Oral follicle-stimulating hormone agonist tested in healthy young women of reproductive age failed to demonstrate effect on follicular development but affected thyroid function

Mireille G. F. Gerrits, Pharm.D.,[a,b] Hester Kramer, Ph.D.,[a] Rachid el Galta, Ph.D.,[a] Geertje van Beerendonk, Ph.D.,[a] Rob Hanssen, Ph.D.,[a] Khalid Abd-Elaziz, M.D.,[c] Christine Klipping, M.D., Ph.D.,[d] Ingrid Duijkers, M.D., Ph.D.,[d] and S. Aubrey Stoch, M.D.[b]

[a] MSD Netherlands, Oss, the Netherlands; [b] Merck & Co., Inc., Kenilworth, New Jersey; [c] QPS, Groningen, the Netherlands; and [d] Dinox, Groningen, the Netherlands

Objective: To assess the safety, pharmacokinetics, and pharmacodynamics of MK-8389.
Design: Double-blind, placebo-controlled, parallel-group, ascending dose study.
Setting: Two clinical research organizations.
Patient(s): Healthy young women.
Intervention(s): Once-daily oral doses of MK-8389 or placebo for 14 days.
Main Outcome Measure(s): Safety, including thyroid function tests (TFTs), pharmacokinetics, and follicular development (follicle size and number and serum E_2 and inhibin B levels).
Result(s): Treatment with MK-8389 was generally safe and well tolerated. An effect on TFTs was observed, which was transient and did not lead to clinical signs or symptoms but prevented dose escalation above 40 mg. MK-8389 was rapidly absorbed, slowly eliminated, and showed a large peak-to-trough ratio. No clinically meaningful effect was seen on follicle size and numbers, which was consistent with the low E_2 levels. At doses >20 mg, inhibin B levels were increased, suggesting early follicular development at higher doses.
Conclusion(s): Oral administration of MK-8389 demonstrated acceptable systemic exposure and was generally well tolerated. This study failed to demonstrate a clinically meaningful effect of MK-8389 on follicular development, whereas MK-8389 unexpectedly affected thyroid function. This study did not explore doses above 40 mg given the changes observed in TFTs, which may relate to high MK-8389 peak concentrations.
Clinical Trial Registration Number: EudraCT Number 2010-022396-57. (Fertil Steril® 2016;105:1056–62. ©2016 by American Society for Reproductive Medicine.)
Key Words: Follicular development, follicle-stimulating hormone, infertility, oral FSH agonist

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Received July 31, 2015; revised December 2, 2015; accepted December 15, 2015; published online January 6, 2016.
M.G.F.G. is a past employee of MSD Netherlands, Oss B.V., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, at the time of study, current consultant for Merck & Co., Inc., and may own stock or stock options in Merck. H.K. is a past employee of MSD Netherlands, Oss B.V., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, at the time of study and may own stock or stock options in Merck. R.e.G. is a past employee of MSD Netherlands, Oss B.V., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, at the time of study and may own stock or stock options in Merck. G.v.B. is a past employee of MSD Netherlands, Oss B.V., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, at the time of study and may own stock or stock options in Merck. R.H. is a past employee of MSD Netherlands, Oss B.V., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, at the time of study and may own stock or stock options in Merck. K.A.-E. is an employee of QPS-NL, a contract research organization (CRO) that received funding from MSD for the conduct of the study. C.K. is an employee of Dinox, a CRO that received funding from MSD for the conduct of the study. I.D. is an employee of Dinox, a CRO that received funding from MSD for the conduct of the study. S.A.S. is a current employee of Merck & Co., Inc., Kenilworth, NJ, may own stock or stock options in Merck.
Supported by Merck & Co., Inc., Kenilworth, NJ. The funding organization was involved in the following: design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the manuscript.
Reprint requests: Mireille G. F. Gerrits, Pharm.D., c/o S. Aubrey Stoch, Merck & Co., Inc., 126 E. Lincoln Ave., RY34-A214, Rahway, NJ 07065-0900 (E-mail: mireille.gerrits@merck.com).

Fertility and Sterility® Vol. 105, No. 4, April 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.12.017

Infertility is a medical condition that results in the inability of a couple to achieve pregnancy within a certain timeframe and has a prevalence of approximately 10% (1, 2). In many instances infertility is treatable. Approximately half of all infertile couples will eventually conceive a child either spontaneously or after therapeutic intervention (3). Therapy for infertility includes assisted reproductive technology (ART), using reproductive technology in women with ovulatory potential, or treating infertility by controlled ovarian stimulation (COS) using gonadotropins (e.g., FSH), including the use of technological procedures like IVF. Women with ovulatory disturbances can be treated using gonadotropins for ovulation induction (OI) as first-line treatment or as second-line treatment after initial treatment with clomiphene citrate.

Follicle-stimulating hormone is necessary for follicle development and acts by binding to the FSH receptor (4, 5). Urinary and recombinant FSH preparations are available that mimic endogenous FSH in COS and OI protocols (6). However, current therapy requires daily injection, which is both inconvenient for the patient and may affect treatment compliance, leading to stress and anxiety (7). The long-acting FSH agonist corifollitropin alfa (Elonva, MSD) replaces seven daily injections of recombinant FSH during the first week of ovarian stimulation and provides a more convenient and simplified treatment regimen, reducing the burden of multiple daily injections (8). To further facilitate ART, innovation in FSH administration has focused on nonparenteral administration, including orally active FSH agonists to be used in COS and OI. Given the challenge of developing high molecular weight proteins for oral administration, drug discovery has focused on low molecular weight (LMW) FSH-receptor agonist compounds.

MK-8389 is a LMW FSH agonist that was developed for the use in IVF protocols. This article describes a clinical trial with MK-8389 in healthy young female volunteers to determine the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of MK-8389 after oral administration.

MATERIALS AND METHODS

Study Design

The study had a double-blind, placebo-controlled, parallel-group, ascending dose design, to investigate the safety, tolerability, PK, and PD after dosing of MK-8389 once daily for up to 14 days. Dose groups were staggered to evaluate the safety and PD of a given dose level before escalation to the next higher dose level. The study was performed at QPS-NL, Groningen, the Netherlands, and gynecologic examinations, including transvaginal ultrasound scans, were outsourced to Dinox, Groningen, the Netherlands. The protocol (EudraCT Number 2010-022396-57) was approved by a local ethics committee (Stichting BEBO in Assen, the Netherlands) and by the Dutch regulatory agency before the start of the study. Subjects were recruited from the databases of QPS-NL and Dinox, and each subject provided written informed consent before participation in the study. The study was conducted in accordance with the Declaration of Helsinki, good clinical practice guidelines, and other statues or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

Subjects

Subjects in this study were healthy young women of childbearing potential, aged 18–39 years, with a body mass index (BMI) between 18 and 30 kg/m^2. Health status was assessed according to medical history, physical examination, vital signs, electrocardiogram, and clinical laboratory parameters. Subjects had to have normal findings on gynecologic examination, with a baseline antral follicle count of three or more follicles. Subjects with (a history of) thyroid disease, (a history of) ovarian or endocrine abnormalities (such as polycystic ovary syndrome), or contraindications to the use of gonadotropins were excluded from participation. The use of concomitant medication was not allowed, and smokers were excluded from the study. During the study there were restrictions on the use of grapefruit juice and caffeine-containing products and on the use of alcohol.

Study Treatments

Eligible subjects were pretreated with oral hormone contraceptives (either with the subject's own contraceptive or with a contraceptive provided by the investigator) for 3–6 weeks to synchronize menstrual cycles. After a contraceptive-free interval of 4 days, during which an antral follicle count was performed, all subjects started treatment with the oral contraceptive 30 μg ethinylestradiol and 150 μg desogestrel (Marvelon, MSD) for pituitary suppression, which continued throughout the entire MK-8389 treatment period. This oral contraceptive was administered daily, without pill-free intervals. Two weeks after the start of treatment, subjects were randomized to receive 5 mg, 10 mg, 20 mg, 30 mg, or 40 mg MK-8389 or placebo. The study medication was administered once daily for a maximum of 14 days. In case of follicular development of three follicles $\geq$14 mm, treatment with MK-8389 was to be discontinued to avoid excessive ovarian stimulation. At each dose level, 10 subjects received active treatment, and 2 subjects received placebo. The study began with the lowest dose of 5 mg MK-8389, and each dose level was completed and evaluated for safety and efficacy before escalating to the next higher dose level. The protocol was amended after completion of the 20-mg dose level, and the study continued with a smaller group of four subjects each (three on active treatment and one on placebo) to test the two highest dose levels of 30 mg and 40 mg MK-8389. The amendment also included cessation of MK-8389 treatment the day after the largest follicle attained a size of 8 mm. A treatment schedule is provided in Figure 1. The oral contraceptive was obtained from the local market by the investigator. The MK-8389 study medication was provided by MSD, as a self-emulsifying oil containing 23.4 mg MK-8389 per mL oil [corn oil/cremophor/maisine (1:1:1)]. Before administration, the required amount of study medication was diluted with placebo oil [corn oil/cremophor/maisine (1:1:1), provided by MSD] and hand-filled in a hard gelatin