A phase IV prospective, multicentre, randomized, open-label trial to assess the efficacy and safety of GONAL f® at a dose based on subject baseline characteristics determined according to the CONSORT calculator compared with a standard dose of GONAL f® 150 IU per day for ovarian stimulation in women undergoing assisted reproductive technology (ART)

Published: 12-08-2008
Last updated: 06-05-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Sexual function and fertility disorders
Study type	Interventional

Summary

ID

NL-OMON32275

Source
ToetsingOnline

Brief title
CONSORT RCT in ART

Condition

- Sexual function and fertility disorders

Synonym
infertility;fertillity problem

Research involving
Human

Sponsors and support

Primary sponsor: Serono
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Assisted Reproductive Techniques(ART), CONSORT CALCULATOR, GONAL f®-pen, IVF

Outcome measures

Primary outcome

The primary efficacy endpoint will be measured by the total number of oocytes retrieved per subject following GONAL f® stimulation and human chorionic gonadotrophin (r hCG (Ovidrel®/Ovitrelle®) injection in both treatment arms.

Secondary outcome

The secondary efficacy endpoints will be measured in both treatment arms by: total dose of GONAL f® used (in IU), mean daily dose of GONAL f® (in IU), total number of GONAL f® stimulation treatment days, cycle cancellation for excessive or inadequate response to GONAL f®, number of biochemical pregnancies (by serum b hCG level), Number of foetal sacs and foetal hearts with activity as seen on an US scan on Day 35-42 post r hCG (to confirm clinical pregnancy), implantation rate (sacs with heartbeat per total number of embryos transferred), total and clinical pregnancy rate per subject (per cycle started,

and per ET), multiple pregnancy, levels of serum AMH (central laboratory

analysis),serum levels of progesterone (central laboratory analysis), genetic

variations associated with response to treatment.

Study description

Background summary

There have been a number of publications in which doctors have identified numerous variables, which are associated with the ovarian response in a stimulation cycle. To further address these associations, the Sponsor (Merck Serono International S.A.) has carried out an analysis of over 2000 ART treatment cycles available from studies carried out over a number of years. The combination of information from the publications and the analysis has revealed that the following 4 variables were highly associated with a patient*s ovarian response: Age, Body Mass Index, Number of small follicles, Serum Follicle Stimulating Hormone (FSH) level. These factors are then entered into a calculator, which provides a GONAL f® starting dose.

Study objective

The purpose of this trial is to compare the ovarian response in assisted reproductive technology (ART) subjects administered a GONAL-f® dose determined according to a calculator system versus a given standard GONAL-f® dose of 150 International Unit (IU) per day. The aim of this calculator, which is based on individual subject characteristics, is to help reduce an inappropriate response of the ovaries, thus resulting in improved stimulation treatment efficiency and safety

Study design

Patients who agree to take part in this trial, will be treated for one single stimulation cycle with GONAL f® Prefilled Pen. They will be asked to visit the centre approximately 9 times and your participation will last for a total duration of up to 20 weeks. All investments are standard practice for IVF treatments. The additional tests on behave of this study are added as follow. Once down-regulation has been confirmed, a pregnancy test will be performed within 7 days prior to GONAL f® treatment start to rule out any pre-existing pregnancy. If the result is negative, the subject will be randomly assigned to one of the two treatment arms of the trial via the electronic case report form (eCRF. .Follicular development will be monitored according to the centre*s standard practice by US and/or E2 levels, until the protocol r hCG requirement

is met (i.e., at least 1 follicle ³ 18 mm and 2 follicles ³ 16 mm) at which time the subject will receive a single injection of 250 mcg of r hCG (Ovidrel®/ Ovitrelle®), in order to induce final oocyte maturation. At a time of 34-38 hours after r hCG administration, oocytes will be recovered vaginally under US monitoring. Oocytes will then be fertilized in vitro and embryos replaced 2-5 days after oocyte recovery. Ovum Pick Up (OPU), in vitro fertilisation (IVF), ET and luteal support will be performed as per centre*s standard practice. A post-treatment safety visit will be performed for all subjects who received r hCG (pregnant and non-pregnant) on post-hCG Day 15-20. For subjects who have withdrawn from treatment (i.e. after starting GONAL f® but before hCG is given) this visit (excluding pregnancy testing) will take place 20-30 days after their first GONAL-f® treatment injection. At the end of the study cycle, between days 15 and 20 after the Ovidrel®/Ovitrelle® injection, you will have to visit the hospital/clinic for a serum pregnancy test (approximately 1.5 ml of blood will be taken).This is not routine and is in addition for this study. The subject will be given a diary card to keep a record of your injection dates and doses. You will report in the diary card any adverse event (i.e. any sign or symptom) you might experience and all medications, including self-prescribed medications that you are taking. This card is not routine and is added for this study. The subject can participate optional with the PGX study(pahrmacogenetica), for this one blood sample of 6 ml will be taken at screening visit.

Intervention

The investigational medicinal product is GONAL f® Prefilled Pen and will be self administered subcutaneously (s.c.) by the subject. The GONAL f® Prefilled Pen will be provided in dose presentations of 450 IU and 900 IU. The Prefilled Pen allows the accurate delivery of a precise dose of GONAL f® in 37.5 IU incrementsPending on the randomisation the patient will recieve: 1-to the CONSORT calculator arm (with doses of GONAL f® starting at minimum of 112.5 IU per day and a maximum of 450 IU per day). The allocated dose must be kept fixed throughout the stimulation cycle unless if, in the investigator*s judgement, the subject is at risk of OHSS, in which case the allocated dose may be decreased according to the centre*s standard practice. or-2- to the GONAL f® standard treatment arm (150 IU of GONAL f® per day) up to day 5 of stimulation (S5) after which the dose can be adjusted (increased or decreased) based upon the subject*s ovarian response and according to the centre*s standard practice.

Study burden and risks

Blood sampling is a standard procedure. It is safe and unlikely to cause you any problems although on occasion it can cause slight local discomfort. There is a slight risk of local pain, bruising, swelling or phlebitis (inflammation of the vein). Some patients may also experience light-headedness, dizziness and rarely fainting, and so you may choose to lay down for your blood draw. Very rarely, a local infection may develop. Transvaginal ultrasonography. This

procedure is standard in all IVF treatments. This procedure is usually painless.Like all medicines, GONAL-f® can cause side effects. During clinical development, the most commonly reported adverse events in association with GONAL f® were ovarian cysts, headaches and mild to severe injection site reactions (pain, redness, bruising, swelling, irritation at the injection site). A condition called ovarian hyperstimulation syndrome (OHSS) associated with various signs/symptoms such as abdominal pain, vomiting and diarrhea may also occur following treatment with GONAL-f®. Severe OHSS and its complications appear uncommon. Very rare cases of mild systemic allergic reactions to GONAL-f®, causing redness of the skin, rash, facial swelling have been reported. These reactions can sometimes be serious and manifest by one or more of the following signs/symptoms: hives, diffuse redness of the skin and edema, facial swelling and difficulty in breathing. Ectopic pregnancy (embryo implanted outside the womb) may occur especially in women with history of prior tubal disease. Like all medicines, Ovidrel®/Ovitrelle® can cause side effects. The majority of the side effects seen to date have been mild to moderate. The most frequent side effects reported have been tiredness, pain, local reaction at the site of injection and headache. Other less common side effects include: very rare systemic allergic reactions (redness of the skin, rash, facial swelling), usually mild but which may be serious and OHSS and its complications. Severe OHSS and its complications appear uncommon. Sometimes treatments for stimulation therapy with hFSH containing preparations for stimulation of ovulation induction lead to the growth of many follicles, which may be associated with the risk of enlargement of the ovaries. This is called Ovarian Hyperstimulation Syndrome (OHSS). In severe cases, this syndrome is associated with pelvic pain, nausea, vomiting, weight gain, abdominal distension, difficulty breathing and accumulation of fluid in the abdomen or lungs. Extremely rare complications associated with OHSS include bleeding into the abdomen (haemoperitoneum) due to rupture of an ovarian cyst, and a risk of the formation of blood clots (thrombosis) which potentially could be dislodged from the involved vein or artery and cause damage to vital organs such as the lungs, heart or brain. In a clinical trial like this one, every risk or side effect cannot be predicted. Each person's reaction to a test, drug or procedure may be different. There is maybe a side effect or be at risk for symptoms, illnesses and/or complications that could not be predicted by the study doctor or by the Sponsor of the trial.

Contacts

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Switzerland
Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Be a female subject justifying an IVF/ET treatment,
Be between her 18th and 35th birthday (35 not included) at the time of the randomisation visit,
A body mass index (BMI) < 30 kg/m2 where the BMI is calculated
Have early follicular phase (day 2-4) serum level of basal FSH £ 12 IU/L measured in the centre*s local laboratory during the screening period (i.e. within 2 months prior to down regulation start),

Exclusion criteria

Had >= 2 previous ART cycles with a poor response to gonadotrophin stimulation (defined as < 5 mature follicles and/or < 3 oocytes collected) or had >= 2 previous ART cycles with a hyper response (defined as ³ 25 oocytes retrieved),

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-09-2008
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	GONAL-f®
Generic name:	follitropin alpha
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-08-2008
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-02-2009
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-02-2009

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2008-001259-22-NL
CCMO	NL23707.091.08