A phase II, multicentre, randomised, assessor blinded, active-comparator, parallel-group dose finding trial to evaluate AS900672-Enriched versus follitropin alfa (GONAL-f) in oligo-anovulatory infertile women undergoing ovulation induction (OI)

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Sexual function and fertility disorders
Study type	Interventional

Summary

ID

NL-OMON31734

Source
ToetsingOnline

Brief title
AS900672-Enriched Phase II in OI

Condition

- Sexual function and fertility disorders

Synonym
no ovulation, oligo-anovulatory

Research involving
Human

Sponsors and support

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

Intervention

Keyword: AS900672-Enriched, GONAL-f®, oligo-anovulatory, ovulation induction

Outcome measures

Primary outcome

The primary efficacy endpoint is the ovulation rate.

Secondary outcome

The main secondary endpoint is the clinical pregnancy rate. Safety endpoints include the stimulation cycle cancellation rates for risk of OHSS and multiple pregnancy, the nature, incidence and severity of adverse events (AEs) and of injection site reactions, changes from baseline in vital signs and in clinical laboratory parameters, incidence and severity of OHSS, and incidence of multiple pregnancy.

Study description

Background summary

AS900672-Enriched has the same mechanism of action as recombinant human folliclestimulating hormone (r-hFSH) and endogenous FSH. FSH is produced by the pituitary and stimulates ovarian follicular growth and maturation during the follicular phase of the menstrual cycle. It acts on the granulosa cells of the ovarian follicles by promoting cell differentiation, LH receptor expression, stimulation of steroidogenesis, and aromatase activity. This contributes to the production of a single dominant follicle that is ovulated at mid-cycle and released into the fallopian tube, where it can be fertilised.

Clomiphene citrate (CC), an oral anti-oestrogen, is the first-line treatment. It restores ovulation in 60-85% of subjects and results in pregnancy in around 30-40% of them. Laparoscopic ovarian drilling, a surgical procedure by which the ovaries are punctured, is an alternative that is particularly effective in thin patients with high LH levels. Gonadotropins are the most common second-line therapy in patients who did not achieve pregnancy with CC. Among several available treatment protocols, the chronic low dose step-up protocol is widely used. Usually, the treatment duration is of 12 to 14 days. With this protocol, stimulation is started with a low FSH dose, which may be increased very slowly (but not before the first 14 days and then at intervals of not less than 7 days), by small amounts (usually 37.5 IU/day), up to a maximum of 225 IU/day. With a starting dose of 75 IU/day, a 70% mono-ovulation rate, 40% pregnancy rate, and 6% multiple pregnancy rate have been reported.
Merck Serono*s market research has shown that patients suffer from a high level of anxiety as they attempt to administer all of their medication correctly. Moreover, ease of drug delivery is a key driver in the choice of gonadotropin product. AS900672-Enriched is intended as a longacting FSH. It has a longer half-life than currently available FSH products and is therefore expected to decrease the total number of injections. This treatment simplification should increase patient convenience and decrease the risk of dosing errors. Based on the available data, a single AS900672-Enriched injection is expected to support ovarian stimulation for the first 6 to 7 days of the stimulation cycle and may then be followed by daily r-hFSH injections to achieve optimal follicular development.

Study objective

Primary objective
The primary objective of this trial is to identify the optimal effective dose of AS900672-Enriched to induce ovulation in oligo-anovulatory infertile women.

Secondary objectives
* To demonstrate that the clinical pregnancy rate of the optimal effective dose of
AS900672-Enriched is within the range of the clinical pregnancy rate obtained with
follitropin alfa daily dosing, and
* To evaluate safety and tolerability of AS900672-Enriched in oligo-anovulatory infertile
women undergoing OI.

Study design

This is a phase II, multicentre, randomised, assessor-blinded, active-comparator, parallelgroup dose finding trial to evaluate AS900672-Enriched versus follitropin alfa (GONAL-f®) in oligo-anovulatory

infertile women undergoing ovulation induction (OI). The trial will be conducted in three stages: i) an initial stage to define effective doses among the four tested doses of AS900672-Enriched, ii) a second stage to identify the optimal effective dose(s) of AS900672-Enriched, and iii) a final stage to gain additional pregnancy data for the selected optimal dose(s) of AS900672-Enriched. A Data Monitoring Committee (DMC) will review the results after the each of the first two stages and make recommendations on the dose(s) of AS900672-Enriched to be tested in the subsequent stage.
The AS900672-Enriched doses to be evaluated are 10, 20, 30 and 40 mcg, administered as a single injection, and, depending upon each subject*s ovarian response, followed by supplemental follitropin alfa 75 IU daily injections, which may begin on stimulation day 7. Subjects enrolled in the comparator arm will receive daily injections of follitropin alfa (GONAL-f®) 75 IU.
Oligo-anovulatory infertile women who are candidates for OI will be prospectively screened for enrolment. Each subject will be allowed one treatment cycle. Treatment will begin on stimulation day 1 (S1), corresponding to day 3 or 4 of an induced
menstrual cycle, at which time the subject will be randomised to receive either one of four doses of AS900672-Enriched or follitropin alfa (GONAL-f®) 75 IU daily injections.Subjects will return to clinic for monitoring of ovarian response on stimulation day 5 (S5), stimulation day 7 (S7), as well as when deemed necessary by the Investigator (Sn). Beginning on S7, and depending upon each subject*s ovarian response, subjects randomised to AS900672-Enriched may receive supplemental r-hFSH, given as follitropin alfa 75 IU daily injections. Ovarian stimulation treatment will continue in all treatment arms until criteria for hCG administration are met or to a maximum of 14 days (S14), unless ovarian response is imminent (i.e. a clinically relevant rise in oestradiol (E2) above baseline), in which case stimulation treatment can continue for 1 or 2 additional days, as judged by the Investigator.
Recombinant hCG (r-hCG) will be administered when the ovarian ultrasound scan shows <= 3 follicles with a mean diameter of >= 14 mm and of these 1 or 2 have a mean diameter of >= 17 mm. A single injection of r-hCG 250 mcg will be given to induce ovulation. Insemination will take place via intercourse and/or intrauterine insemination (IUI) within 48
hours following r-hCG administration. No luteal support will be given. Blood sampling for progesterone (P4) levels will be performed 5 to 7 days and, again, 8 to10 days, post-hCG administration, with 3 days between samplings.
All subjects will return to the trial centre for a post-treatment follow-up visit on day 15 to 20 post-hCG. Subjects with a positive pregnancy test (beta-hCG > 10 IU/L) will undergo an ultrasound 35 to 42 days post-hCG to confirm clinical pregnancy.
Throughout the treatment period, samples will also be collected from all subjects for a population pharmacokinetic (PK) and pharmacodynamic (PD) analysis.

Intervention

This trial will be conducted in tree stages. During the first stage (define effetive doses) there are 5 groups: one group will inject the comparator GONAL-f® daily, the other 4 groups will be injected with respectively a single dose of 10, 20, 30 or 40 microgram AS900672-Enriched (followed by supplemental GONAL-f® injections). In the second stage the most ineffective dose(s) of AS900672-Enriched will be dropped out to continue to compare GONAL-f® with the other doses of AS900672-Enriched to identify the optimal effective dose. In the third stage additional pregnancy data will be gained with again the remaining doses after the second stage.

Study burden and risks

Based on the results of the phase I trial, AS900672-Enriched appears to be well tolerated. Based upon the results of non-clinical testing, a teratogenic potential exists. Therefore, tests will be performed to exclude pregnancy prior to initiating therapy with AS900672-Enriched. No anti-AS900672-Enriched antibodies were detected in the phase I trial. It may, however, be that when exposing a higher number of subjects to the compound, as will be done in this phase II trial, an immune response could be revealed, although this is highly unlikely after exposure to a single injection. Furthermore, the compound*s longer elimination half-life may lead to an increased incidence of OHSS or, in order to prevent hyperstimulation, to a higher incidence of cycle cancellation, compared to follitropin alfa treatment. Given the early stage of development of AS900672-Enriched, it is unknown whether subjects can expect any clinical benefit from taking part in this trial, compared to the standard care of therapy and in terms of pregnancy rate. Based on the phase I results, AS900672-Enriched is able to stimulate multiple follicular development. However it remains to be demonstrated whether AS900672-Enriched treatment will induce ovulation in oligo-anovulatory women, given the high variability of ovarian response in this population, and whether the obtained pregnancy rate is clinically acceptable.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Oligo-anovulation defined by a menstrual period duration of 35 days to 6 months,
2. Spontaneous menses or a positive response to progestin or clomiphene citrate withdrawal within the prior 6 months,
3. Aged between 18 and 36 years, inclusive, at time of informed consent signature,
4. Body mass index 18 to 30 kg/m2, inclusive,
5. Early follicular phase serum TSH, DHEA-S, prolactin, and FSH within the normal range for the central laboratory,
Exception: Subjects with low TSH level who receive replacement therapy can be enrolled at the discretion of the investigator if local laboratory results (T4) demonstrate satisfactory thyroid function,
6. Fasting glucose and fasting insulin within the normal range for the central laboratory,
7. Normal uterine cavity and presence of at least one ovary with ipsilateral patent fallopian tube, as determined by means of HSG and/or laparoscopy-hysteroscopy within the prior 3 years,
8. PAP smear test without clinically significant abnormalities within 6 months prior to randomisation,
9. Negative pregnancy test prior to randomisation,
10. Male partner with semen analysis demonstrating adequacy for insemination via intercourse and/or IUI within 6 months prior to randomisation,
Note: Use of donor sperm is not allowed,
11. Willing and able to comply with the protocol,
12. Voluntary provision of written informed consent, prior to any trial-related procedure that was not part of normal medical care, with the understanding that the subject can withdraw consent at any time without prejudice to her future medical care, including willingness to provide follow-up information on babies born as part of this trial.

Exclusion criteria

1. History of >= 2 consecutive gonadotrophin stimulation cycles that did not lead to ovulation,
2. History of clomiphene citrate stimulation cycles of which none led to ovulation,
3. Prior excessive response to gonadotrophin stimulation, defined as the development of L4 mature follicles (>17 mm) or cancellation of the OI cycle due to excessive follicular response after treatment with FSH at a dose of <= 75 IU/day,
4. Previous severe ovarian hyperstimulation syndrome (OHSS),
5. Administration of any gonadotrophin, clomiphene citrate, GnRH analogue, tamoxifen or aromatase inhibitors within the prior 30 days,
6. Laparoscopic ovarian drilling and/or ovarian cauterisation within the prior 6 months,
7. Any contraindication to pregnancy and/or to carrying pregnancy to term,
8. A clinical pregnancy that ended in a miscarriage within the prior 3 months,
9. History of >= 3 consecutive miscarriages, due to any cause,
10. Abnormal gynaecological bleeding of undetermined origin,
11. Clinically significant abnormal findings of the uterine cavity evident on a transvaginal pelvic ultrasound performed during screening,
12. Presence of endometriosis grade III * IV,
13. Ovarian cyst with a mean diameter of >25 mm and E2 > 80 pg/mL on the day of randomisation,
14. History of ovarian, uterine or mammary cancer,
15. Adrenal congenital hyperplasia, partial or complete enzymatic block,
16. Use of metformin related to infertility within the prior 2 months,
17. Known allergy or hypersensitivity to human gonadotrophin preparations or to compounds that are structurally similar to any of the other medications administered during the trial,
18. Any contra-indication to gonadotrophin therapy,
19. Known infection with human immunodeficiency virus (HIV), or positive hepatitis B surface antigen (HBsAg) or anti-hepatitis C antibodies in the trial subject or her male partner,
20. Any active substance abuse or history of drug, medication or alcohol abuse within the prior 5 years,

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	01-01-2008
Enrollment:	50
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	GONAL-f®
Generic name:	follitropin alpha
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	long acting FSH
Generic name:	AS900672-Enriched, hyperglycosylated recombinant human follicle stimulating hormone (r-hFSH)

Ethics review

Approved WMO

Date:	24-01-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	24-04-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2007-002823-34-NL
CCMO	NL19546.029.07