

## **RU-COH**

### **Anti-progestin used as oral GnRH-antagonists**

Pantarhei Bioscience has discovered a new, orally active GnRH-antagonist. Obviously, this compound has therefore a major advantage over existing parenteral compounds, such as Cetrotide® and Orgalutran/Antagon®.

#### Back-ground

Controlled ovarian hyperstimulation (COH) protocols to induce multiple follicle growth for in-vitro fertilization (IVF) include the administration of exogenous gonadotropins and a gonadotropin-releasing hormone (GnRH) analogue to prevent premature LH surges. Premature LH surges are detrimental to adequate follicular development and lead to cycle cancellation.

A long GnRH agonist protocol is currently the most widely used COH regimen, which has proven to be safe and effective. In recent years, GnRH antagonists were introduced to replace GnRH agonists in the prevention of premature LH surges. GnRH antagonist treatment has also shown to be safe and effective. A major benefit of GnRH antagonist treatment is the short duration of treatment as compared to GnRH agonist treatment in the long protocol. GnRH antagonists are administered either from a fixed day of stimulation onwards, mostly from Day 6 onwards, or from a pre-set follicular diameter, mostly >14 mm, onwards. As a result, this co-treatment is on average used for 4 to 7 days in most cases rather than the approximately 3 weeks administration of GnRH agonist. A major drawback of both GnRH agonist and GnRH antagonist treatment is the parenteral administration through subcutaneous injections, which contributes to the burden to women undergoing IVF.

#### Concept

In search of new methods taking into account the successful results with central inhibition by GnRH agonist or antagonist treatment, Pantarhei Bioscience developed the concept of using antiprogestins as an oral GnRH antagonist for the prevention of premature LH surges during COH.

Apart from a more convenient mode of administration in a stressful situation to patients, Pantarhei Bioscience also hypothesized that antiprogestins may further improve the results of COH and IVF±ICSI as it is known that premature LH surges are not completely ruled out despite treatment with a GnRH agonist (or antagonist) and late follicular (slowly) increasing serum progesterone levels prior to induction of final oocyte maturation even without a clear LH surge can be observed in some patients that may lead to premature luteinization and out-phasing the endometrium thus compromising implantation. It has been shown that administration of progesterone before oocyte retrieval negatively affects the implantation rate, which would further support the use of antiprogestins in a stimulation protocol.

#### Proof-of-principle

The concept was clinically investigated in a small-scale feasibility study performed in a leading IVF clinic in Europe comparing co-administration of mifepristone in a standard stimulation protocol and a GnRH agonist in a long protocol as a reference. The study has been conducted under the supervision of an opinion leader in the field of infertility.

Intriguing results were obtained showing very effective central inhibition employing a very low dose of mifepristone. Most likely, the dose can and should be further reduced without compromising efficacy for which a dose-finding study is required. No safety concerns emerged.

#### Next step

A dose finding study will be the next clinical step, thereafter a standard phase III study.

#### Future market

The use of anti-progestogens (e.g.: mifepristone, compound is off patent) could lead to a treatment method, with the following advantages:

1. oral administration;
2. prevention of LH-surge;
3. potential improvement of implantation rates.

This will lead to a medical superior method, with a higher patient compliance rate, with a low side effect profile (if any) and very cost effective (low COG). Potentially this results in a dominant market position.

#### Patent application

PRB has filed a patent application on the concept of using anti-progestins in general, to suppress the LH-surge. The PCT-application has been published under number WO 03/055524

#### Publication

The concept, a proof-of-principle study and study results have been published in the *Journal of Clinical Endocrinology & Metabolism*: Mifepristone is an effective oral alternative for the prevention of premature luteinizing hormone surges and/or premature luteinization in women undergoing Controlled Ovarian Hyperstimulation for in vitro fertilization. Ernesto L. Escudero, et al., JCEM 90(4):2081-2088, 2005

Comment of reviewer 1: *This is a very interesting study of a concept that could have marked utility in in vitro fertilization if the therapy could be fine tuned.*

Comment of reviewer 2: *Overall this is an interesting description of a novel study.*

#### Partnering

PRB is looking for a partner that is willing to develop the concept further and subsequently will take care of the commercialization.