PLEASE NOTE: *This study has been imported from ClinicalTrials.gov without additional data checks.*

Trial Description

Title

Significance of the FSH Receptor Polymorphism p.N680S for the Efficacy of FSH Therapy of Idiopathic Male Infertility: a Pharmacogenetic Approach

Trial Acronym

[---]*

URL of the trial

[---]*

Brief Summary in Lay Language

CONDITION: Idiopathic male infertility In men with idiopathic infertility, the sperm DNA fragmentation index (DFI) within 12 weeks of FSH therapy and 12 weeks follow-up improves depending on the FSHR genotype as assessed by the non-synonymous SNP rs6166 (wild type or p.N680S).

This is a phase II b, multicenter, prospective, open label, one arm, clinical trial stratified according to the patient's genotype.

INTERVENTION: FSH therapy (150 I.U. sc every other day for 12 weeks) in infertile men who are homozygous for the wild-type FSHR or the p.N680S allele of the FSHR. Duration of intervention per patient: 12 weeks

Primary efficacy endpoint: Sperm DFI. Number of patients with an improvement in DFI > 60%
Key secondary endpoint(s): pregnancy, semen parameters, serum levels of inhibin B and AMH.

Brief Summary in Scientific Language

Male factor infertility is responsible for about 50% of cases of involuntary couple infertility and remains idiopathic in about half of the cases. At present, there are no consistently effective treatments for male idiopathic infertility. Since follicle-stimulating hormone (FSH) is fundamental for spermatogenesis, recombinant hFSH is

empirically used for male infertility treatment. The response to FSH, however, is highly variable and while sperm parameters improve in some patients, about 50% of the subjects do not clearly respond to FSH. Several studies were performed in the past and a recent Cochrane meta-analysis showed that FSH treatment of male idiopathic infertility overall significantly improves pregnancy rate. Nevertheless, no predictive marker of response to FSH, allowing a stratified therapeutic approach, was identified so far.

The sperm DNA fragmentation index (DFI) provides an estimation of genetic integrity of spermatozoa and was shown to improve significantly after FSH treatment. Therefore, DFI could be used as a pharmacodynamic marker of FSH in the male.

In women, the response to FSH varies depending on the FSH receptor (FSHR) genotype, as determined by the non-synonymous SNP rs6166, which exchanges the amino acid Asn to Ser in codon 680. This SNP is very common, with a minor allele frequency of 0.4. Women homozygous for Ser at amino acid position 680 of the FSHR are less sensitive to endogenous and exogenous FSH compared to those homozygous for Asn and require more FSH for multiple follicular growth and maturation in assisted reproduction. The investigators hypothesize that the variable response to FSH in unselected infertile men is due to a different individual sensitivity to FSH as determined by the common FSHR polymorphism rs6166. In particular the investigators will test the hypothesis that men homozygous for Asn at 680 (wild type) will respond better to exogenous FSH treatment in terms of sperm DFI compared to men homozygous for Ser, assessing sperm DFI as pharmacodynamic parameter of FSH.

Men with idiopathic infertility and normal serum FSH levels, candidate for treatment with FSH, will be recruited. Men with a sperm DFI > 15% will be included in the trial if carriers of the homozygous Asn/Asn or Ser/Ser at aminoacid position 680. The FSHR genotype will be assessed centrally and the physician will only receive the information whether the patient is eligible for entering the trial (i.e. homozygous) but both the physician and the patient will remain blind to the genotype. Human recombinant FSH (Gonal-f, Merck Serono) will be self-administered sc at the dose of 150 IU every other day for 12 weeks, followed by 12

weeks of observation (follow up). Changes in sperm DFI will be the primary end point and compared between the two arms. In addition, the effects on pregnancy rate and other clinical and hormonal parameters will be evaluated.

Should this pilot, proof-of-principle trial demonstrate that the response to FSH in male idiopathic infertility depends on FSHR genotype, larger interventional trials aiming at assessing the effects on pregnancy rate will be justified.

Do you plan to share individual participant data with other researchers?

[---]*

Description IPD sharing plan

[---]*

Organizational Data

- DRKS-ID: **DRKS00009485**
- Date of Registration in DRKS: **2015/10/23**
- Date of Registration in Partner Registry or other Primary Registry: **2015/01/16**
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **[---]***
- (leading) Ethics Committee Nr.: **[---]***

Secondary IDs

- EudraCT-No. (for studies acc. to Drug Law): **2010-020240-35**
- Primary Registry-ID: **NCT02349945 (ClinicalTrials.gov)**
- Sponsor-ID: **EudraCT 2010-020240-35 (Azienda USL Modena)**

Health condition or Problem studied

- Free text: **Male Infertility**
- ICD10: **N46 - Male infertility**

Interventions/Observational Groups

- Arm 1: **Drug: follitropin alpha**

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Non-randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **caregiver**
- Control: **[---]***
- Purpose: **Treatment**
- Assignment: **Parallel**
- Phase: **II-III**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **[---]***

Primary Outcome

- Sperm DFI; time frame: "after 12 weeks"

Secondary Outcome

- Sperm DFI (DNA Fragmentation Index); time frame: "Baseline"
- Sperm DFI; time frame: "after 24 weeks"

Countries of recruitment

- DE **Germany**
- IT **Italy**

Locations of Recruitment

- **Zentrums für Reproduktions-medizin und Andrologie Universitätsklinikum Halle (Saale), Martin-Luther-Universität Halle-Wittenberg, Halle**

Recruitment

- Planned/Actual: **[---]***
- (Anticipated or Actual) Date of First Enrollment: **2011/01/31**
-

Planned/Actual: **[---]***

(Anticipated or Actual) Date of First Enrollment: **2011/01/31**

Target Sample Size: **88**

- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **International**

Inclusion Criteria

- Gender: **Male**
- Minimum Age: **20 Years**
- Maximum Age: **50 Years**

Additional Inclusion Criteria

- age 20-50 years

- idiopathic male factor infertility for at least one year;

- homozygous FSHR allele at codon 680 (wild type: Asn/Asn or Ser/Ser);

- sperm DFI > 15%;

- normal serum FSH levels (< 8 IU/L)

- normal serum LH, testosterone, prolactin and estradiol levels

- normal ovulatory female partner These men might have impaired ejaculate parameters (decreased sperm count and/or decreased proportion of sperm with progressive motility and/or decreased proportion of sperm with normal morphology) of unknown aetiology.

Exclusion criteria

- azoospermia

- all known aetiologies of male infertility (endocrine disorders, genetic disorders, chromosome abnormalities, congenital bilateral absence of the vas deferens, microdeletions within the AZF regions of the Y chromosome, varicocele, cryptorchidism, infections, immunological infertility, and obstructive infertility)

- all known aetiologies of female infertility in the partner (tubal blockage, endocrine abnormalities including anovulation and PCO, anatomical abnormalities,

infections)

- **heterozygous FSHR allele at codon 680**
- **drug abuse and major systemic diseases**
- **testicular insufficiency**

Addresses

■ **Primary Sponsor**

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Sources of Monetary or Material Support

- **[---]***

  Bitte wenden Sie sich an den Sponsor / Please refer to primary sponsor

  Telephone: **[---]***
  Fax: **[---]***
  E-mail: **[---]***
  URL: **[---]***

Status

- Recruitment Status: **Recruiting complete, follow-up continuing**
-

Study Closing (LPLV): **[---]***

Trial Publications, Results and other documents

The parameters in ClinicalTrials.gov and DRKS are not identical. Therefore the data import from ClinicalTrials.gov required adjustments. For full details please see the DRKS FAQs.

- Translation on version: 3

- Last processed date by ClinicalTrials.gov: 2016/01/14

Please note:
There are additional attributes available concerning this trial. To open an extended view please click here.