Predictive Factors for Ovarian Stimulation Using a Fixed Daily Dose of 200 IU Recombinant FSH (Study 142003)(P05696) (Xpect)

This study has been completed.

Sponsor:
Merck Sharp & Dohme Corp.

Information provided by (Responsible Party):
Merck Sharp & Dohme Corp.

ClinicalTrials.gov Identifier:
NCT00778999

First received: October 23, 2008
Last updated: November 14, 2014
Last verified: November 2014
History of Changes

Purpose

The success of assisted reproductive technologies (ART) is critically dependent on optimizing protocols for controlled ovarian stimulation to provide adequate numbers of good quality oocytes and embryos. This optimization is mainly valuable to a group of infertility patients (9%-24%) who respond poorly to Controlled Ovarian Stimulation(COS). It is also important for an additional 2.6% of the infertility patients who manifest a high response to gonadotropin and are at risk for hyperstimulation syndrome, a life-threatening situation. Extensive research was carried out and led to the introduction of GnRH antagonist, as an alternative to Gonadotropin Releasing Hormone (GnRH) agonist, for the prevention of premature Luteinizing Hormone (LH) surges. Further research to optimize the GnRH antagonist regimen concluded that a daily treatment with 200 IU of recombinant Follicle Stimulating Hormone (recFSH) in a GnRH antagonist regimen is safe, well tolerated and results in a good clinical outcome. This protocol is now frequently applied in the US and Europe.

Predicting a woman's response (based on the assessment of ovarian reserve) to COS is useful in determining individualized clinical management strategies for low and high responders and thus avoiding cancellation. Such prediction when based on reliable scientific evidence is valuable in consulting patients about their chances of success. A large number of studies have been performed, which used certain clinical, ultrasonographic and hormonal markers (called predictive factors), to try to optimize a COS protocol for patients who were down-regulated with a long GnRH agonist protocol. Prospective trials of predictive models have also been used to adjust the starting dose of FSH to prevent a too low or too high ovarian response. To date, however, none have been performed for women undergoing ovarian stimulation with a GnRH antagonist protocol.

The primary objective of this randomized, open-label, multicenter clinical trial was to identify one or more factors capable of predicting ovarian response in women treated with a daily dose of 200 IU recFSH in a GnRH antagonist protocol. Since many ART centers now use oral contraceptives as a means to schedule patients stimulated with recFSH and a GnRH antagonist for assisted reproduction, the trial evaluated also whether intervention with oral contraceptives affects the accuracy of predictive models for ovarian response.

Condition	Intervention	Phase
Infertility	Drug: Marvelon	Phase 4

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label

Primary Purpose: Treatment

Official Title: A Randomized, Open-Label Clinical Trial to Identify Predictive Factors for Controlled Ovarian Stimulation Using a Fixed Daily Dose of 200 IU Recombinant FSH in GnRH Antagonist Regimen With or Without Oral Contraceptive Scheduling

Resource links provided by NLM:

MedlinePlus related topics: Infertility

U.S. FDA Resources

Further study details as provided by Merck Sharp & Dohme Corp.:

Primary Outcome Measures:

- Total Number of Oocytes [Time Frame: 12 weeks] [Designated as safety issue: No]
  The total number of oocytes on the Day of oocyte pick-up is an indication of ovarian response

Secondary Outcome Measures:

- Number of Mature Oocytes [Time Frame: 12 weeks] [Designated as safety issue: No]
  This is not a prespecified key secondary outcome; therefore, results will not be disclosed.
- Number of Follicles on Stimulation Day 8 [Time Frame: 12 weeks] [Designated as safety issue: No]
  This is not a prespecified key secondary outcome; therefore, results will not be disclosed.
- Number of Follicles on Day of hCG [Time Frame: 12 weeks] [Designated as safety issue: No]
  This is not a prespecified key secondary outcome; therefore, results will not be disclosed.
- Number of Fertilized (2PN) Oocytes [Time Frame: 12 weeks] [Designated as safety issue: No]
  This is not a prespecified key secondary outcome; therefore, results will not be disclosed.
- Number of Good Quality Embryos [Time Frame: 12 weeks] [Designated as safety issue: No]
  This is not a prespecified key secondary outcome; therefore, results will not be disclosed.

Enrollment:	442
Study Start Date:	October 2006
Study Completion Date:	July 2008
Primary Completion Date:	July 2008 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Active Comparator: Oral Contraceptive Use of oral contraceptive pills prior to controlled ovarian stimulation	Drug: Marvelon oral contraceptive 1 tablet daily for 14 to 21 days
No Intervention: Non-Oral Contraceptive No use of oral contraceptive pills prior to controlled ovarian stimulation	

Eligibility

Ages Eligible for Study:	18 Years to 39 Years
Genders Eligible for Study:	Female
Accepts Healthy Volunteers:	Yes

Criteria

Inclusion Criteria:

- Females of couples with an indication for In Vitro Fertilization (IVF) and/or Intracytoplasmic Sperm Injection (ICSI) scheduled for their first COS treatment cycle
- Females >18 and <=39 years of age at the time of signing informed consent
- Body Mass Index (BMI) <= 32 kg/m^2
- Normal menstrual cycle length; 24-35 days
- Availability of ejaculatory sperm (use of donated and/or cryopreserved sperm is allowed)
- Willing and able to sign informed consent

Exclusion Criteria:

- History of/or any current endocrine abnormality
- Less than 2 ovaries or any other ovarian abnormality (inc.>10mm endometrioma)
- Presence of unilateral or bilateral hydrosalpinx
- Presence of any clinically relevant pathology affecting the uterine cavity or fibroids >= 5cm
- History of recurrent miscarriage (3 or more, even when unexplained)
- FSH or LH > 12 IU/L as measured by a local laboratory (sample taken during the early follicular phase: menstrual day 2-5)
- Any clinically relevant abnormal laboratory value (FSH, LH, estradiol (E2), Progesterone (P), total Testosterone (T), prolactin, Thyroid Stimulating Hormone (TSH), blood biochemistry, hematology and urinalysis) based on a sample during the screening phase.
- Contraindications for the use of gonadotropins (tumors, pregnancy, lactation, undiagnosed vaginal bleeding, hypersensitivity, ovarian cysts)
- Contraindications for the use of oral contraceptive pills (history of (h/o) thromboembolism, breast cancer, undiagnosed vaginal bleeding)
- Recent history of/or current epilepsy, Human Immunodeficiency Virus (HIV) infection, diabetes, cardiovascular, gastrointestinal, hepatic, renal or pulmonary disease
- Abnormal karyotyping of the patient or her partner (if karyotyping is performed)
- History or presence of alcohol or drug abuse within 12 months of signing the consent
- Use of hormonal preparations within one month prior to randomization
- Hypersensitivity to any of the concomitant medication prescribed as part of the treatment regimen in this protocol
- Administration of investigational drugs within three months prior to signing the informed consent

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

No Contacts or Locations Provided

More Information

Publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):

Broekmans FJ, Verweij PJ, Eijkemans MJ, Mannaerts BM, Witjes H. Prognostic models for high and low ovarian responses in controlled ovarian stimulation using a GnRH antagonist protocol. Hum Reprod. 2014 Aug;29(8):1688-97. doi: 10.1093/humrep/deu090. Epub 2014 Jun 5.

Andersen AN, Witjes H, Gordon K, Mannaerts B; Xpect investigators. Predictive factors of ovarian response and clinical outcome after IVF/ICSI following a rFSH/GnRH antagonist protocol with or without oral contraceptive pre-treatment. Hum Reprod. 2011 Dec;26(12):3413-23. doi: 10.1093/humrep/der318. Epub 2011 Sep 27.

Responsible Party:	Merck Sharp & Dohme Corp.
ClinicalTrials.gov Identifier:	NCT00778999 History of Changes
Obsolete Identifiers:	NCT00628641
Other Study ID Numbers:	P05696 142003
Study First Received:	October 23, 2008
Results First Received:	June 23, 2009
Last Updated:	November 14, 2014
Health Authority:	United States: Food and Drug Administration

Additional relevant MeSH terms:

Contraceptive Agents	Physiological Effects of Drugs

Contraceptives, Oral
Contraceptive Agents, Female
Pharmacologic Actions

Reproductive Control Agents
Therapeutic Uses

ClinicalTrials.gov processed this record on May 08, 2016

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Results First Received: June 23, 2009

Study Type:	Interventional
Study Design:	Allocation: Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Parallel Assignment; Masking: Open Label; Primary Purpose: Treatment
Condition:	Infertility
Intervention:	Drug: Marvelon

Participant Flow

Hide Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
No text entered.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
No text entered.

Reporting Groups

	Description
Oral Contraceptive	

	Use of oral contraceptive pills prior to controlled ovarian stimulation
Non-Oral Contraceptive	No use of oral contraceptive pills prior to controlled ovarian stimulation

Participant Flow: Overall Study

	Oral Contraceptive	Non-Oral Contraceptive
STARTED	**223**	**219**
COMPLETED	**195**	**185**
NOT COMPLETED	**28**	**34**
Discontinuation: no embryo transfer	**14**	**14**
Did not receive recFSH	**14**	**20**

Baseline Characteristics

Hide Baseline Characteristics

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
No text entered.

Reporting Groups

	Description
Oral Contraceptive	Use of oral contraceptive pills prior to controlled ovarian stimulation
Non-Oral Contraceptive	No use of oral contraceptive pills prior to controlled ovarian stimulation
Total	Total of all reporting groups

Baseline Measures

	Oral Contraceptive	Non-Oral Contraceptive	Total
Number of Participants [units: participants]	**223**	**219**	**442**
Age [units: participants]			
<=18 years	**0**	**0**	**0**
Between 18 and 65 years	**223**	**219**	**442**
>=65 years	**0**	**0**	**0**
Gender [units: participants]			
Female	**223**	**219**	**442**
Male	**0**	**0**	**0**

Outcome Measures

1. Primary: Total Number of Oocytes [Time Frame: 12 weeks]

Hide Outcome Measure 1

Measure Type	Primary
Measure Title	Total Number of Oocytes
Measure Description	The total number of oocytes on the Day of oocyte pick-up is an indication of ovarian response
Time Frame	12 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-treat, defined as all randomized subjects who received recombinant follicle stimulating hormone

Reporting Groups

	Description
Oral Contraceptive	Use of oral contraceptive pills prior to controlled ovarian stimulation
Non-Oral Contraceptive	No use of oral contraceptive pills prior to controlled ovarian stimulation

Measured Values

	Oral Contraceptive	**Non-Oral Contraceptive**
Number of Participants Analyzed [units: participants]	**209**	**199**
Total Number of Oocytes [units: Number of oocytes] Mean (Standard Deviation)	**12.4 (6.7)**	**12.1 (7.7)**

No statistical analysis provided for Total Number of Oocytes

2. Secondary: Number of Mature Oocytes [Time Frame: 12 weeks]

Results not yet reported. Anticipated Reporting Date: No text entered. **Safety Issue:** No

3. Secondary: Number of Follicles on Stimulation Day 8 [Time Frame: 12 weeks]

Results not yet reported. Anticipated Reporting Date: No text entered. **Safety Issue:** No

4. Secondary: Number of Follicles on Day of hCG [Time Frame: 12 weeks]

Results not yet reported. Anticipated Reporting Date: No text entered. **Safety Issue:** No

5. Secondary: Number of Fertilized (2PN) Oocytes [Time Frame: 12 weeks]

Results not yet reported. Anticipated Reporting Date: No text entered. **Safety Issue:** No

6. Secondary: Number of Good Quality Embryos [Time Frame: 12 weeks]

Results not yet reported. **Anticipated Reporting Date:** No text entered. **Safety Issue:** No

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	No text entered.
Additional Description	No text entered.

Reporting Groups

	Description
Oral Contraceptive	Use of oral contraceptive pills prior to controlled ovarian stimulation
Non-Oral Contraceptive	No use of oral contraceptive pills prior to controlled ovarian stimulation

Serious Adverse Events

	Oral Contraceptive	Non-Oral Contraceptive
Total, serious adverse events		
# participants affected / at risk	**10/209 (4.78%)**	**9/199 (4.52%)**
Gastrointestinal disorders		
Colitis ulcerative †		
# participants affected / at risk	**1/209 (0.48%)**	**0/199 (0.00%)**
# events	**1**	**0**
Pancreatitis †		
# participants affected / at risk	**1/209 (0.48%)**	**0/199 (0.00%)**
# events	**1**	**0**
Pregnancy, puerperium and perinatal conditions		
Abortion spontaneous †		
# participants affected / at risk	**0/209 (0.00%)**	**1/199 (0.50%)**
# events	**0**	**1**
Antepartum haemorrhage †		
# participants affected / at risk	**1/209 (0.48%)**	**0/199 (0.00%)**
# events	**1**	**0**
Ectopic pregnancy †		
# participants affected / at risk	**2/209 (0.96%)**	**2/199 (1.01%)**
# events	**2**	**2**
Retroplacental haematoma †		
# participants affected / at risk	**1/209 (0.48%)**	**1/199 (0.50%)**
# events	**1**	**1**
Ruptured ectopic pregnancy †		

# participants affected / at risk	2/209 (0.96%)	1/199 (0.50%)
# events	2	1
Reproductive system and breast disorders		
Ovarian cyst †		
# participants affected / at risk	0/209 (0.00%)	1/199 (0.50%)
# events	0	1
Ovarian cyst ruptured †		
# participants affected / at risk	1/209 (0.48%)	0/199 (0.00%)
# events	1	0
Ovarian hyperstimulation syndrome †		
# participants affected / at risk	2/209 (0.96%)	3/199 (1.51%)
# events	2	3
Surgical and medical procedures		
Abortion induced †		
# participants affected / at risk	1/209 (0.48%)	0/199 (0.00%)
# events	1	0

† Events were collected by systematic assessment

Other Adverse Events

Hide Other Adverse Events

Time Frame	No text entered.
Additional Description	No text entered.

Frequency Threshold

Threshold above which other adverse events are reported	5%

Reporting Groups

	Description
Oral Contraceptive	Use of oral contraceptive pills prior to controlled ovarian stimulation
Non-Oral Contraceptive	No use of oral contraceptive pills prior to controlled ovarian stimulation

Other Adverse Events

	Oral Contraceptive	Non-Oral Contraceptive
Total, other (not including serious) adverse events		
# participants affected / at risk	88/209 (42.11%)	81/199 (40.70%)
Gastrointestinal disorders		
Nausea †		

# participants affected / at risk	8/209 (3.83%)	15/199 (7.54%)
# events	8	18
Injury, poisoning and procedural complications		
Procedural pain †		
# participants affected / at risk	53/209 (25.36%)	45/199 (22.61%)
# events	55	45
Nervous system disorders		
Headache †		
# participants affected / at risk	17/209 (8.13%)	12/199 (6.03%)
# events	23	12
Pregnancy, puerperium and perinatal conditions		
Abortion spontaneous †		
# participants affected / at risk	8/209 (3.83%)	12/199 (6.03%)
# events	8	12
Antepartum haemorrhage †		
# participants affected / at risk	11/209 (5.26%)	9/199 (4.52%)
# events	14	13
Reproductive system and breast disorders		
Ovarian hyperstimulation syndrome †		
# participants affected / at risk	5/209 (2.39%)	11/199 (5.53%)
# events	5	11
Pelvic discomfort †		
# participants affected / at risk	20/209 (9.57%)	14/199 (7.04%)
# events	21	16
Pelvic pain †		
# participants affected / at risk	18/209 (8.61%)	14/199 (7.04%)
# events	20	14

† Events were collected by systematic assessment

Limitations and Caveats

Hide Limitations and Caveats

Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data
No text entered.

More Information

Hide More Information

Certain Agreements:

Principal Investigators are **NOT** employed by the organization sponsoring the study.
There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.
The agreement is:

☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed.

☑ **Restriction Description:** Sponsor recognizes the right of the investigator(s) to publish, but all communication concerning the clinical trial must be based on data validated and released and will first be submitted to the Sponsor for written consent, which shall not be withheld unreasonably. Sponsor is free to use the data for publication. The investigator(s) may be invited to be co author(s). In any communication concerning this clinical trial, the author(s) of this protocol will be included in the list of authors.

Results Point of Contact:

Name/Title: Senior Vice President, Global Clinical Development
Organization: Merck Sharp & Dohme Corp.
e-mail: ClinicalTrialsDisclosure@merck.com

Publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):

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