hyperprolactinaemia	0	1 (<1)	1 (<1)
Hyperthyroidism	1 (<1)	2 (<1)	3 (<1)
Hypothyroidism	32 (8)	29 (7)	61 (7)
Thyroid disorder	2 (<1)	4 (<1)	6 (<1)
Thyroid mass	0	1 (<1)	1 (<1)
Immune system disorders	60 (15)	56 (14)	116 (14)
Allergy to animal	3 (<1)	6 (1)	9 (1)
Allergy to metals	3 (<1)	1 (<1)	4 (<1)
Drug hypersensitivity	33 (8)	31 (8)	64 (8)
Dust allergy	1 (<1)	0	1 (<1)
Food allergy	3 (<1)	3 (<1)	6 (<1)
Human seminal plasma hypersensitivity	1 (<1)	0	1 (<1)
Hypersensitivity	1 (<1)	1 (<1)	2 (<1)
Iodine allergy	0	1 (<1)	1 (<1)
Mite allergy	2 (<1)	4 (<1)	6 (<1)
Mycotic allergy	1 (<1)	0	1 (<1)
Perfume sensitivity	1 (<1)	0	1 (<1)
Rubber sensitivity	3 (<1)	1 (<1)	4 (<1)
Sarcoidosis	0	1 (<1)	1 (<1)
Seasonal allergy	15 (4)	17 (4)	32 (4)
Reproductive system and breast disorders	44 (11)	41 (10)	85 (10)
Adenomyosis	1 (<1)	0	1 (<1)
Bartholin's cyst	0	1 (<1)	1 (<1)
Breast enlargement	0	1 (<1)	1 (<1)
Cervical dysplasia	1 (<1)	0	1 (<1)
Endometriosis	14 (3)	13 (3)	27 (3)
Fallopian tube disorder	0	2 (<1)	2 (<1)

System organ class MedDRA 19.1 preferred term, n (%)	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Fallopian tube obstruction	6 (1)	7 (2)	13 (2)
Hydrosalpinx	1 (<1)	0	1 (<1)
Infertility	1 (<1)	2 (<1)	3 (<1)
Infertility female	1 (<1)	5 (1)	6 (<1)
Ovarian cyst	0	2 (<1)	2 (<1)
Ovarian disorder	0	2 (<1)	2 (<1)
Polycystic ovaries	22 (5)	11 (3)	33 (4)
Uterine cervix stenosis	1 (<1)	0	1 (<1)
Uterine polyp	0	2 (<1)	2 (<1)

MedDRA=medical dictionary of drug activities; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category.
Note: Patients were counted only once in each preferred term category, and only once in each system organ class category.
The denominator used for calculating the percentage was N in the column header.
MedDRA version 19.1 was used.
Source: Summary 15.4.1

10.2.3 Reproductive History

Reproductive history is summarised in in-text Table 8 (by treatment group) and post-text Summary 15.4.4 (by country and treatment group). Individual reproductive history is presented in Listing 16.2.4.3.

A total of 520 patients (64%) had no former pregnancies, including 256 patients (63%) in the Ovaleap arm and 264 patients (65%) in the Gonal-f arm. The majority of patients had no former miscarriages (647 patients, 79%), including 317 patients (78%) in the Ovaleap arm and 330 patients (80%) in the Gonal-f arm. Of 170 patients (21%) who had former miscarriages, 147 patients (18%) had 1 to 2 former miscarriages and 20 patients (2%) had 3 or more former miscarriages. The majority of patients had no former still births (808 patients, 99%), including 401 patients (98%) in the Ovaleap arm and 407 patients (>99%) in the Gonal-f arm. Of 9 patients (1%) who had former still births, 6 patients (<1%) had 1 former still birth, 1 patient (<1%) had 3 or more former still births, and 2 patients (<1%) had unknown number of still births. The majority of patients had no former live births (704 patients, 86%), including 354 patients (87%) in the Ovaleap arm and 350 patients (86%) in the Gonal-f arm. Of 113 patients (14%) who had former live births, 87 patients (11%) had 1 former live birth, 14 patients (2%) had 2 former live births, and 10 patients (1%) had 3 or more former live births.

The mean (SD) infertility durations in the Ovaleap and Gonal-f arms were 32.4 (53.86) months and 36.9 (95.61) months, respectively. The majority of patients had menstrual cycle lengths between 22 days and 35 days (751 patients, 92%). The mean (SD) days from last menstrual cycle to first date of treatment in the Ovaleap and Gonal-f arms were 31.5 (82.80) days and 24.3 (30.35) days, respectively. The median antral follicular counts were similar between the Ovaleap and Gonal-f arms (median counts: 7 versus 6 in

the left ovary and 7 versus 7 in the right ovary) and the majority of patients had antral follicular counts <12 (509 [62%] patients for the left ovary and 524 [64%] patients for the right ovary). The mean (SD) basal serum AMH levels in the Ovaleap and Gonal-f arms were 4.9 (8.95) ng/mL and 3.9 (6.67) ng/mL, respectively. Approximately half of patients had basal serum AMH levels <3.5 ng/mL (415 patients, 51%), including 199 patients (49%) in the Ovaleap arm and 216 patients (53%) in the Gonal-f arm.

Table 8 Reproductive History by Treatment Group (Full Analysis Set)

Variable	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Patients with no former pregnancies, n (%)			
Yes	256 (63)	264 (65)	520 (64)
No	152 (37)	145 (35)	297 (36)
Patients with former miscarriage(s), n (%)			
Yes	91 (22)	79 (19)	170 (21)
No	317 (78)	330 (81)	647 (79)
If yes, number miscarriages, n (%)			
1 to 2	75 (18)	72 (18)	147 (18)
3 or more	13 (3)	7 (2)	20 (2)
Unknown	3 (<1)	0	3 (<1)
Patients who had former still birth(s), n (%)			
Yes	7 (2)	2 (<1)	9 (1)
No	401 (98)	407 (>99)	808 (99)
If yes, number of still birth(s), n (%)			
1	5 (1)	1 (<1)	6 (<1)
2	0	0	0
3 or more	0	1 (<1)	1 (<1)
Unknown	2 (<1)	0	2 (<1)
Patients with former live birth(s), n (%)			
Yes	54 (13)	59 (14)	113 (14)
No	354 (87)	350 (86)	704 (86)
If yes, number of live birth(s), n (%)			
1	39 (10)	48 (12)	87 (11)
2	6 (1)	8 (2)	14 (2)
3 or more	7 (2)	3 (<1)	10 (1)
Unknown	2 (<1)	0	2 (<1)
Infertility duration (months)			
n	408	409	817
Mean	32.4	36.9	34.6
SD	53.86	95.61	77.60

Variable	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Median	22.0	21.0	22.0
Min, max	1, 720	1, 1245	1, 1245
Menstrual cycle length, n (%)			
<21 Days	3 (<1)	1 (<1)	4 (<1)
≥22 Days to ≤35 Days	372 (91)	379 (93)	751 (92)
>35 Days	33 (8)	29 (7)	62 (8)
Missing	0	0	0
Days since last menstrual cycle			
n	389	367	756
Mean	31.5	24.3	28.0
SD	82.80	30.35	63.11
Median	20.0	23.0	21.0
Min, max	1, 1457	1, 236	1, 1457
Antral follicular count - right ovary			
n	304	302	606
Mean	8.1	7.3	7.7
SD	4.95	4.28	4.64
Median	7.0	7.0	7.0
Min, max	1, 40	1, 25	1, 40
Antral follicular count − right ovary, n (%)			
<12	256 (63)	268 (66)	524 (64)
≥12	49 (12)	39 (10)	88 (11)
Missing	103 (25)	102 (25)	205 (25)
Antral follicular count − left ovary			
n	303	299	602
Mean	7.7	7.3	7.5
SD	5.12	4.16	4.67
Median	7.0	6.0	7.0
Min, max	1, 40	1, 29	1, 40
Antral follicular count − left ovary, n (%)			
<12	243 (60)	266 (65)	509 (62)
≥12	64 (16)	41 (10)	105 (13)
Missing	101 (25)	102 (25)	203 (25)
Basal serum level of AMH (ng/mL)			
n	311	317	628
Mean	4.856	3.871	4.359
SD	8.9477	6.6700	7.8898
Median	2.670	2.460	2.580
Min, max	0.07, 83.20	0.04, 91.10	0.04, 91.10

Variable	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Basal serum level of AMH (ng/mL), n (%)			
<3.5	199 (49)	216 (53)	415 (51)
≥3.5	112 (27)	102 (25)	214 (26)
Missing	97 (24)	91 (22)	188 (23)

AMH=anti-Mullerian hormone; max=maximum; min=minimum; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category; SD=standard deviation.
Note: Days since last menstrual cycle was calculated as start date of treatment - date of last menstrual cycle + 1.
The denominator used for calculating the percentage was the N in the column header.
Source: Summary 15.4.3

10.3 Outcome Data

The outcome data of the primary and secondary analyses are presented in Section 10.4 and other analyses in Section 10.5.

10.4 Main Results

10.4.1 Primary Analysis

Incidence rates and rate differences of OHSS by country and treatment group are summarised in in-text Table 9.

Overall, 21 out of 408 patients in the Ovaleap arm and 13 out of 409 patients in the Gonal-f arm experienced OHSS during the study. The OHSS incidence rate was 5.1% (95% CI: 3.4%, 7.7%) in the Ovaleap arm and 3.2% (95% CI: 1.9%, 5.4%) in the Gonal-f arm. The rate difference between the Ovaleap and Gonal-f arms was 2.0% (95% CI: -0.8%, 4.9%) and no statistically significant difference (p=0.1589) was observed between the two treatment groups.

Similar results were also observed in subgroups per country, i.e., Germany, Italy, and the pooled countries of Belgium, France, Spain, and the United Kingdom.

Table 9 Incidence of Ovarian Hyperstimulation Syndrome by Country and Treatment Group (Full Analysis Set)

	Ovaleap		Gonal-f		Ovaleap - Gonal-f	
Country Parameter	m / n	Incidence Risk % (95% CI)	m / n	Incidence Risk % (95% CI)	Diff in Incidence Risk % (95% CI)	p-value
Overall	21 / 408	5.147 (3.391, 7.740)	13 / 409	3.178 (1.867, 5.362)	1.969 (-0.833, 4.874)	0.1589
Belgium, Spain, UK, and France	9 / 230	3.913 (2.072, 7.268)	3 / 216	1.389 (0.473, 4.003)	2.524 (-0.673, 6.002)	0.1429
Germany	5 / 77	6.494 (2.805, 14.316)	2 / 86	2.326 (0.640, 8.088)	4.168 (-2.674, 12.170)	0.1901

Country Parameter	Ovaleap m / n	Ovaleap Incidence Risk % (95% CI)	Gonal-f m / n	Gonal-f Incidence Risk % (95% CI)	Ovaleap - Gonal-f Diff in Incidence Risk % (95% CI)	p-value
Italy	7 / 101	6.931 (3.398, 13.620)	8 / 107	7.477 (3.837, 14.064)	-0.546 (-8.021, 7.069)	1.0000

CI=confidence interval; m=number of events; n=number of patients; UK=United Kingdom.
Notes: Subjects were counted only once, even if they experienced multiple events.
m was the number of patients who experienced OHSS during the study; n was the number of patients in the subgroup.
CIs were estimated using the Newcombe-Wilson score method. The p-value was based on the chi-squared test or Fisher's exact test if there were fewer than 5 events in any category.
For Belgium, France, Spain and UK with few events, the p-value was calculated for the pooled countries.
Source: Summary 15.5.1

The OR for potential confounder associations with OHSS incidence and OR for treatment effect on OHSS incidence, adjusted for the confounder, using the univariate logistic regression models are summarised in in-text Table 10.

The potential confounders including age, BMI, ovarian stimulation protocol, oocyte maturation triggering, number of embryos transferred, menstrual cycle length, medications used in the luteal phase support, and total FSH dose had no statistically significant association with OHSS incidence ($p>0.05$) at the univariate level; whilst the other potential confounders including country, PCOS, embryo transfer, antral follicle count, basal serum level of AMH, pregnancy, FSH dose reduction, and FSH treatment duration had a statistically significant association with OHSS incidence at the univariate level ($p<0.05$).

The univariate logistic regression analysis showed that no statistically significant difference in OHSS incidence was observed between the Ovaleap and Gonal-f treatments after univariate adjustment for each potential confounder mentioned above ($p>0.05$).

Due to insufficient sample size (<20 patients) in subpopulation, the potential confounder of " FSH dose missed in the 4 days preceding oocyte retrieval", was not analysed and the results were not available.

Table 10 Incidence of Ovarian Hyperstimulation Syndrome (OHSS) – Univariate Logistic Regression Adjustment for Each Potential Confounder (Full Analysis Set)

Potential confounder	Complete cases [n (%)]	Odds ratio for confounder effect (95% Wald CI)	P-value for confounder effect	Odds ratio for treatment effect (Ovaleap vs. Gonal-f) (95% Wald CI)	P-value for treatment effect
Age (years)	817			1.658 (0.815, 3.372)	0.1630
<30	147 (18.0)	1.070 (0.428, 2.671)	0.7510		
30 to <34	288 (35.3)	0.867 (0.395, 1.905)	0.6480		
34 and above	382 (46.8)	Reference			
BMI (kg/m^2)	814			1.625 (0.802, 3.294)	0.1780
<18.5	43 (5.3)	0.514 (0.068, 3.911)	0.5940		
18.5 to <25.0	497 (61.1)	Reference			
25.0 and above	274 (33.7)	0.794 (0.372, 1.694)	0.8680		
Country[a]	817			1.703 (0.838, 3.463)	0.1410
Belgium, Spain, UK, or France	446 (54.6)	0.349 (0.160, 0.761)	0.0380		
Germany	163 (20.0)	0.580 (0.230, 1.460)	0.9670		
Italy	208 (25.5)	Reference			
PCOS	817			1.545 (0.757, 3.150)	0.2320
No	784 (96.0)	Reference			
Yes	33 (4.0)	4.342 (1.553, 12.143)	0.0050		
Ovarian stimulation protocol	791			1.654 (0.816, 3.351)	0.1630
GnRH antagonist	686 (86.7)	Reference			
GnRH agonist	105 (13.3)	1.130 (0.427, 2.990)	0.8060		
Oocyte maturation triggering	751			1.669 (0.817, 3.409)	0.1600
GnRH agonist	107 (14.2)	Reference			
hCG	644 (85.8)	0.247 (0.119, 0.511)	0.9820		
Embryo transfer	782			1.544 (0.757, 3.149)	0.2330
No	252 (32.2)	Reference			
Yes	530 (67.8)	0.283 (0.139, 0.575)	<.0001		
Number of embryos transferred	530			2.454 (0.746, 8.070)	0.1400
1	302 (57.0)	Reference			
>1	228 (43.0)	1.118 (0.370, 3.382)	0.8430		
Menstrual cycle length	817			1.659 (0.819, 3.361)	0.1600
<21 Days	4 (0.5)	<0.001(<0.001, >999.999)	0.9780		
≥22 Days to ≤35 Days	751 (91.9)	Reference			
>35 Days	62 (7.6)	1.160 (0.344, 3.915)	0.9770		
Antral follicle count	617			1.815 (0.793, 4.155)	0.1580
<12	238 (38.6)	Reference			
≥12	379 (61.4)	3.482 (1.183, 10.251)	0.0240		
Basal serum level of AMH	629			1.900 (0.857, 4.211)	0.1140
<3.5	415 (66.0)	Reference			
≥3.5	214 (34.0)	6.552 (2.747, 15.628)	<.0001		

Potential confounder	Complete cases [n (%)]	Odds ratio for confounder effect (95% Wald CI)	P-value for confounder effect	Odds ratio for treatment effect (Ovaleap vs. Gonal-f) (95% Wald CI)	P-value for treatment effect
Medications used in the luteal phase support	574			1.745 (0.666, 4.570)	0.2570
Other	556 (96.9)	Reference			
hCG	18 (3.1)	1.907 (0.239, 15.233)	0.5430		
Pregnancy	549			2.863 (0.880, 9.314)	0.0810
Negative	340 (61.9)	Reference			
Positive	209 (38.1)	4.438 (1.368, 14.405)	0.0130		
FSH dose reduction	817			1.608 (0.790, 3.272)	0.1900
No	664 (81.3)	Reference			
Yes	153 (18.7)	3.198 (1.575, 6.496)	0.0010		
FSH dose missed in the 4 days preceding oocyte retrieval	817				
No	5 (0.6)	N/A	N/A	N/A	N/A
Yes	41 (5.0)	N/A	N/A	N/A	N/A
Missing	771 (94.4)	N/A	N/A	N/A	N/A
Total FSH dose	817			1.697 (0.836, 3.443)	0.1430
<Q1	206 (25.2)	Reference			
Q1-<Q3	416 (50.9)	0.674 (0.315, 1.442)	0.8940		
>Q3	195 (23.9)	0.412 (0.142, 1.195)	0.1620		
FSH treatment duration	817			1.444 (0.708, 2.946)	0.3120
<Q1	267 (32.7)	Reference			
Q1-<Q3	348 (42.6)	13.948(1.848,105.299)	0.0490		
>Q3	202 (24.7)	20.489(2.680,156.673)	0.0030		

AMH=anti-Mullerian hormone; BMI=body mass index; CI=confidence interval; FSH=follicle stimulating hormone; GnRH=gonadotrophin-releasing hormone; hCG=human chorionic gonadotropin; n=number of patients; N/A=not available; PCOS=polycystic ovary syndrome; Q=quartile; SAP=statistical analysis plan.
Notes: Results were based on a series of univariate logistic regression models, including treatment and one potential confounder at a time. For example, the logistic model adjusted for age included treatment and age-group as factors and whether OHSS was observed as the response variable.
Complete cases was the number of patients in the univariate model (excluding patients with missing data for the potential confounder being examined).
The odds ratio for treatment was adjusted for the potential confounder variable shown in the most-left column. Subjects were counted only once, even if they experienced multiple OHSS events.
P-values were based on the chi-squared test, testing the null hypothesis that an individual predictor's regression coefficient was zero, given the other predictor in the model.
a. The country or centre with the largest sample overall was the reference group. Countries or centres with few events were pooled as per SAP section 3.6.
Source: Summary 15.5.2

The multivariate logistic regression analysis was not performed as an insufficient number of OHSS events was observed during the study (post-text Summary 15.5.3).

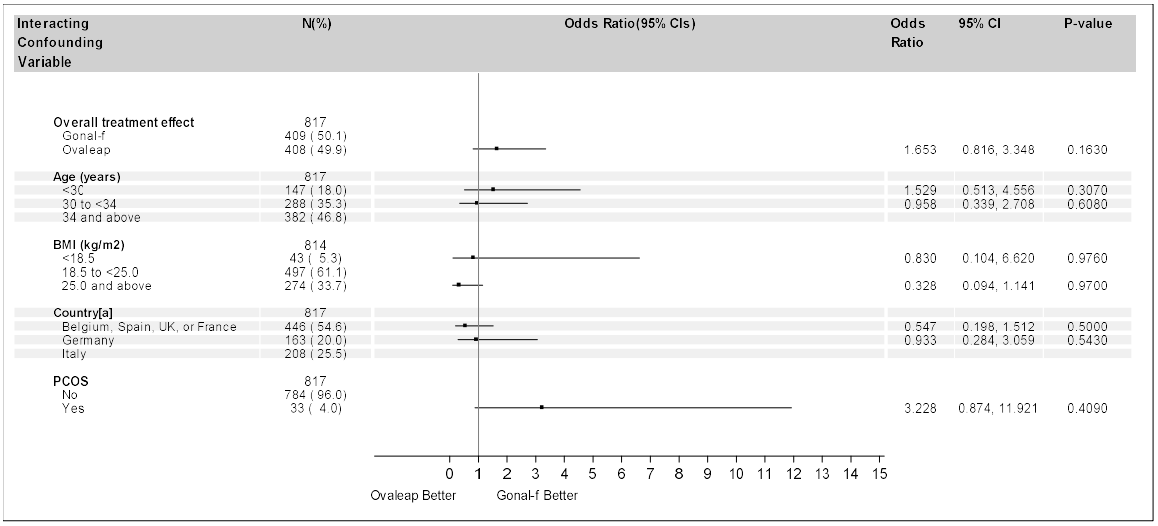
The pairwise correlations between all potential confounders examined in logistic regression analyses were summarised in post-text Summary 15.5.7.

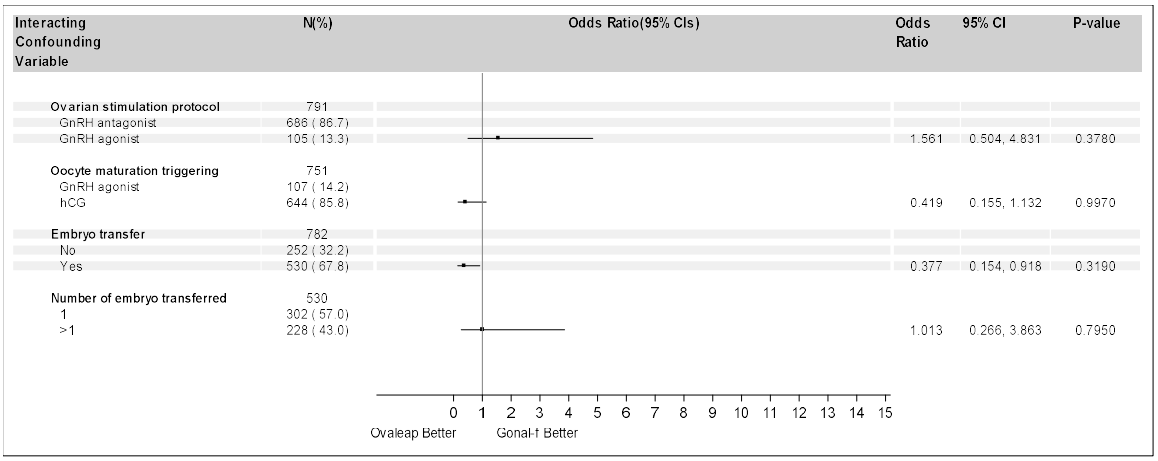
ORs and their 95% CIs for interaction between treatment groups and each confounding factor are summarised in post-text Summary 15.5.4 and in-text Figure 2 to explore the

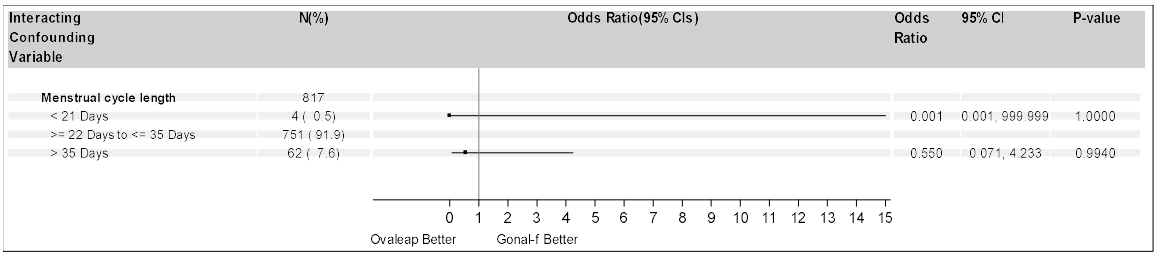
homogeneity of findings by including the effect of an interaction term between treatment and each potential confounder in the univariate logistic regression models.

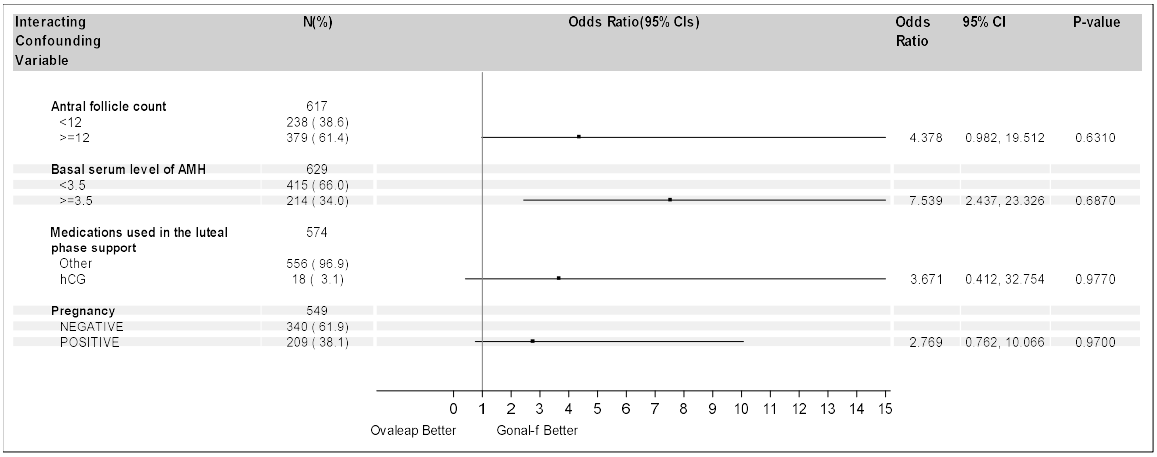
No statistically significant association between selected confounders and treatment differences in OHSS incidences was observed (no evidence of departure from homogeneity; treatment effect size is constant across confounders) and neither Ovaleap nor Gonal-f treatment was favoured in terms of OHSS incidence (p>0.05).

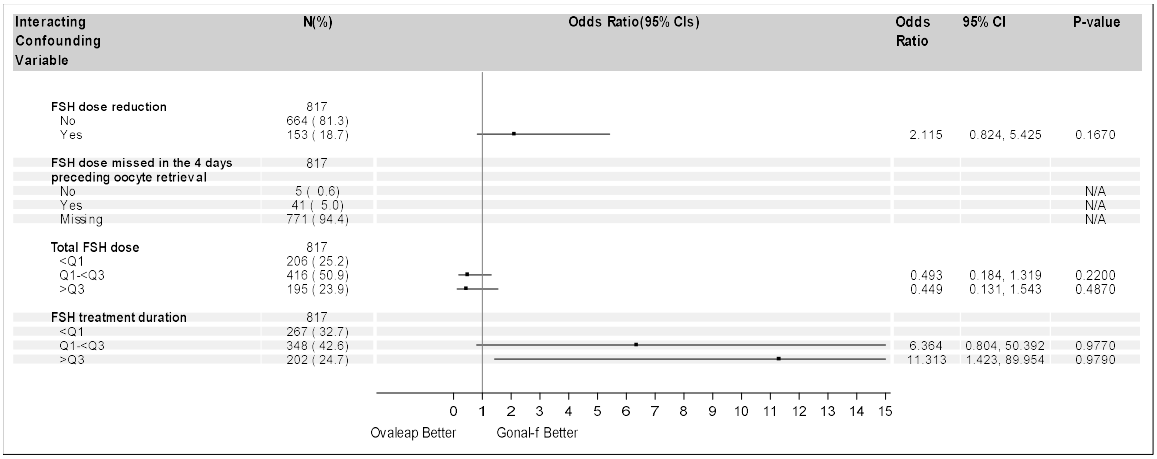
Figure 2 Incidence of Ovarian Hyperstimulation Syndrome (OHSS) – Forest Plot for Homogeneity of the Effects of Selected Interacting Confounders on Treatment Differences in OHSS Incidence Rates (Full Analysis Set)











AMH=anti-Mullerian hormone; BMI=body mass index; CI=confidence interval; FSH=follicle stimulating hormone; GnRH=gonadotrophin-releasing hormone; hCG=human chorionic gonadotropin; N=number of patients; PCOS=polycystic ovary syndrome; Q=quartile.

Notes: Results were based on a series of univariate logistic regression models including treatment as a main effect, the confounder of interest (excluding observations with missing data) and the interaction between this confounder and treatment (for which the odds ratios are presented here).

Odds ratio was for the interaction of treatment (Ovaleap versus Gonal-f) and potential confounder variable shown in the most-left column in the figure.

P-values were based on the chi-squared test, testing the null hypothesis that the regression coefficient for the interaction between treatment and confounder was zero, given the other predictors in the model.

a. The country with the largest sample overall was the reference group. Countries with few events were pooled.

Source: Figure 1

OHSS incidences by potential confounders and treatment group are descriptively summarised in post-text Summary 15.5.5 and in-text Table 11.

Table 11 Descriptive Statistics for Incidence of Ovarian Hyperstimulation Syndrome by Potential Confounders and Treatment Group (Full Analysis Set)

Potential confounder assessed in exploratory analysis	Ovaleap (N=408) n (% of N)	Ovaleap (N=408) OHSS # events (% of n)	Gonal-f (N=409) n (% of N)	Gonal-f (N=409) OHSS # events (% of n)
Age (years)				
<30	85 (20.8)	6 (7.1)	62 (15.2)	1 (1.6)
30 to <34	154 (37.7)	7 (4.5)	134 (32.8)	4 (3.0)
34 and above	169 (41.4)	8 (4.7)	213 (52.1)	8 (3.8)
Missing	0	0	0	0
BMI (kg/m^2)				
<18.5	18 (4.4)	1 (5.6)	25 (6.1)	0 (0.0)
18.5 to <25.0	257 (63.0)	17 (6.6)	240 (58.7)	6 (2.5)
25.0 and above	132 (32.4)	3 (2.3)	142 (34.7)	7 (4.9)
Missing	1 (0.2)	0 (0.0)	2 (0.5)	0 (0.0)
Country				
Spain	99 (24.3)	1 (1.0)	110 (26.9)	1 (0.9)
Italy	101 (24.8)	7 (6.9)	107 (26.2)	8 (7.5)
Germany	77 (18.9)	5 (6.5)	86 (21.0)	2 (2.3)
France	80 (19.6)	3 (3.8)	61 (14.9)	0 (0.0)
United Kingdom	29 (7.1)	4 (13.8)	21 (5.1)	1 (4.8)
Belgium	22 (5.4)	1 (4.5)	24 (5.9)	1 (4.2)
Missing	0	0	0	0
PCOS				
No	386 (94.6)	18 (4.7)	398 (97.3)	11 (2.8)
Yes	22 (5.4)	3 (13.6)	11 (2.7)	2 (18.2)
Missing	0	0	0	0
Ovarian stimulation protocol				
GnRH agonist	53 (13.0)	4 (7.5)	52 (12.7)	1 (1.9)
GnRH antagonist	342 (83.8)	17 (5.0)	344 (84.1)	12 (3.5)
Missing	13 (3.2)	0 (0.0)	13 (3.2)	0 (0.0)
Oocyte maturation triggering				
GnRH agonist	56 (13.7)	6 (10.7)	51 (12.5)	7 (13.7)
hCG	313 (76.7)	15 (4.8)	331 (80.9)	6 (1.8)
Missing	2 (0.5)	0 (0.0)	6 (1.5)	0 (0.0)

Potential confounder assessed in exploratory analysis	Ovaleap (N=408) n (% of N)	Ovaleap (N=408) OHSS # events (% of n)	Gonal-f (N=409) n (% of N)	Gonal-f (N=409) OHSS # events (% of n)
Embryo transfer				
No	136 (33.3)	12 (8.8)	116 (28.4)	9 (7.8)
Yes	256 (62.7)	9 (3.5)	274 (67.0)	4 (1.5)
Missing	16 (3.9)	0 (0.0)	19 (4.6)	0 (0.0)
Number of embryos transferred				
1	143 (35.0)	5 (3.5)	159 (38.9)	2 (1.3)
>1	113 (27.7)	4 (3.5)	115 (28.1)	2 (1.7)
Missing	152 (37.3)	12 (7.9)	135 (33.0)	9 (6.7)
Menstrual cycle length				
< 21 Days	3 (0.7)	0 (0.0)	1 (0.2)	0 (0.0)
≥ 22 Days to ≤ 35 Days	372 (91.2)	20 (5.4)	379 (92.7)	11 (2.9)
> 35 Days	33 (8.1)	1 (3.0)	29 (7.1)	2 (6.9)
Missing	0	0	0	0
Antral follicle count				
<12	110 (27.0)	2 (1.8)	128 (31.3)	2 (1.6)
≥12	200 (49.0)	15 (7.5)	179 (43.8)	7 (3.9)
Missing	98 (24.0)	4 (4.1)	102 (24.9)	4 (3.9)
Basal serum level of AMH				
<3.5	199 (48.8)	4 (2.0)	216 (52.8)	3 (1.4)
≥3.5	112 (27.5)	15 (13.4)	102 (24.9)	7 (6.9)
Missing	97 (23.8)	2 (2.1)	91 (22.2)	3 (3.3)
Medications used in the luteal phase support				
Other	267 (65.4)	10 (3.7)	289 (70.7)	7 (2.4)
hCG	8 (2.0)	1 (12.5)	10 (2.4)	0 (0.0)
Missing	133 (32.6)	10 (7.5)	110 (26.9)	6 (5.5)
Pregnancy				
Negative	172 (42.2)	4 (2.3)	168 (41.1)	0 (0.0)
Positive	97 (23.8)	6 (6.2)	112 (27.4)	4 (3.6)
Missing	139 (34.1)	11 (7.9)	129 (31.5)	9 (7.0)
FSH dose reduction				
No	327 (80.1)	14 (4.3)	337 (82.4)	6 (1.8)
Yes	81 (19.9)	7 (8.6)	72 (17.6)	7 (9.7)
Missing	0	0	0	0

Potential confounder assessed in exploratory analysis	Ovaleap (N=408) n (% of N)	Ovaleap (N=408) OHSS # events (% of n)	Gonal-f (N=409) n (% of N)	Gonal-f (N=409) OHSS # events (% of n)
FSH dose missed in the 4 days preceding oocyte retrieval				
No	3 (0.7)	0 (0.0)	2 (0.5)	0 (0.0)
Yes	16 (3.9)	0 (0.0)	25 (6.1)	2 (8.0)
Missing	389 (95.3)	21 (5.4)	382 (93.4)	11 (2.9)
Total FSH dose				
<Q1	96 (23.5)	8 (8.3)	110 (26.9)	4 (3.6)
Q1-<Q3	210 (51.5)	9 (4.3)	206 (50.4)	8 (3.9)
>Q3	102 (25.0)	4 (3.9)	93 (22.7)	1 (1.1)
Missing	0	0	0	0
FSH treatment duration				
<Q1	113 (27.7)	1 (0.9)	154 (37.7)	0 (0.0)
Q1-<Q3	186 (45.6)	10 (5.4)	162 (39.6)	8 (4.9)
>Q3	109 (26.7)	10 (9.2)	93 (22.7)	5 (5.4)
Missing	0	0	0	0

AMH=anti-Mullerian hormone; BMI=body mass index; CI=confidence interval; FSH=follicle stimulating hormone; GnRH=gonadotrophin-releasing hormone; hCG=human chorionic gonadotropin; N=number of patients in treatment group; n=number of patients in treatment group within the confounder sub-category; OHSS=Ovarian Hyperstimulation Syndrome; PCOS=polycystic ovary syndrome; Q=quartile.
Source: Summary 15.5.5

10.4.2 Secondary Analysis

The severity grades of OHSS overall and in each country are summarised by treatment group in in-text Table 12. Individual OHSS information is presented in Listing 16.2.7.4.

Overall, the majority of patients with OHSS were of Grade I (mild) or Grade II (moderate) level in the two treatment groups: 14 patients (3%) of Grade I (mild) and 5 patients (1%) of Grade II (moderate) in the Ovaleap arm, and 8 patients (2%) of Grade I (mild) and 4 patients (<1%) of Grade II (moderate) in the Gonal-f arm. Two patients (<1%) in the Ovaleap arm and 1 patient (<1%) in the Gonal-f arm experienced Grade III (severe) OHSS during the study. No statistically significant difference (p=0.865) was observed in OHSS severity grades between the two treatment groups.

Similar results were also observed between the two treatment groups in Belgium, France, Germany, Italy, Spain, and the United Kingdom.

Table 12 Severity Grades of Ovarian Hyperstimulation Syndrome by Country and Treatment Group (Full Analysis Set)

Overall Countries and by Country OHSS Severity Grade [n (%)]	Ovaleap (N=408)	Gonal-f (N=409)	p-value
Overall			
Grade I (mild)	14 (3)	8 (2)	0.865
Grade II (moderate)	5 (1)	4 (<1)	0.865
Grade III (severe)	2 (<1)	1 (<1)	0.865
Belgium			
Grade I (mild)	1 (<1)	1 (<1)	0.618
Grade II (moderate)	0	0	0.618
Grade III (severe)	0	0	0.618
France			
Grade I (mild)	2 (<1)	0	0.618
Grade II (moderate)	1 (<1)	0	0.618
Grade III (severe)	0	0	0.618
Germany			
Grade I (mild)	4 (<1)	1 (<1)	1.000
Grade II (moderate)	1 (<1)	1 (<1)	1.000
Grade III (severe)	0	0	1.000
Italy			
Grade I (mild)	3 (<1)	5 (1)	0.782
Grade II (moderate)	3 (<1)	2 (<1)	0.782
Grade III (severe)	1 (<1)	1 (<1)	0.782
Spain			
Grade I (mild)	1 (<1)	1 (<1)	0.618
Grade II (moderate)	0	0	0.618
Grade III (severe)	0	0	0.618
United Kingdom			
Grade I (mild)	3 (<1)	0	0.618
Grade II (moderate)	0	1 (<1)	0.618
Grade III (severe)	1 (<1)	0	0.618

N=number of patients in treatment group; n=number of patients in treatment group within each sub-category; OHSS=Ovarian Hyperstimulation Syndrome.
The p-value was provided for descriptive purposes to evaluate if there were statistically significant differences between treatment groups in the distribution of OHSS grade, for patients with OHSS. The p-value was based on the chi-squared test or Fisher's exact test if there were fewer than 5 events in any sub-category. For Belgium, France, Spain and UK with few events, the p-value was calculated for the pooled countries.
The denominator used for calculating the percentage was the N in the column headers.
Source: Summary 15.6.1

The analyses of the other secondary endpoints AEs and ADRs are presented in Section 10.6.

10.5 Other Analyses

10.5.1 Exposure to Ovaleap and Gonal-f

Exposure to Ovaleap and Gonal-f is summarised by treatment group in in-text Table 13 (over all countries) and post-text Summary 15.8.2 (by country).

The mean (SD) durations of FSH treatment exposure in the Ovaleap and Gonal-f arms were 10.1 (2.02) days and 9.9 (1.94) days, respectively. Most of patients in the two treatment groups, i.e., 394 patients (97%) in the Ovaleap arm and 374 patients (91%) in the Gonal-f arm, remained on the same FSH treatment for the duration of the treatment cycle. Two patients each in the two treatment groups missed one dose of the FSH treatments. For patients who had oocyte maturation triggering performed, 16 patients (4%) in the Ovaleap arm and 25 patients (6%) in the Gonal-f arm missed FSH doses in the 4 days prior to maturation triggering; of those who had oocyte retrieval performed, 358 patients (88%) in the Ovaleap arm and 366 patients (89%) in the Gonal-f arm missed FSH doses in the 2 days preceding oocyte retrieval. During the FSH treatments, 81 patients (20%) increased doses and 62 patients (15%) decreased doses in the Ovaleap arm, while 72 patients (18%) increased doses and 94 patients (23%) decreased doses in the Gonal-f arm. The mean (SD) total doses received in the Ovaleap and Gonal-f arms were 2064.5 (805.38) IU and 2039.7 (855.13) IU, respectively.

Overall, the FSH treatment exposures were generally comparable between the two treatment groups.

Table 13 Follicle Stimulating Hormone Treatment Exposure – Over All Countries (Full Analysis Set)

Variable Statistic	Ovaleap (N=408)	Gonal-f (N=409)
Duration of treatment (days)[a]		
Mean	10.1	9.9
SD	2.02	1.94
Median	10.0	10.0
Min, max	4, 16	5, 19
Patients remained on the same FSH treatment for the duration of this treatment cycle, n (%)		
Yes	394 (97)	374 (91)
No	14 (3)	35 (9)
Number of days on initial treatment[b]		
Mean	10.1	9.9
SD	2.02	1.94
Median	10.0	10.0

Variable Statistic	Ovaleap (N=408)	Gonal-f (N=409)
Min, max	4, 16	5, 19
Number of days with missed doses[c]		
n	2	2
Mean	1.0	1.0
SD	0.00	0.00
Median	1.0	1.0
Min, max	1, 1	1, 1
Patients who missed a dose in the 4 days prior to oocyte maturation triggering[d], n(%)	16 (4)	25 (6)
Patients who missed a dose in the 2 days preceding oocyte retrieval[e], n(%)	358 (88)	366 (89)
Patients with dose decreased[f], n(%)	81 (20)	72 (18)
Patients with dose increased[f], n(%)	62 (15)	94 (23)
Total dose received (IU)		
Mean	2064.5	2039.7
SD	805.38	855.13
Median	1875.0	1925.0
Min, max	750, 5400	600, 6750

FSH=follicle stimulating hormone; IU=International Units; max=maximum; min=minimum; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category; SD=standard deviation.
The denominator used for calculating the percentage was the N in the column headers.
a. Total duration was calculated as last day of study drug – first day of study drug + 1.
b. Calculated as last day of study drug or date of treatment switch (whichever was earlier) - first day of study drug + 1. No patients had a date of switch recorded so end date of initial dose was not available for all patients.
c. A day with missed dose was defined as a day for which a dose was not taken between the start of FSH treatment up to and including the date of treatment completion or early treatment discontinuation.
d. Restricted to patients who had oocyte maturation triggering performed. The day of missed dose relative to the date of oocyte maturation triggering was calculated as: date dose missed – date of oocyte maturation triggering. A patient satisfied this criterion if the result was between -4 and -1.
e. Restricted to patients who had oocyte retrieval performed. The day of missed dose relative to the date of oocyte retrieval was calculated as: date dose missed – date of oocyte retrieval. A patient satisfied this criterion if the result was -2 or -1.
f. Compared to first dose.
Source: Summary 15.8.1

FSH treatment completion/discontinuation is summarised in in-text Table 14 (over all countries) and post-text Summary 15.8.4 (by country).

The majority of patients in the two treatment groups completed FSH treatment, including 382 patients (94%) in the Ovaleap arm and 390 patients (95%) in the Gonal-f arm.

Of 26 patients (6%) who discontinued FSH treatment in the Ovaleap arm, 16 patients (4%) were due to insufficient ovarian response, 7 patients (2%) due to other reasons, 2 patients (<1%) due to investigator decision, and 1 patient (<1%) due to prevent OHSS.

Of 19 patients (5%) who discontinued FSH treatment in the Gonal-f arm, 10 patients (2%) were due to insufficient ovarian response, 8 patients (2%) due to other reasons, and 1 patient (<1%) was due to investigator decision.

Table 14 Follicle Stimulating Hormone Treatment Completion/Discontinuation – Over All Countries (Full Analysis Set)

Variable Statistic	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Patients completed treatment			
Yes	382 (94)	390 (95)	772 (94)
No	26 (6)	19 (5)	45 (6)
Reason not completed			
To prevent OHSS	1 (<1)	0	1 (<1)
Insufficient ovarian response	16 (4)	10 (2)	26 (3)
Adverse event	0	0	0
Investigator decision	2 (<1)	1 (<1)	3 (<1)
Treatment switch	0	0	0
Other	7 (2)	8 (2)	15 (2)

N=number of patients in treatment group; OHSS=Ovarian Hyperstimulation Syndrome.
The denominator used for calculating the percentage was the N in the column headers.
Please refer to the source listing 16.2.1.3 for free text where Other specified.
Source: Summary 15.8.3

Individual exposure data is presented in Listings 16.2.5.1 and 16.2.5.2.

10.5.2 Ovulation Triggering and Oocytes Retrieval

Ovulation triggering and oocytes retrieval are summarised by treatment group in in-text Table 15. Individual ovulation triggering and oocytes retrieval data are presented in Listing 16.2.6.1.

The majority of patients in the two treatment groups used GnRH antagonist as the ovarian stimulation protocol, including 342 patients (84%) in the Ovaleap arm and 344 patients (84%) in the Gonal-f arm. The median numbers of follicles prior to ovulation triggering in current cycle were 10.5 (range: 0 to 54) in the Ovaleap arm and 10.0 (range: 0 to 44) in the Gonal-f arm. The mean (SD) serum oestradiol levels prior to ovulation triggering were 1910.1 (1381.97) pg/mL in the Ovaleap arm and 1755.3 (1262.60) pg/mL in the Gonal-f arm. Most of patients performed oocyte maturation triggering, including 372 patients (91%) in the Ovaleap arm and 388 patients (95%) in the Gonal-f arm. A total of 36 patients (9%) in the Ovaleap arm and 21 patients (5%) in the Gonal-f arm did not perform oocyte

maturation triggering due to insufficient response to FSH treatments (24 patients [6%] versus 13 patients [3%]) or other reasons (12 patients [3%] versus 8 patients [2%]). More than half of the patients used choriogonadotropin alfa as the medication for oocyte maturation triggering (206 patients [50%] versus 238 patients [58%]). The majority of patients performed oocytes retrieval under the current treatment, including 370 patients (91%) in the Ovaleap arm and 382 patients (93%) in the Gonal-f arm. The median numbers of oocytes retrieved were 10 (range: 0 to 43) in the Ovaleap arm and 8 (range: 0 to 29) in the Gonal-f arm. The mean (SD) serum oestradiol levels around the time of oocytes retrieval were 1717.3 (1573.56) pg/mL in the Ovaleap arm and 1514.8 (1274.88) pg/mL in the Gonal-f arm.

Overall, ovulation triggering and oocytes retrieval were comparable between the two treatment groups.

Table 15 Ovulation Triggering and Oocytes Retrieval by Treatment Group (Full Analysis Set)

Variable Statistic	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Stimulation protocol use in current cycle	395 (97)	396 (97)	791 (97)
GnRH antagonist	342 (84)	344 (84)	686 (84)
GnRH agonist	53 (13)	52 (13)	105 (13)
Prior to ovulation triggering:			
Number of follicles prior to ovulation triggering in current cycle			
n	394	395	789
Mean	12.0	10.9	11.4
SD	8.05	6.79	7.46
Median	10.5	10.0	10.0
Min, max	0, 54	0, 44	0, 54
Most recent serum E2 level prior to ovulation triggering (pg/mL)			
n	336	352	688
Mean	1910.1	1755.3	1830.9
SD	1381.97	1262.60	1323.54
Median	1589.5	1510.5	1550.0
Min, max	13, 9325	18, 9999	13, 9999
Oocyte maturation under the current treatment:			
Oocyte maturation triggering performed?	408 (100)	409 (100)	817 (100)
Yes	372 (91)	388 (95)	760 (93)
No	36 (9)	21 (5)	57 (7)

Variable Statistic	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Reason oocyte maturation triggering not performed:	36 (9)	21 (5)	57 (7)
Insufficient response to FSH treatment	24 (6)	13 (3)	37 (5)
Overresponse to FSH treatment (to prevent OHSS)	0	0	0
Cycle cancellation due to OHSS	0	0	0
Other	12 (3)	8 (2)	20 (2)
Medication used[a] for oocyte maturation triggering:	371 (91)	388 (95)	759 (93)
Buserelin	1 (<1)	0	1 (<1)
Buserelin acetate	3 (<1)	4 (<1)	7 (<1)
Choriogonadotropin alfa	206 (50)	238 (58)	444 (54)
Chorionic gonadotropin	107 (26)	93 (23)	200 (24)
Leuprorelin	1 (<1)	1 (<1)	2 (<1)
Leuprorelin acetate	3 (<1)	0	3 (<1)
Triptorelin	42 (10)	39 (10)	81 (10)
Triptorelin acetate	6 (1)	7 (2)	13 (2)
Missing	2 (<1)	6 (1)	8 (<1)
Oocyte retrieval under the current treatment:			
Oocyte retrieval performed?	408 (100)	409 (100)	817 (100)
Yes	370 (91)	382 (93)	752 (92)
No	38 (9)	27 (7)	65 (8)
If yes, number of oocytes retrieved			
n	370	382	752
Mean	10.7	9.4	10.0
SD	6.78	6.11	6.48
Median	10.0	8.0	9.0
Min, max	0, 43	0, 29	0, 43
E2 level around the time of oocyte retrieval (pg/mL)			
n	116	118	234
Mean	1717.3	1514.8	1615.2
SD	1573.56	1274.88	1431.28
Median	1299.5	1254.5	1263.5
Min, max	0, 9325	0, 7360	0, 9325

E2=oestradiol; FSH=follicle stimulating hormone; GnRH=gonadotropin-releasing hormone; max=maximum; min=minimum; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category; OHSS=Ovarian Hyperstimulation Syndrome; SD=standard deviation.
The denominator used for calculating the percentage was the N in the column headers.
Please refer to the source listing 16.2.6.1 for free text where Other specified.

A total of 760 patients recorded oocyte maturation triggering but only 759 medications were recorded as the start date for one medication was later than the data cut-off date.
[a] The details of medications used were described under concomitant medications.
Source: Summary 15.9.1

10.5.3 Embryo Transfer and Pregnancy Investigation

Embryo transfer and pregnancy investigation by treatment group are summarised in in-text Table 16. Individual embryo transfer and pregnancy investigation are presented in Listings 16.2.6.2 and 16.2.6.3.

The majority of patients underwent fresh embryo transfer during the study, including 256 patients (63%) in the Ovaleap arm and 274 patients (67%) in the Gonal-f arm. The median numbers of fresh embryos transferred were both 1 (ranges: 1 to 3) in the Ovaleap and Gonal-f arms. Time between oocyte retrieval and embryo transfer was similarly distributed in each treatment group, with approximately half of patients having 4 to 5 days (97 patients [24%] in the Ovaleap arm and 104 patients [25%] in the Gonal-f arm) or >5 days (94 patients [23%] in the Ovaleap arm and 101 patients [25%] in the Gonal-f arm). As of data cut-off, positive biochemical pregnancy was reported in 97 patients (24%) in the Ovaleap arm and 112 patients (27%) in the Gonal-f arm; positive vital pregnancy was reported in 84 patients (21%) in the Ovaleap arm and 87 patients (21%) in the Gonal-f arm; negative biochemical pregnancy was reported in 172 patients (42%) in the Ovaleap arm and 168 patients (41%) in the Gonal-f arm; and negative vital pregnancy was reported in 48 patients (12%) in the Ovaleap arm and 46 patients (11%) in the Gonal-f arm.

Of 136 patients (33%) who did not undergo fresh embryo transfer in the Ovaleap arm, 80 patients (20%) had other reasons, 36 patients (9%) had no embryo obtained, and 20 patients (5%) had all embryos frozen (freeze all). Of 116 patients (28%) patients who did not undergo fresh embryo transfer in the Gonal-f arm, 67 patients (16%) had other reasons, 35 patients (9%) had no embryo obtained, and 14 patients (3%) had all embryos frozen (freeze all).

Table 16 Embryo Transfer and Pregnancy Investigation by Treatment Group (Full Analysis Set)

Variable	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Fresh embryo transfer performed? n (%)			
Yes	256 (63)	274 (67)	530 (65)
No	136 (33)	116 (28)	252 (31)
Missing	16 (4)	19 (5)	35 (4)
If fresh embryo transfer not performed, reason:			
No embryo obtained	36 (9)	35 (9)	71 (9)
All embryos were frozen (Freeze all)	20 (5)	14 (3)	34 (4)
Other	80 (20)	67 (16)	147 (18)
Number of fresh embryos transferred			
n	256	274	530
Mean	1.5	1.5	1.5
SD	0.56	0.57	0.57
Median	1.0	1.0	1.0
Min, max	1, 3	1, 3	1, 3
Time between oocyte retrieval and embryo transfer[a], n (%)			
< 2 days	2 (<1)	3 (<1)	5 (<1)
2 to 3 days	63 (15)	66 (16)	129 (16)
4 to 5 days	97 (24)	104 (25)	201 (25)
>5 days	94 (23)	101 (25)	195 (24)
Biochemical pregnancy[b], n (%)			
Positive	97 (24)	112 (27)	209 (26)
Negative	172 (42)	168 (41)	340 (42)
Unknown	123 (30)	110 (27)	233 (29)
Vital pregnancy[c], n (%)			
Positive	84 (21)	87 (21)	171 (21)
Negative	48 (12)	46 (11)	94 (12)
Unknown/Not Available	260 (64)	257 (63)	517 (63)

max=maximum; min=minimum; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category; SD=standard deviation.
The denominator used for calculating the percentage was the N in the column headers.
Please refer to the source listing 16.2.6.2 for free text where Other specified.
a. Calculated when both dates were complete (day, month, year) as: date of transfer - date of oocyte retrieval + 1.
b. Based on beta-hCG test.
c. Based on sonographic diagnosis.
Source: Summary 15.9.2

OHSS incidence by embryo transfer and treatment group was summarised in in-text Table 17.

Embryo transfer practice did not have a statistically significant association with OHSS incidence differences between the two treatment groups (p=0.1627).

OHSS incidence differences were not analysed for the categories "freeze all", "no embryo obtained to be transferred", and "missing", due to no OHSS events per each embryo practice within treatment group.

Table 17 Incidence of Ovarian Hyperstimulation Syndrome by Embryo Transfer Practice and Treatment Group (Full Analysis Set)

	Ovaleap		Gonal-f		Ovaleap - Gonal-f	
Embryo Transfer Practice	m / n	Incidence Risk % (95% CI)	m / n	Incidence Risk % (95% CI)	Diff in Incidence Risk % (95% CI)	p-value
Fresh embryo transfer	9 / 256	3.516 (1.860, 6.545)	4 / 274	1.460 (0.569, 3.693)	2.056 (-0.724, 5.214)	0.1627
Freeze all	0 / 20	0.000 (,)	0 / 14	0.000 (,)		
No embryo obtained to be transferred	0 / 36		0 / 35			
Other	12 / 80	15.000 (8.794, 24.413)	9 / 67	13.433 (7.231, 23.600)	1.567 (-10.345, 12.840)	0.8177
Missing	0 / 16		0 / 19			

CI=confidence interval; m=number of events; n=number of patients.
Notes: Subjects were counted only once, even if they experienced multiple events.
m was the number of patients in each subgroup who experienced OHSS during the study; n was the number of patients in the subgroup.
CIs were estimated using the Newcombe-Wilson score method. The p-value was based on the chi-squared test or Fisher's exact test if there were fewer than 5 events in any category.
Please refer to Listing 16.2.6.2 for free text where Other specified.
Source: Summary 15.5.6

10.5.4 Concomitant Medications

The ovarian stimulation protocol medications by treatment group are summarised in post-text Summary 15.10.1 and in-text Table 18. Individual ovarian stimulation protocol is presented in Listing 16.2.8.1.

In the GnRH agonist stimulation protocol, the two most common medications were buserelin acetate (15 patients [4%] versus 14 patients [3%]) and triptorelin acetate (13 patients [3%] versus 11 patients [3%]) in the Ovaleap and Gonal-f arms.

In the GnRH antagonist stimulation protocol, ganirelix acetate (213 patients [52%] versus 186 patients [45%]) and cetrorelix (119 patients [29%] versus 130 patients [32%]) were the two most common medications used in the Ovaleap and Gonal-f arms.

Table 18 Ovarian Stimulation Protocol Medications by Treatment Group (Full Analysis Set)

Product Type WHODrug preferred term	Ovaleap (N=408) n (%)	Gonal-f (N=409) n (%)	Total (N=817) n (%)
GnRH agonist	53 (13)	50 (12)	103 (13)
Buserelin	4 (<1)	1 (<1)	5 (<1)
Buserelin acetate	15 (4)	14 (3)	29 (4)
Cetrorelix	0	3 (<1)	3 (<1)
Ganirelix acetate	1 (<1)	4 (<1)	5 (<1)
Leuprorelin	4 (<1)	1 (<1)	5 (<1)
Leuprorelin acetate	1 (<1)	2 (<1)	3 (<1)
Nafarelin	1 (<1)	0	1 (<1)
Nafarelin acetate	5 (1)	6 (1)	11 (1)
Triptorelin	9 (2)	8 (2)	17 (2)
Triptorelin acetate	13 (3)	11 (3)	24 (3)
GnRH antagonist	342 (84)	337 (82)	679 (83)
Cetrorelix	119 (29)	130 (32)	249 (30)
Follitropin alfa	0	3 (<1)	3 (<1)
Ganirelix	10 (2)	14 (3)	24 (3)
Ganirelix acetate	213 (52)	186 (45)	399 (49)
Triptorelin	0	2 (<1)	2 (<1)
Triptorelin acetate	0	2 (<1)	2 (<1)

GnRH=gonadotrophin-releasing hormone; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category; WHODrug=World Health Organization drug dictionary.
Note: Product name was coded by preferred term, based on the WHODrug version March 2016.
The denominator used for calculating the percentage was the N in the column headers.
Treatment duration was calculated as date of last treatment – date of first treatment shown + 1.
Note: Treatment duration was not calculated if any of the dates were partial or missing.
Source: Summary 15.10.1

The medications for oocyte maturation triggering by treatment group are summarised in in-text Table 19. Individual medication used for oocyte maturation triggering is presented in Listing 16.2.8.2.

In GnRH agonist medications, the most common drug product was triptorelin (42 patients [10%] versus 39 patients [10%]) in the Ovaleap and Gonal-f arms.

In hCG medications, choriogonadotropin alfa (206 patients [50%] versus 238 patients [58%]) and chorionic gonadotropin (107 patients [26%] versus 93 patients [23%]) were the two drug products in the Ovaleap and Gonal-f arms.

Table 19 Medications for Oocyte Maturation Triggering by Treatment Group (Full Analysis Set)

Product Type WHODrug preferred term	Ovaleap (N=408) n (%)	Gonal-f (N=409) n (%)	Total (N=817) n (%)
GnRH agonist	56 (14)	51 (12)	107 (13)
Buserelin	1 (<1)	0	1 (<1)
Buserelin acetate	3 (<1)	4 (<1)	7 (<1)
Leuprorelin	1 (<1)	1 (<1)	2 (<1)
Leuprorelin acetate	3 (<1)	0	3 (<1)
Triptorelin	42 (10)	39 (10)	81 (10)
Triptorelin acetate	6 (1)	7 (2)	13 (2)
hCG	313 (77)	331 (81)	644 (79)
Choriogonadotropin alfa	206 (50)	238 (58)	444 (54)
Chorionic gonadotropin	107 (26)	93 (23)	200 (24)

GnRH=gonadotrophin-releasing hormone; hCG=human chorionic gonadotropin; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category; WHODrug=World Health Organization drug dictionary.
Note: Product name was coded by preferred term, based on the WHODrug version March 2016.
The denominator used for calculating the percentage was the N in the column headers.
Source: Summary 15.10.2

The medications for luteal support by treatment group are summarised in post-text Summary 15.10.3 and in-text Table 20. Individual medication use for luteal support is presented in Listing 16.2.8.3.

The most common medication for luteal support was progesterone (260 patients [64%] versus 274 patients [67%]) in the Ovaleap and Gonal-f arms.

Table 20 Medications for Luteal Support by Treatment Group (Full Analysis Set)

Product Type WHODrug preferred term	Ovaleap (N=408) n (%)	Gonal-f (N=409) n (%)	Total (N=817) n (%)
Progesterone	270 (66)	287 (70)	557 (68)
Cyclacur	0	1 (<1)	1 (<1)
Dydrogesterone	10 (2)	12 (3)	22 (3)
Progesterone	260 (64)	274 (67)	534 (65)
Progestin	14 (3)	18 (4)	32 (4)
Dydrogesterone	1 (<1)	9 (2)	10 (1)
Hydroxyprogesterone caproate	1 (<1)	3 (<1)	4 (<1)
Progesterone	12 (3)	6 (1)	18 (2)

Product Type WHODrug preferred term	Ovaleap (N=408) n (%)	Gonal-f (N=409) n (%)	Total (N=817) n (%)
GnRH agonist	16 (4)	6 (1)	22 (3)
Oestradiol	1 (<1)	0	1 (<1)
Ganirelix acetate	3 (<1)	1 (<1)	4 (<1)
Triptorelin	12 (3)	4 (<1)	16 (2)
Triptorelin acetate	0	1 (<1)	1 (<1)
hCG	11 (3)	12 (3)	23 (3)
Choriogonadotropin alfa	0	4 (<1)	4 (<1)
Chorionic gonadotropin	8 (2)	6 (1)	14 (2)
Triptorelin	3 (<1)	2 (<1)	5 (<1)

GnRH=gonadotrophin-releasing hormone; hCG=human chorionic gonadotropin; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category; WHODrug=World Health Organization drug dictionary.
Note: Product name was coded by preferred term, based on the WHODrug version March 2016.
The denominator used for calculating the percentage was the N in the column headers.
Treatment duration was calculated as last date of treatment – first date of treatment shown + 1.
Note: Treatment duration was not calculated if any of the dates was partial or missing.
Source: Summary 15.10.3

Other concomitant medications by therapeutic class, PT, and treatment group are summarised in post-text Summary 15.10.4 and those with percentages ≥5% in any group are presented in in-text Table 21. Individual other concomitant medications are presented in Listing 16.2.8.4.

A total of 155 patients (38%) in the Ovaleap arm and 158 patients (39%) in the Gonal-f arm received other concomitant medications.

The most common therapeutic class in the Ovaleap and Gonal-f arm was sex hormones and modulators of the genital system (76 patients [19%] versus 95 patients [23%]), followed by thyroid therapy (34 patients [8%] versus 27 patients [7%]), antianemic preparations (25 patients [6%] versus 20 patients [5%]), and antithrombotic agents (21 patients [5%] versus 19 patients [5%]).

The two most common drug PTs in the Ovaleap and Gonal-f arm were menotrophin (42 patients [10%] versus 51 patients [12%]) and levothyroxine sodium (30 patients [7%] versus 25 patients [6%]).

Table 21 Other Concomitant Medications with Incidences ≥5% in Any Treatment Group by Therapeutic Class, Preferred Term, and Treatment Group (Full Analysis Set)

Therapeutic class WHODrug preferred term, n (%)	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Patients receiving concomitant medications	155 (38)	158 (39)	313 (38)
Antianemic preparations	25 (6)	20 (5)	45 (6)
Folic acid	19 (5)	18 (4)	37 (5)
Femibion /01597501/	2 (<1)	1 (<1)	3 (<1)
Folic acid w/inositol/melatonin/selenium	2 (<1)	1 (<1)	3 (<1)
Yodocefol	2 (<1)	1 (<1)	3 (<1)
Calcium levofolinate	1 (<1)	0	1 (<1)
Cyanocobalamin	0	1 (<1)	1 (<1)
Ferrous sulfate	1 (<1)	0	1 (<1)
Folic acid w/potassium iodide/vitamin b12 nos	1 (<1)	0	1 (<1)
Inofolic	0	1 (<1)	1 (<1)
Antithrombotic agents	21 (5)	19 (5)	40 (5)
Acetylsalicylic acid	6 (1)	9 (2)	15 (2)
Enoxaparin sodium	7 (2)	6 (1)	13 (2)
Dalteparin sodium	6 (1)	6 (1)	12 (1)
Nadroparin calcium	2 (<1)	2 (<1)	4 (<1)
Sex hormones and modulators of the genital system	76 (19)	95 (23)	171 (21)
Menotrophin	42 (10)	51 (12)	93 (11)
Progesterone	19 (5)	27 (7)	46 (6)
Oestradiol	6 (1)	8 (2)	14 (2)
Lutropin alfa	6 (1)	7 (2)	13 (2)
Choriogonadotropin alfa	6 (1)	2 (<1)	8 (<1)
Cilest[a]	3 (<1)	1 (<1)	4 (<1)
Chorionic gonadotropin	0	3 (<1)	3 (<1)
Hydroxyprogesterone caproate	0	3 (<1)	3 (<1)
Ethinyloestradiol	1 (<1)	1 (<1)	2 (<1)
Follitropin alfa	2 (<1)	0	2 (<1)
Mifepristone	1 (<1)	1 (<1)	2 (<1)
Thyroid therapy	34 (8)	27 (7)	61 (7)
Levothyroxine sodium	30 (7)	25 (6)	55 (7)
Levothyroxine	4 (<1)	1 (<1)	5 (<1)
Thiamazole	0	1 (<1)	1 (<1)

N=number of patients in treatment group; n=number of patients in treatment group within each sub-category; WHODrug=World Health Organization drug dictionary.
Note: Preferred terms were sorted by descending order of incidence within therapeutic class for the active treatment group. Patients were counted only once in each preferred term category, and only once in each therapeutic class category. The denominator used for calculating the percentage was the header N. “Other”

concomitant medications excluded medications prescribed for the ovarian stimulation protocol, oocyte maturation triggering and luteal support (summarized separately).
WHODrug version March 2016.
[a] Cilest is the trade name for ethinyloestradiol/norgestimate.
Source: Summary 15.10.4

10.6 Adverse Events/Adverse Reactions

AEs are summarised by category and treatment group in in-text Table 22 (over all countries) and post-text Summary 15.7.1 (per country). Individual AE and SAE information are presented in Listings 16.2.7.1, 16.2.7.2 and 16.2.7.3. Individual AE associated with pregnancy is presented in Listing 16.2.7.5.

Overall, 80 patients (20%) experienced 96 cases of AEs in the Ovaleap arm and 58 patients (14%) experienced 64 cases of AE in the Gonal-f arm. Of these patients, 47 patients (12%) experienced 52 cases of drug-related AEs in the Ovaleap arm and 34 patients (8%) experienced 34 cases of drug-related AEs in the Gonal-f arm. SAEs were reported in 31 patients (8%) in the Ovaleap arm and 21 patients (5%) in the Gonal-f arm. Drug-related SAEs were reported in 7 patients (2%) in the Ovaleap arm and 4 patients (<1%) in the Gonal-f arm. Severe AEs were reported in 13 patients (3%) in the Ovaleap arm and 4 patients (<1%) in the Gonal-f arm. Drug-related severe AEs were reported in 2 patients (<1%) in the Ovaleap arm and 1 patient (<1%) in the Gonal-f arm. Two patients (<1%) in the Ovaleap arm experienced 2 cases of AEs leading to study discontinuation, one of which was considered to be drug-related; 1 patient (<1%) in the Gonal-f arm experienced 1 case of drug-related AE leading to study discontinuation.

Table 22 Summary of Adverse Events by Adverse Event Category and Treatment Group – Over All Countries (Full Analysis Set)

Adverse Event Category [n (%) m]	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Any adverse events	80 (20) 96	58 (14) 64	138 (17) 160
Any drug-related adverse events	47 (12) 52	34 (8) 34	81 (10) 86
Any serious adverse events	31 (8) 38	21 (5) 23	52 (6) 61
Any drug-related serious adverse events	7 (2) 8	4 (<1) 4	11 (1) 12
Any severe adverse events	13 (3) 16	4 (<1) 5	17 (2) 21
Any drug-related severe adverse events	2 (<1) 2	1 (<1) 1	3 (<1) 3
Any adverse events leading to study discontinuation	2 (<1) 2	1 (<1) 1	3 (<1) 3

Adverse Event Category [n (%) m]	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Any drug-related adverse events leading to study discontinuation	1 (<1) 1	1 (<1) 1	2 (<1) 2

m=number of events; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category.
Note: For each category, subjects were included only once, even if they experienced multiple events in that category.
The denominator used for calculating the percentage was the N in the column headers.
Source: Summary 15.7

AEs are summarised by SOC, PT, and treatment group in post-text Summary 15.7.2 and those SOCs with incidences ≥5% in any treatment group are presented in in-text Table 23.

The most common AE SOC in the Ovaleap and Gonal-f arms was investigations (27 patients [7%] versus 18 patients [4%]), followed by reproductive system and breast disorders (24 patients [6%] versus 17 patients [4%]), and pregnancy, puerperium and perinatal conditions (20 patients [5%] versus 15 patients [4%]).

The most common AE PT in the Ovaleap and Gonal-f arms was OHSS (21 patients [5%] versus 13 patients [3%]), followed by antral follicle count high (20 patients [5%] versus 11 patients [3%]) and abortion spontaneous (13 patients [3%] versus 6 patients [1%]).

Table 23 Adverse Event System Organ Classes with Incidences ≥5% in Any Treatment Group by System Organ Class, Preferred Term, and Treatment Group (Full Analysis Set)

System organ class MedDRA 19.1 preferred term [n (%) m]	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Patients with at least 1 AE	80 (20) 96	58 (14) 64	138 (17) 160
Investigations	27 (7) 27	18 (4) 18	45 (6) 45
Antral follicle count high	20 (5) 20	11 (3) 11	31 (4) 31
Oestradiol increased	5 (1) 5	7 (2) 7	12 (1) 12
Progesterone increased	2 (<1) 2	0	2 (<1) 2
Pregnancy, puerperium and perinatal conditions	20 (5) 23	15 (4) 15	35 (4) 38
Abortion spontaneous	13 (3) 13	6 (1) 6	19 (2) 19
Abortion missed	1 (<1) 2	3 (<1) 3	4 (<1) 5
Abortion	0	2 (<1) 2	2 (<1) 2
Ectopic pregnancy	1 (<1) 1	1 (<1) 1	2 (<1) 2
Gestational diabetes	1 (<1) 1	1 (<1) 1	2 (<1) 2
Abortion complete	0	1 (<1) 1	1 (<1) 1
Abortion early	1 (<1) 1	0	1 (<1) 1
Abortion incomplete	0	1 (<1) 1	1 (<1) 1
Cervical incompetence	1 (<1) 1	0	1 (<1) 1
Foetal death	1 (<1) 1	0	1 (<1) 1

System organ class MedDRA 19.1 preferred term [n (%) m]	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Pre-eclampsia	1 (<1) 1	0	1 (<1) 1
Premature baby	1 (<1) 1	0	1 (<1) 1
Premature rupture of membranes	1 (<1) 1	0	1 (<1) 1
Reproductive system and breast disorders	24 (6) 26	17 (4) 17	41 (5) 43
Ovarian Hyperstimulation Syndrome	21 (5) 23	13 (3) 13	34 (4) 36
Hydrosalpinx	1 (<1) 1	0	1 (<1) 1
Ovarian cyst	0	1 (<1) 1	1 (<1) 1
Ovarian enlargement	0	1 (<1) 1	1 (<1) 1
Pelvic pain	0	1 (<1) 1	1 (<1) 1
Testicular atrophy	0	1 (<1) 1	1 (<1) 1
Vaginal haemorrhage	1 (<1) 1	0	1 (<1) 1
Vulvovaginal pruritus	1 (<1) 1	0	1 (<1) 1

AE=adverse event; m=number of events; MedDRA=medical dictionary of regulatory activities; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category.
Note: Adverse events were coded using MedDRA version 19.1. Preferred terms were sorted by descending order of incidence within system organ class for the total column. Patients were counted only once in each preferred term category, and only once in each system organ class category. The denominator used for calculating the percentage was the N in the column headers.
The adverse event of testicular atrophy reflected a congenital defect in a new born baby.
Source: Summary 15.7.2

Drug-related AEs are summarised by SOC, PT, and treatment group in in-text Table 24.

The two most common drug-related AE SOCs in the Ovaleap and Gonal-f arms were investigations (26 patients [6%] versus 17 patients [4%]), and reproductive system and breast disorders (20 patients [5%] versus 14 patients [3%]).

The two most common drug-related AE PTs in the Ovaleap and Gonal-f arms were OHSS (20 patients [5%] versus 13 patients [3%]) and antral follicle count high (20 patients [5%] versus 10 patients [2%]).

Table 24 Drug-related Adverse Events (Full Analysis Set)

System organ class MedDRA 19.1 preferred term [n (%) m]	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Patients with at least 1 drug-related AE	47 (12) 52	34 (8) 34	81 (10) 86
Gastrointestinal disorders	2 (<1) 2	2 (<1) 2	4 (<1) 4
Abdominal distension	2 (<1) 2	1 (<1) 1	3 (<1) 3
Abdominal discomfort	0	1 (<1) 1	1 (<1) 1
Injury, poisoning and procedural complications	0	1 (<1) 1	1 (<1) 1
Procedural pain	0	1 (<1) 1	1 (<1) 1

System organ class MedDRA 19.1 preferred term [n (%) m]	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Investigations	26 (6) 26	17 (4) 17	43 (5) 43
Antral follicle count high	20 (5) 20	10 (2) 10	30 (4) 30
Oestradiol increased	5 (1) 5	7 (2) 7	12 (1) 12
Progesterone increased	1 (<1) 1	0	1 (<1) 1
Psychiatric disorders	1 (<1) 2	0	1 (<1) 2
Insomnia	1 (<1) 1	0	1 (<1) 1
Irritability	1 (<1) 1	0	1 (<1) 1
Reproductive system and breast disorders	20 (5) 22	14 (3) 14	34 (4) 36
Ovarian Hyperstimulation Syndrome	20 (5) 22	13 (3) 13	33 (4) 35
Ovarian cyst	0	1 (<1) 1	1 (<1) 1

AE=adverse event; m=number of events; MedDRA=medical dictionary of drug activities; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category.
Note: Adverse events were coded using MedDRA version 19.1. Preferred terms were sorted by descending order of incidence within system organ class for the total column. Patients were counted only once in each preferred term category, and only once in each system organ class category. The denominator used for calculating the percentage was the N in the column headers.
Source: Summary 15.7.3

SAEs are summarised in in-text Table 25.

The two most common SAE SOCs in the Ovaleap and Gonal-f arms were pregnancy, puerperium and perinatal conditions (19 patients [5%] versus 14 patients [3%]), and reproductive system and breast disorders (8 patients [2%] versus 5 patients [1%]).

The two most common SAE PTs in the Ovaleap and Gonal-f arms were abortion spontaneous (13 patients [3%] versus 6 patients [1%]) and OHSS (7 patients [2%] versus 4 patients [<1%]).

Table 25 Serious Adverse Events (Full Analysis Set)

System organ class MedDRA 19.1 preferred term [n (%) m]	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Patients with at least 1 SAE	31 (8) 38	21 (5) 23	52 (6) 61
Congenital, familial and genetic disorders	5 (1) 5	1 (<1) 1	6 (1) 6
Trisomy 21	2 (<1) 2	0	2 (<1) 2
Cardiac septal defect	1 (<1) 1	0	1 (<1) 1
Hydrocele	0	1 (<1) 1	1 (<1) 1
Talipes	1 (<1) 1	0	1 (<1) 1
Trisomy 8	1 (<1) 1	0	1 (<1) 1
Gastrointestinal disorders	0	1 (<1) 2	1 (<1) 2
Abdominal pain	0	1 (<1) 1	1 (<1) 1
Vomiting	0	1 (<1) 1	1 (<1) 1
Infections and infestations	2 (<1) 2	0	2 (<1) 2
Amniotic cavity infection	1 (<1) 1	0	1 (<1) 1
Injection site infection	1 (<1) 1	0	1 (<1) 1
Injury, poisoning and procedural complications	0	1 (<1) 1	1 (<1) 1
Procedural haemorrhage	0	1 (<1) 1	1 (<1) 1
Pregnancy, puerperium and perinatal conditions	19 (5) 22	14 (3) 14	33 (4) 36
Abortion spontaneous	13 (3) 13	6 (1) 6	19 (2) 19
Abortion missed	1 (<1) 2	3 (<1) 3	4 (<1) 5
Abortion	0	2 (<1) 2	2 (<1) 2
Ectopic pregnancy	1 (<1) 1	1 (<1) 1	2 (<1) 2
Abortion complete	0	1 (<1) 1	1 (<1) 1
Abortion early	1 (<1) 1	0	1 (<1) 1
Abortion incomplete	0	1 (<1) 1	1 (<1) 1
Cervical incompetence	1 (<1) 1	0	1 (<1) 1
Foetal death	1 (<1) 1	0	1 (<1) 1
Pre-eclampsia	1 (<1) 1	0	1 (<1) 1
Premature baby	1 (<1) 1	0	1 (<1) 1
Premature rupture of membranes	1 (<1) 1	0	1 (<1) 1
Reproductive system and breast disorders	8 (2) 9	5 (1) 5	13 (2) 14
Ovarian Hyperstimulation Syndrome	7 (2) 8	4 (<1) 4	11 (1) 12
Testicular atrophy	0	1 (<1) 1	1 (<1) 1
Vaginal haemorrhage	1 (<1) 1	0	1 (<1) 1

MedDRA=medical dictionary of drug activities; m=number of events; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category; SAE=serious adverse event.
Note: Adverse events were coded using MedDRA version 19.1. Preferred terms were sorted by descending order of incidence within system organ class for the total column. Patients were counted only once in each

preferred term category, and only once in each system organ class category. The denominator used for calculating the percentage was the N in the column headers.
The adverse event of testicular atrophy reflected a congenital defect in a new born baby.
Source: Summary 15.7.4

Drug-related SAEs are summarised in in-text Table 26.

OHSS was the only drug-related SAEs reported in the Ovaleap and Gonal-f arms (7 patients [2%] versus 4 patients [<1%]).

Table 26 Drug-related Serious Adverse Events (Full Analysis Set)

System organ class MedDRA 19.1 preferred term [n (%) m]	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Patients with at least 1 drug-related SAE	7 (2) 8	4 (<1) 4	11 (1) 12
Reproductive system and breast disorders	7 (2) 8	4 (<1) 4	11 (1) 12
Ovarian Hyperstimulation Syndrome	7 (2) 8	4 (<1) 4	11 (1) 12

m=number of events; MedDRA=medical dictionary of drug activities; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category; SAE=serious adverse event.
Note: Adverse events were coded using MedDRA version 19.1. Preferred terms were sorted by descending order of incidence within system organ class for the total column. Patients were counted only once in each preferred term category, and only once in each system organ class category. The denominator used for calculating the percentage was the N in the column headers.
Source: Summary 15.7.5

Severe AEs are summarised in in-text Table 27.

In the Ovaleap arm, abortion spontaneous was reported in 7 patients (2%), OHSS was reported in 2 patients (<1%), and other severe AEs were reported in single patients (<1%). Except OHSS, all other severe AEs were not considered to be drug-related.

In the Gonal-f arm, all severe AEs were reported in single patients (<1%) and only OHSS was considered to be drug-related.

Table 27 Severe Adverse Events (Full Analysis Set)

System organ class MedDRA 19.1 preferred term [n (%) m]	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Patients with at least 1 severe AE	13 (3) 16	4 (<1) 5	17 (2) 21
Congenital, familial and genetic disorders	2 (<1) 2	0	2 (<1) 2
Trisomy 21	1 (<1) 1	0	1 (<1) 1
Trisomy 8	1 (<1) 1	0	1 (<1) 1
Gastrointestinal disorders	0	1 (<1) 2	1 (<1) 2
Abdominal pain	0	1 (<1) 1	1 (<1) 1
Vomiting	0	1 (<1) 1	1 (<1) 1

System organ class MedDRA 19.1 preferred term [n (%) m]	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Infections and infestations	1 (<1) 1	0	1 (<1) 1
Amniotic cavity infection	1 (<1) 1	0	1 (<1) 1
Pregnancy, puerperium and perinatal conditions	10 (2) 11	2 (<1) 2	12 (1) 13
Abortion spontaneous	7 (2) 7	1 (<1) 1	8 (<1) 8
Abortion complete	0	1 (<1) 1	1 (<1) 1
Foetal death	1 (<1) 1	0	1 (<1) 1
Pre-eclampsia	1 (<1) 1	0	1 (<1) 1
Premature baby	1 (<1) 1	0	1 (<1) 1
Premature rupture of membranes	1 (<1) 1	0	1 (<1) 1
Reproductive system and breast disorders	2 (<1) 2	1 (<1) 1	3 (<1) 3
Ovarian Hyperstimulation Syndrome	2 (<1) 2	1 (<1) 1	3 (<1) 3

AE=adverse event; m=number of events; MedDRA=medical dictionary of drug activities; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category.
Note: Adverse events were coded using MedDRA version 19.1. Preferred terms were sorted by descending order of incidence within system organ class for the total column. Patients were counted only once in each preferred term category, and only once in each system organ class category. The denominator used for calculating the percentage was the N in the column headers.
Source: Summary 15.7.6

Drug-related severe AEs are summarised in in-text Table 28. OHSS was the only drug-related severe AEs reported in the Ovaleap and Gonal-f arms (2 patients [<1%] versus 1 patient [<1%]).

Table 28 Drug-related Severe Adverse Events (Full Analysis Set)

System organ class MedDRA 19.1 preferred term [n (%) m]	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Patients with at least 1 drug-related severe AE	2 (<1) 2	1 (<1) 1	3 (<1) 3
Reproductive system and breast disorders	2 (<1) 2	1 (<1) 1	3 (<1) 3
Ovarian Hyperstimulation Syndrome	2 (<1) 2	1 (<1) 1	3 (<1) 3

AE=adverse event; m=number of events; MedDRA=medical dictionary of drug activities; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category.
Note: Adverse events were coded using MedDRA version 19.1. Preferred terms were sorted by descending order of incidence within system organ class for the total column. Patients were counted only once in each preferred term category, and only once in each system organ class category. The denominator used for calculating the percentage was the N in the column headers.
Source: Summary 15.7.7

AEs leading to study discontinuation are summarised in in-text Table 29.

In the Ovaleap arm, one patient each experienced antral follicle count high and progesterone increased, both of which led to study discontinuation.

In the Gonal-f arm, one patient experienced ovarian cyst, which led to study discontinuation.

Table 29 Adverse Events Leading to Study Discontinuation (Full Analysis Set)

System organ class MedDRA 19.1 preferred term [n (%) m]	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Patients with at least 1 AE leading to study discontinuation	2 (<1) 2	1 (<1) 1	3 (<1) 3
Investigations	2 (<1) 2	0	2 (<1) 2
Antral follicle count high	1 (<1) 1	0	1 (<1) 1
Progesterone increased	1 (<1) 1	0	1 (<1) 1
Reproductive system and breast disorders	0	1 (<1) 1	1 (<1) 1
Ovarian cyst	0	1 (<1) 1	1 (<1) 1

AE=adverse event; m=number of events; MedDRA=medical dictionary of drug activities; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category.
Note: Adverse events were coded using MedDRA version 19.1. Preferred terms were sorted by descending order of incidence within system organ class for the total column. Patients were counted only once in each preferred term category, and only once in each system organ class category. The denominator used for calculating the percentage was the N in the column headers.
Source: Summary 15.7.8

Drug-related AEs leading to study discontinuation are summarised in in-text Table 30.

One patient in the Ovaleap arm experienced antral follicle count high and one patient in the Gonal-f arm experienced ovarian cyst, and they were both considered to be drug-related.

Table 30 Drug-related Adverse Events Leading to Study Discontinuation (Full Analysis Set)

System organ class MedDRA 19.1 preferred term [n (%) m]	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Patients with at least 1 drug-related AE leading to study discontinuation	1 (<1) 1	1 (<1) 1	2 (<1) 2
Investigations	1 (<1) 1	0	1 (<1) 1
Antral follicle count high	1 (<1) 1	0	1 (<1) 1
Reproductive system and breast disorders	0	1 (<1) 1	1 (<1) 1

System organ class MedDRA 19.1 preferred term [n (%) m]	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Ovarian cyst	0	1 (<1) 1	1 (<1) 1

AE=adverse event; m=number of events; MedDRA=medical dictionary of drug activities; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category.
Note: Adverse events were coded using MedDRA version 19.1. Preferred terms were sorted by descending order of incidence within system organ class for the total column. Patients were counted only once in each preferred term category, and only once in each system organ class category. The denominator used for calculating the percentage was the N in the column headers.
Source: Summary 15.7.9

AEs related to pregnancy are summarised in in-text Table 31.

The most common AE PT related to pregnancy in the Ovaleap and Gonal-f arms was abortion spontaneous (13 patients [3%] versus 6 patients [1%]). They were in different severity grades from mild to severe, but none of them were considered to be drug-related. All other AE PTs related to pregnancy were reported in 1 to 3 cases, and not considered to be drug-related.

Table 31 Adverse Events Related to Pregnancy (Full Analysis Set)

AE Term MedDRA 19.1 preferred term [n (%) m]	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Pregnancy, puerperium and perinatal conditions	20 (5) 23	15 (4) 15	35 (4) 38
Abortion spontaneous	13 (3) 13	6 (1) 6	19 (2) 19
Mild	4 (<1) 4	3 (<1) 3	7 (<1) 7
Moderate	2 (<1) 2	2 (<1) 2	4 (<1) 4
Severe	7 (2) 7	1 (<1) 1	8 (<1) 8
Unknown	0 (0) 0	0 (0) 0	0 (0) 0
Abortion missed	1 (<1) 2	3 (<1) 3	4 (<1) 5
Mild	1 (<1) 2	0 (0) 0	1 (<1) 2
Moderate	0 (0) 0	3 (<1) 3	3 (<1) 3
Severe	0 (0) 0	0 (0) 0	0 (0) 0
Unknown	0 (0) 0	0 (0) 0	0 (0) 0
Abortion	0 (0) 0	2 (<1) 2	2 (<1) 2
Mild	0 (0) 0	1 (<1) 1	1 (<1) 1
Moderate	0 (0) 0	1 (<1) 1	1 (<1) 1
Severe	0 (0) 0	0 (0) 0	0 (0) 0
Unknown	0 (0) 0	0 (0) 0	0 (0) 0
Ectopic pregnancy	1 (<1) 1	1 (<1) 1	2 (<1) 2
Mild	1 (<1) 1	0 (0) 0	1 (<1) 1
Moderate	0 (0) 0	1 (<1) 1	1 (<1) 1

AE Term MedDRA 19.1 preferred term [n (%) m]	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Severe	0 (0) 0	0 (0) 0	0 (0) 0
Unknown	0 (0) 0	0 (0) 0	0 (0) 0
Gestational diabetes	1 (<1) 1	1 (<1) 1	2 (<1) 2
Mild	1 (<1) 1	1 (<1) 1	2 (<1) 2
Moderate	0 (0) 0	0 (0) 0	0 (0) 0
Severe	0 (0) 0	0 (0) 0	0 (0) 0
Unknown	0 (0) 0	0 (0) 0	0 (0) 0
Abortion complete	0 (0) 0	1 (<1) 1	1 (<1) 1
Mild	0 (0) 0	0 (0) 0	0 (0) 0
Moderate	0 (0) 0	0 (0) 0	0 (0) 0
Severe	0 (0) 0	1 (<1) 1	1 (<1) 1
Unknown	0 (0) 0	0 (0) 0	0 (0) 0
Abortion early	1 (<1) 1	0 (0) 0	1 (<1) 1
Mild	1 (<1) 1	0 (0) 0	1 (<1) 1
Moderate	0 (0) 0	0 (0) 0	0 (0) 0
Severe	0 (0) 0	0 (0) 0	0 (0) 0
Unknown	0 (0) 0	0 (0) 0	0 (0) 0
Abortion incomplete	0 (0) 0	1 (<1) 1	1 (<1) 1
Mild	0 (0) 0	1 (<1) 1	1 (<1) 1
Moderate	0 (0) 0	0 (0) 0	0 (0) 0
Severe	0 (0) 0	0 (0) 0	0 (0) 0
Unknown	0 (0) 0	0 (0) 0	0 (0) 0
Cervical incompetence	1 (<1) 1	0 (0) 0	1 (<1) 1
Mild	0 (0) 0	0 (0) 0	0 (0) 0
Moderate	1 (<1) 1	0 (0) 0	1 (<1) 1
Severe	0 (0) 0	0 (0) 0	0 (0) 0
Unknown	0 (0) 0	0 (0) 0	0 (0) 0
Foetal death	1 (<1) 1	0 (0) 0	1 (<1) 1
Mild	0 (0) 0	0 (0) 0	0 (0) 0
Moderate	0 (0) 0	0 (0) 0	0 (0) 0
Severe	1 (<1) 1	0 (0) 0	1 (<1) 1
Unknown	0 (0) 0	0 (0) 0	0 (0) 0
Pre-eclampsia	1 (<1) 1	0 (0) 0	1 (<1) 1
Mild	0 (0) 0	0 (0) 0	0 (0) 0
Moderate	0 (0) 0	0 (0) 0	0 (0) 0
Severe	1 (<1) 1	0 (0) 0	1 (<1) 1
Unknown	0 (0) 0	0 (0) 0	0 (0) 0
Premature baby	1 (<1) 1	0 (0) 0	1 (<1) 1
Mild	0 (0) 0	0 (0) 0	0 (0) 0

AE Term MedDRA 19.1 preferred term [n (%) m]	Ovaleap (N=408)	Gonal-f (N=409)	Total (N=817)
Moderate	0 (0) 0	0 (0) 0	0 (0) 0
Severe	1 (<1) 1	0 (0) 0	1 (<1) 1
Unknown	0 (0) 0	0 (0) 0	0 (0) 0
Premature rupture of membranes	1 (<1) 1	0 (0) 0	1 (<1) 1
Mild	0 (0) 0	0 (0) 0	0 (0) 0
Moderate	0 (0) 0	0 (0) 0	0 (0) 0
Severe	1 (<1) 1	0 (0) 0	1 (<1) 1
Unknown	0 (0) 0	0 (0) 0	0 (0) 0

AE=adverse event; m=number of events; MedDRA=medical dictionary of drug activities; N=number of patients in treatment group; n=number of patients in treatment group within each sub-category.
Note: Adverse events were coded using MedDRA version 19.1. Preferred terms were sorted by descending order of incidence.
Patients were counted only once in each preferred term category.
The denominator used for calculating the percentage was the N in the column headers.
Source: Summary 15.7.10

No deaths were observed during the study (Listing 16.2.7.6).

11 DISCUSSION

11.1 Key Results

11.1.1 Patient Demographics and Baseline Characteristics

A total of 1147 patients from 55 sites in 6 European countries, i.e., Belgium, France, Germany, Italy, Spain, and the United Kingdom, were registered to participate in the study. Of all registered patients, 833 patients were enrolled in the study, including 419 and 414 patients that were planned to receive Ovaleap and Gonal-f treatments, respectively, upon the time of enrolment. A total of 817 patients were included in the FAS, including 408 patients in the Ovaleap arm and 409 patients in the Gonal-f arm. The enrolled and FAS patient numbers between the two treatment groups were at a ratio of close to 1:1, both over all countries and in each country.

A total of 107 patients (13%) were reported to have protocol deviations during the study, including 55 patients (13%) in the Ovaleap arm and 52 patients (13%) in the Gonal-f arm. The two most common protocol deviation categories in both arms were assessment safety (failure or delay of safety/pregnancy assessment or reporting) and informed consent. Overall, the numbers of patients with protocol deviations and categories of protocol deviations were comparable between the two treatment groups.

In the FAS, the mean (SD) age was 33.5 (4.67) years in the Ovaleap arm and 34.3 (4.55) years in the Gonal-f arm. Approximately half (382 patients, 47%) of the patients were >34 years old, 288 patients (35%) were aged between 30 and 34 years, and 147 patients (18%) were aged between 18 and 30 years. The majority (691 patients, 85%)

of patients were Caucasian, followed by Asian (27 patients, 3%) and Black (23 patients, 3%). The mean (SD) weight, height, and BMI between the Ovaleap and Gonal-f arms were 65.1 (12.29) kg and 66.0 (13.14) kg, 165.0 (6.68) cm and 165.2 (6.54) cm, and 23.9 (4.15) kg/m^2 and 24.1 (4.39) kg/m^2, respectively. The majority (497 patients, 61%) of patients had BMI ranges of 18.5 to 25 kg/m^2. Most of patients were not current smokers (661 patients, 81%) and had no alcohol consumption (689 patients, 84%) or illicit drug use (736 patients, 90%). The patient demographics and baseline characteristics were well balanced between the two treatment groups both overall and in each country.

A total of 333 patients (41%) were reported to have a past medical history of at least one medical condition, including 180 patients (44%) in the Ovaleap arm and 153 patients (37%) in the Gonal-f arm. The most common medical history SOC in the two treatment groups was immune system disorders, followed by reproductive system and breast disorders, and endocrine disorders; the most common medical history PT was drug hypersensitivity, followed by hypothyroidism, polycystic ovaries, seasonal allergy, endometriosis, and fallopian tube obstruction. The numbers and percentages of all these medical history SOCs and PTs were similar between the two treatment groups.

A total of 520 patients (64%) had no former pregnancies, including 256 patients (63%) in the Ovaleap arm and 264 patients (65%) in the Gonal-f arm. The majority of patients had no former miscarriages (647 patients, 79%), no former still births (808 patients, 99%), and no former live births (704 patients, 86%). The mean (SD) infertility durations in the Ovaleap and Gonal-f arms were 32.4 (53.86) months and 36.9 (95.61) months, respectively. The majority of patients had menstrual cycle lengths between 22 days and 35 days (751 patients, 92%). The median antral follicular counts were similar between the Ovaleap and Gonal-f arms (median counts: 7 versus 6 in the left ovary and 7 versus 7 in the right ovary) and the majority of patients had antral follicular counts <12 (509 [62%] patients for the left ovary and 524 [64%] patients for the right ovary). The mean (SD) basal serum AMH levels in the Ovaleap and Gonal-f arms were 4.9 (8.95) ng/mL and 3.9 (6.67) ng/mL, respectively. Approximately half of patients had basal serum AMH levels <3.5 ng/mL (415 patients, 51%), including 199 patients (49%) in the Ovaleap arm and 216 patients (53%) in the Gonal-f arm.

11.1.2 Incidence of Ovarian Hyperstimulation Syndrome

Overall, 21 out of 408 patients in the Ovaleap arm and 13 out of 409 patients in the Gonal-f arm experienced OHSS during the study. The OHSS incidence rate was 5.1% (95% CI: 3.4&, 7.7%) in the Ovaleap arm and 3.2% (95% CI: 1.9%, 5.4%) in the Gonal-f arm. The rate difference between the Ovaleap and Gonal-f arms was 2.0% (95% CI: -0.8%, 4.9%) and no statistically significant difference (p=0.1589) was observed between the two treatment groups. Similar results were also observed in subgroups per country, i.e., Germany, Italy, and the pooled countries of Belgium, France, Spain, and the United Kingdom.

The potential confounders including age, BMI, ovarian stimulation protocol, oocyte maturation triggering, number of embryos transferred, menstrual cycle length, medications used in the luteal phase support, and total FSH dose had no statistically significant association with OHSS incidence at the univariate level ($p>0.05$); whilst other potential confounders including country, PCOS, embryo transfer, antral follicle count, basal serum level of AMH, pregnancy, FSH dose reduction, and FSH treatment duration had a statistically significant association with OHSS incidence at the univariate level ($p<0.05$).

The univariate logistic regression analysis showed that no statistically significant difference in OHSS incidence was observed between Ovaleap and Gonal-f treatments after univariate adjustment for each potential confounder mentioned above ($p>0.05$). In addition, no evidence of heterogeneity (effect modification) was observed between potential confounders and the association between treatment (Ovaleap versus Gonal-f) and OHSS incidence ($p>0.05$), and neither Ovaleap nor Gonal-f treatment was favoured in terms of OHSS incidence ($p>0.05$).

The multivariate logistic regression analysis was not performed as an insufficient number of OHSS events was observed during the study.

11.1.3 Severity of Ovarian Hyperstimulation Syndrome

Overall, the majority of patients with OHSS were of Grade I (mild) or Grade II (moderate) level in the two treatment groups: 14 patients (3%) of Grade I (mild) and 5 patients (1%) of Grade II (moderate) in the Ovaleap arm, and 8 patients (2%) of Grade I (mild) and 4 patients (<1%) of Grade II (moderate) in the Gonal-f arm. Two patients (<1%) in the Ovaleap arm and 1 patient (<1%) in the Gonal-f arm experienced Grade III (severe) OHSS during the study. No statistically significant difference ($p=0.865$) was observed in OHSS severity grades between the two treatment groups. Similar results were also observed between the two treatment groups in Belgium, France, Germany, Italy, Spain, and the United Kingdom.

11.1.4 Adverse Events/Adverse Drug Reactions

Overall, 80 patients (20%) experienced 96 cases of AEs in the Ovaleap arm and 58 patients (14%) experienced 64 cases of AEs in the Gonal-f arm. The most common AE SOC in the Ovaleap and Gonal-f arm was investigations (27 patients [7%] versus 18 patients [4%]), followed by reproductive system and breast disorders (24 patients [6%] versus 17 patients [4%]), and pregnancy, puerperium and perinatal conditions (20 patients [5%] versus 15 patients [4%]). The most common AE PT in the Ovaleap and Gonal-f arms was OHSS (21 patients [5%] versus 13 patients [3%]), followed by antral follicle count high (20 patients [5%] versus 11 patients [3%]) and abortion spontaneous (13 patients [3%] versus 6 patients [1%]).

A total of 47 patients (12%) experienced 52 cases of drug-related AEs in the Ovaleap arm and 34 patients (8%) experienced 34 cases of drug-related AEs in the Gonal-f arm. The

two most common drug-related AE SOCs in the Ovaleap and Gonal-f arms were investigations (26 patients [6%] versus 17 patients [4%]), and reproductive system and breast disorders (20 patients [5%] versus 14 patients [3%]). The two most common drug-related AE PTs in the Ovaleap and Gonal-f arms were OHSS (20 patients [5%] versus 13 patients [3%]) and antral follicle count high (20 patients [5%] versus 10 patients [2%]).

SAEs were reported in 31 patients (8%) in the Ovaleap arm and 21 patients (5%) in the Gonal-f arm. The two most common SAE SOCs in the Ovaleap and Gonal-f arms were pregnancy, puerperium and perinatal conditions (19 patients [5%] versus 14 patients [3%]), and reproductive system and breast disorders (8 patients [2%] versus 5 patients [<1%]). The two most common SAE PTs were abortion spontaneous (13 patients [3%] versus 6 patients [1%]) and OHSS (7 patients [2%] versus 4 patients [<1%]).

Drug-related SAEs were reported in 7 patients (2%) in the Ovaleap arm and 4 patients (<1%) in the Gonal-f arm, and OHSS was the only drug-related SAEs reported in the two treatment groups.

Severe AEs were reported in 13 patients (3%) in the Ovaleap arm and 4 patients (<1%) in the Gonal-f arm, and OHSS was the only drug-related severe AEs reported in the two treatment groups (2 patients [<1%] versus 1 patient [<1%]).

Two patients (<1%) in the Ovaleap arm experienced 2 cases of AEs leading to study discontinuation, i.e., antral follicle count high and progesterone increased, and antral follicle count high was considered to be drug-related; 1 patient (<1%) in the Gonal-f arm experienced 1 case of drug-related AE leading to study discontinuation, i.e., ovarian cyst.

The most common AE PT related to pregnancy in the Ovaleap and Gonal-f arms was abortion spontaneous (13 patients [3%] versus 6 patients [1%]). They were in severity grades from mild to severe, but none of them was considered to be drug-related. All other AE PTs related to pregnancy were reported in 1 to 3 cases, and not considered to be drug-related.

No deaths were observed during the study.

11.1.5 Exposure

The mean (SD) durations of FSH treatment exposure in the Ovaleap and Gonal-f arms were 10.1 (2.02) days and 9.9 (1.94) days, respectively. Most of patients in the two treatment groups, i.e., 394 patients (97%) in the Ovaleap arm and 374 patients (91%) in the Gonal-f arm, remained on the same FSH treatment for the duration of the treatment cycle. The mean (SD) total doses received in the Ovaleap and Gonal-f arms were 2064.5 (805.38) IU and 2039.7 (855.13) IU, respectively. Overall, the FSH treatment exposures were generally comparable between the two treatment groups. Most of patients in the two treatment groups completed FSH treatment, including 382 patients (94%) in the Ovaleap arm and 390 patients (95%) in the Gonal-f arm.

The majority of patients in the two treatment groups used GnRH antagonist as the ovarian stimulation protocol, including 342 patients (84%) in the Ovaleap arm and 344 patients (84%) in the Gonal-f arm. Most of the patients performed oocyte maturation triggering, including 372 patients (91%) in the Ovaleap arm and 388 patients (95%) in the Gonal-f arm. The majority of patients performed oocytes retrieval under the current treatment, including 370 patients (91%) in the Ovaleap arm and 382 patients (93%) in the Gonal-f arm. Overall, ovulation triggering (i.e., ovarian stimulation protocol and oocyte maturation triggering) and oocytes retrieval were comparable between the two treatment groups.

The majority of patients underwent fresh embryo transfer during the study, including 256 patients (63%) in the Ovaleap arm and 274 patients (67%) in the Gonal-f arm. The median numbers of fresh embryos transferred were both 1 (ranges: 1 to 3) in the Ovaleap and Gonal-f arms. As of data cut-off, positive biochemical pregnancy was reported in 97 patients (24%) in the Ovaleap arm and 112 patients (27%) in the Gonal-f arm; positive vital pregnancy was reported in 84 patients (21%) in the Ovaleap arm and 87 patients (21%) in the Gonal-f arm. Embryo transfer practice did not have a statistically significant association with OHSS incidence differences between the two treatment groups (p=0.1627).

With respect to the ovarian stimulation medications, buserelin acetate (15 patients [4%] versus 14 patients [3%]) and triptorelin acetate (13 patients [3%] versus 11 patients [3%]) were the two most common medications in the GnRH agonist stimulation protocol in the Ovaleap and Gonal-f arms; ganirelix acetate (213 patients [52%] versus 186 patients [45%]) and cetrorelix (119 patients [29%] versus 130 patients [32%]) were the two most common medications in the GnRH antagonist stimulation protocol in the Ovaleap and Gonal-f arms.

With respect to oocyte maturation triggering, triptorelin was the most common drug product in GnRH agonist medications in the Ovaleap and Gonal-f arms (42 patients [10%] versus 39 patients [10%]); in hCG medications, choriogonadotropin alfa (206 patients [50%] versus 238 patients [58%]) and chorionic gonadotropin (107 patients [26%] versus 93 patients [23%]) were the two drug products in the Ovaleap and Gonal-f arms.

The most common medication for luteal support was progesterone (260 patients [64%] versus 274 patients [67%]) in the Ovaleap and Gonal-f arms.

A total of 155 patients (38%) in the Ovaleap arm and 158 patients (39%) in the Gonal-f arm received other concomitant medications. The most common therapeutic class in the Ovaleap and Gonal-f arm was sex hormones and modulators of the genital system (76 patients [19%] versus 95 patients [23%]), followed by thyroid therapy (34 patients [8%] versus 27 patients [7%]), antianemic preparations (25 patients [6%] versus 20 patients [5%]), and antithrombotic agents (21 patients [5%] versus 19 patients [5%]). The two most common drug PTs were menotrophin (42 patients [10%] versus 51 patients [12%]) and levothyroxine sodium (30 patients [7%] versus 25 patients [6%]).

11.2 Limitations

Selection bias may have been introduced with regards to the selection of the participating study centres or individuals who consented to participate or who completed the study. A total of 1147 patients were registered to participate in the study and 833 of them were enrolled after meeting the eligibility criteria. The characteristics of non-enrolled patients are unknown to compare with those of enrolled patients overall and within each country. This may have affected the representativeness of the sample selected and affected the generalizability of the findings as nonparticipation bias. Furthermore, selection bias may also have been introduced due to different site and patient numbers between the 6 European countries.

Many potential confounding factors may have had an impact on the difference in incidence of OHSS between the two treatment groups. To explore this further, an univariate logistic regression analysis was conducted to examine the association between each potential confounder and the incidence of OHSS (after adjusting for treatment). Confounding factors included in the univariate logistic regression model were selected based on their clinical relevance to OHSS and low expected pairwise correlations among each other.

The OR for treatment effect, after univariate adjustment for potential confounding factors, showed no statistically significant difference in OHSS incidence between the two treatment groups using the univariate logistic regression models. However, a limitation of the analysis was that due to the insufficient number of OHSS events, multivariate logistic regression analysis was not performed. Therefore, there is likely to be residual confounding in the results from the univariate analysis.

11.3 Interpretation

OHSS is one of the most common ADRs that occur during ART. During the study, 21 patients (5.1%) in the Ovaleap arm and 13 patients (3.2%) in the Gonal-f arm experienced OHSS (all grades of severity). The rate difference was not statistically significant (p=0.1589). The OR for treatment effect, after univariate adjustment for each potential confounder, also showed no statistically significant difference in OHSS incidence between the two treatment groups using the univariate logistic regression models. The potential confounders including country, PCOS, embryo transfer, antral follicle count, basal serum level of AMH, pregnancy, FSH dose reduction, and FSH treatment duration had a statistically significant association with OHSS incidence at the univariate level.

Only moderate or severe cases of OHSS would be considered clinically significant and relevant, and therefore prompt recognition of women with OHSS judged as moderate or severe is fundamental in OHSS management.[22] In this study, the majority of patients (14 out of 21 patients in the Ovaleap arm and 8 out of 13 patients in the Gonal-f arm) experienced mild OHSS. Moderate OHSS was observed in 5 patients (1%) in the Ovaleap arm and 4 patients (<1%) in the Gonal f arm, and severe OHSS was observed in 2 patients (<1%) in the Ovaleap arm and 1 patient (<1%) in the Gonal-f arm. These findings are

consistent with results obtained in a real-world, non-interventional German study which assessed the effectiveness and safety of Ovaleap in which the risk of OHSS was 5.0% (23/463): mild in 14 patients (3.0%), moderate in 8 patients (1.7%), and severe in 1 patient (0.2%).[23]

The Ovaleap arm had a relatively higher number and percentage of patients who experienced drug-related SAEs of OHSS than the Gonal-f arm (7 patients [2%] versus 4 patients [<1%]). However, the numbers and percentages of patients were both low in the two treatment groups. The incidences of AEs leading to study discontinuation were also low in the two treatment groups (2 patients [<1%] in the Ovaleap arm and 1 patient [<1%] in the Gonal-f arm). Finally, the most common AE PT related to pregnancy in the Ovaleap and Gonal-f arms was abortion spontaneous (13 patients [3%] versus 6 patients [1%]). They were in severity grades from mild to severe, but none of them were considered to be drug-related. Taken together, the safety profiles of Ovaleap and Gonal-f are generally comparable.

11.4 Generalisability

The sample size in this study had the sufficient statistical power to demonstrate the difference in OHSS incidence between the two treatment groups. Therefore, the primary outcome of the statistical analysis, i.e., no statistically significant difference in OHSS incidence rate between Ovaleap and Gonal-f, can be applicable to the general population in the participating countries treated with these medications.

The safety results of AEs/ADRs besides OHSS were also collected and compared between the two treatment groups. The preliminary results demonstrated comparable safety profiles between Ovaleap and Gonal-f.

12 OTHER INFORMATION

Not applicable; there is no additional or complementary information on specific aspects of the study.

13 CONCLUSIONS

The conclusions of this study are as follows:

- The enrolled patient demographics and baseline characteristics were well balanced between the Ovaleap and Gonal-f arms.
- No statistically significant difference in OHSS incidence rate was observed between the two treatment groups; the univariate logistic regression analysis supported this result.

- The potential confounders including country, PCOS, embryo transfer, antral follicle count, basal serum level of AMH, pregnancy, FSH dose reduction, and FSH treatment duration had a statistically significant association with OHSS incidence at the univariate level.

- The majority of patients experienced mild OHSS (14 out of 21 patients in the Ovaleap arm and 8 out of 13 patients in the Gonal-f arm). Moderate OHSS was observed in 5 patients (1%) in the Ovaleap arm and 4 patients (<1%) in the Gonal-f arm, and severe OHSS was observed in 2 patients (<1%) in the Ovaleap arm and 1 patient (<1%) in the Gonal-f arm. The safety profiles were generally comparable between the two treatment groups.

- The exposure of FSH treatments, ovarian stimulation medications, oocyte maturation triggering, luteal phase support, and other concomitant medications were also similar between the two treatment groups.

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15 POST-TEXT TABLES AND GRAPHICS

Table Number	Title
Summary 15.1.1	Patient Disposition by Treatment Group (All Enrolled Patients)
Summary 15.1.2	Patient Disposition by Country and Treatment Group (All Enrolled Patients)
Summary 15.2.1	Protocol Deviations (All Enrolled Patients)
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Summary 15.4.1	Relevant Medical History by Treatment Group (Full Analysis Set)
Summary 15.4.2	Relevant Medical History by Country and Treatment Group (Full Analysis Set)
Summary 15.4.3	Reproductive History by Treatment Group (Full Analysis Set)
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Summary 15.9.1	Ovulation Triggering and Oocyte Retrieval by Treatment Group (Full Analysis Set)
Summary 15.9.2	Embryo Transfer and Pregnancy Investigation by Treatment Group (Full Analysis Set)
Summary 15.10.1	Ovarian Stimulation Protocol Medications by Treatment Group (Full Analysis Set)
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APPENDICES

ANNEX 1 LIST OF STAND-ALONE DOCUMENTS

Number	Document	Date	Title
1.	Protocol Version 4.0 with Amendment 01, Study XM17-WH-50005	27 October 2016	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
2.	Letter of Clarification 01	09 May 2018	Letter of Clarification 01: Non-substantial Amendment to the Protocol
3.	Protocol Clarification Letter	15 November 2019	Protocol Clarification Letter Study Number: XM17-WH-50005
4.	Statistical Analysis Plan Version 1.2, Study XM17-WH-50005	16 January 2019	Statistical Analysis Plan
5.	Listings	22 July 2020	Listings
6.	List of Investigators	18 May 2020	List of Investigators
7.	SmPC of Gonal-f	04 July 2011	Summary of Product Characteristics

ANNEX 2 ADDITIONAL INFORMATION

Not applicable.