

ORIGINAL ARTICLE

# Patient experience with follitropin alfa prefilled pen versus previously used injectable gonadotropins for ovulation induction in oligoanovulatory women

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Gonal-f Prefilled Pen in OI Study 24785 Group\*

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**Key words:** Drug administration – Gonadotropins – Injections – Ovulation induction – Patient satisfaction

## ABSTRACT

**Objective:** To evaluate patient satisfaction with the follitropin alfa prefilled pen (Gonal-f RFF Pen†), compared with previously used injectable gonadotropins (vial/ampoules and syringe), in women undergoing ovulation induction (OI).

**Research design and methods:** Women aged 18–40 years undergoing OI for oligoanovulatory infertility were enrolled from nine US fertility centers in this prospective, open-label clinical trial. Participants received recombinant follitropin alfa using a prefilled pen. Patient satisfaction was determined using a pre-treatment questionnaire to assess gonadotropin treatments undertaken within 6 months of study initiation and an in-treatment questionnaire to assess satisfaction with the prefilled pen.

**Main outcome measures:** The primary endpoint was the proportion of patients who preferred the prefilled pen compared to previous injectable gonadotropin therapies. Efficacy and safety were also assessed.

**Results:** Seventy-three subjects were screened for the study; 62 enrolled, were treated with the follitropin alfa pre-filled pen, and 61 completed the in-treatment questionnaire. Sixty-one of 61 patients who stated a preference preferred the prefilled pen to previous injectable gonadotropin therapies (61/61; 100%; 95% confidence interval: [94.1–100.0%]). One patient did not state a preference. Of these 61 patients, 54 (89%) found that the prefilled pen instructions were easy to understand compared to 17 of 59 (29%) who thought instructions for the conventional syringes were easy to understand. When preparing their dose, significantly fewer patients contacted their healthcare provider two or more times during the treatment cycle when receiving treatment with the prefilled pen (2/61, 3%) than during the first treatment cycle with prior gonadotropin treatment, 11/59 (19%,  $p = 0.007$ ). The pen interfered slightly or not at all with patients' normal daily activities in 61 of 61 patients (100%) versus 50 of 59 patients (85%) who had this opinion

\* Members of the Gonal-f Prefilled Pen in OI Study 24785 Group are listed in the Acknowledgments

† Gonal-f RFF Pen (RFF: Revised Formulation Female) is a registered trademark of Serono, Inc., Rockland, MA, USA; available in Europe as Gonal-f (FbM) Prefilled Pen, Serono, Geneva, Switzerland

regarding injections during their prior treatment cycles ( $p = 0.003$ ). All 61 patients who stated a method of injection preference found the prefilled pen less stressful to use than syringes and would recommend the pen to another woman considering gonadotropin treatment. A total of 10/62 (16%) subjects reported 18 treatment-emergent adverse events (AEs). Two cases of ovarian hyperstimulation syndrome occurred post-treatment and one serious AE occurred (post-treatment ectopic pregnancy). Injection site reactions were generally mild to moderate, with mild itching (6 patients, 9.7%) and moderate redness in one patient. Fifteen patients

reported mild redness (24.2%). Mild bruising (21.0%), mild pain (33.9%), and mild burning (32.3%) were also reported by patients. Seven patients (11.3%) had moderate pain.

**Conclusions:** In this open-label, non-comparative study, patients undergoing OI preferred administering gonadotropins using the follitropin alfa prefilled pen compared to their prior use of vials/ampoules and a syringe. Patients using the prefilled pen found it less stressful, easier to use and more convenient than a conventional syringe and would recommend the pen to another woman considering gonadotropin treatment.

## Introduction

More than one in five women who attend infertility clinics present with anovulation as their primary cause of infertility<sup>1</sup>. Many of these women can be treated successfully with ovulation induction (OI) using anti-estrogenic therapies such as clomiphene citrate or exogenous gonadotropins<sup>2</sup>. Today, recombinant gonadotropins, such as follitropin alfa, follitropin beta, lutropin alfa, and choriogonadotropin alfa, are available, which provide a highly pure and consistent source of exogenous gonadotropin<sup>3,4</sup>. Follitropin alfa is indicated for the treatment of infertility associated with oligoanovulation, when anovulation is functional and not due to primary ovarian failure<sup>1,2,5</sup>.

Until recently, follitropin alfa was produced as a lyophilized formulation in glass ampoules or vials and was administered subcutaneously using syringes in either single or multi-dose applications. These conventional delivery systems were designed for administration by a health care professional, a friend or family member, or the patient herself. Given the option to self-administer, women appreciated active involvement in their own treatment and gained a sense of self-sufficiency<sup>6</sup>. However, the technical issues of drawing up the medication, determining the proper dosage, and administering the injection may present problems for some women. For example, in studies evaluating patient acceptance of self-administration of contraceptives, approximately one-third of patients preferred not to self-administer<sup>7,8</sup>. The most common reasons given for this were a fear of needles<sup>7,8</sup> or concerns about administering the medication incorrectly<sup>7</sup>.

To enable easier and more convenient self-administration of recombinant human follicle-stimulating hormone (r-hFSH), liquid formulations of follitropin alfa and follitropin beta have been developed for administration using pen devices. Pen injection devices for insulin delivery have been well received by patients with diabetes, which supports the rationale for their

use with gonadotropins. For example, in a multicenter randomized study comparing insulin delivery using a prefilled pen device or conventional vial/ampoule and syringe, 74% of patients preferred the prefilled pen device (95% confidence interval [CI] 77–87%)<sup>9</sup>. Furthermore, the pen device was considered to be more discreet for use in public (85% versus 9%), easier to use (74% versus 21%), and easier to read for setting the dosage (85% versus 10%), compared with the conventional syringe<sup>9</sup>. Other studies have reported that convenience, comfort, ease-of-use ( $p = 0.012$ ), minimal interference with activities ( $p < 0.01$ ), and social acceptability ( $p < 0.001$ ) are strong positive attributes of the insulin pen device, compared with conventional vial/ampoule and syringe administration<sup>10,11</sup>.

In a study by Bohannon *et al.*<sup>12</sup>, physicians and patients alike preferred the pen device to a conventional vial/ampoule and syringe delivery system. After a 6-week trial of the injector pen in 311 patients, 76% of patients were satisfied with the pen, 78% would continue using the pen, and 80% would recommend the pen to others<sup>12</sup>. Furthermore, of the 33 physicians who participated, 97% thought the pen device was better than the vial/ampoule and syringe delivery system, and 88% thought it took less time to train subjects in the use of the pen<sup>12</sup>.

For several years, cartridges containing follitropin beta solution which require loading in a reusable injector pen have been available. Pang *et al.*<sup>13</sup> reported that 90% of patients rated their overall experience of injecting follitropin beta using the pen device as 'very good', while Kettel *et al.*<sup>13</sup> reported a similar result, with 100% of patients rating their experience as 'very good' to 'good'. This pen device has been shown to be more convenient<sup>15</sup>, and less painful<sup>15,16</sup>, than vial/ampoule and syringe delivery.

The prefilled pen device available for use with follitropin alfa is a disposable, ready-to-use pen containing follitropin alfa solution (Gonal-f RFF Pen\*). The aim of this study (Serono Study 24785) was to evaluate patient satisfaction with the follitropin alfa prefilled

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pen compared with previously used injectable gonadotropins, in women aged 18–40 years undergoing OI for oligoanovulatory infertility. The efficacy and safety of the follitropin alfa prefilled pen were also assessed during the study.

## Patients and methods

### Study design

This was a Phase IIIb, prospective, open-label study conducted at nine fertility centers in the US. Oligoanovulatory women undergoing fertility treatment were provided with a prefilled pen device for administration of follitropin alfa for ovarian stimulation during one cycle of OI. Prior to initiating treatment, patients were asked to complete a pre-treatment questionnaire to assess their experiences with previously used gonadotropin injection methods (recalling treatment[s] used within the last 6-months). Patients completed an in-treatment questionnaire on stimulation day 6 to assess their satisfaction with the prefilled pen device and to compare this with their prior experience using other gonadotropin injection methods. Each patient served as her own control.

All patients and their partners gave informed consent prior to the study. The study was approved by the local ethics committee or institutional review board, and conducted according to the principles of good clinical practice and the Declaration of Helsinki.

### Patients

Premenopausal women aged 18–40 years, inclusive, and eligible for OI were enrolled in the study if they had undergone at least one previous treatment cycle with injectable gonadotropins within the past 6 months, excluding treatment administered by a pen device. To be eligible for the study, patients had to have documented at least 12 months with failure to conceive (6 months for patients > 35 years). Women included in the study had ovulatory dysfunction, defined by: usual cycle length < 21 or > 35 days with  $\geq 6$  menses per year; or usual cycle length > 35 days with < 6 menses per year and a positive progesterone challenge response within the past 6 months or during the screening period.

Other inclusion criteria for the study included: (1) body mass index (BMI) < 35.0 kg/m<sup>2</sup>; (2) documented patency and apparent normality of at least one fallopian tube with an ipsilateral functional ovary; and (3) normal levels of prolactin, follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH), according to local laboratory screening within the past

year (patients with low TSH levels who were receiving replacement therapy could be enrolled at the discretion of the investigator). Partners of study participants were required to have had a semen analysis within the previous 6 months that was considered acceptable for OI, according to the standard practice at the clinic. Use of donor sperm was also considered acceptable.

Patients were excluded from the study if they had previously shown a poor response (estradiol level < 100 pg/mL per mature follicle,  $\geq 16$  mm mean diameter) or an excessive response (development of > 3 mature follicles with 75 IU FSH/day) to gonadotropin stimulation. Women who had previously experienced severe ovarian hyperstimulation syndrome (OHSS) were not included in the study. Women were excluded from the study if they had received treatment with gonadotropins, clomiphene citrate, insulin-sensitizing agents or gonadotropin-releasing hormone analogues within 1 month prior to study entry, or had previously participated in another investigational drug or drug delivery system trial, within 3 months prior to study entry.

Other exclusion criteria included: (1) any significant allergic disease (e.g. allergic response to gonadotropin preparations) which could interfere with study treatment; (2) clinically significant abnormal findings evident on a transvaginal pelvic ultrasound performed within two cycles (maximum 90 days) of study entry; (3) known current American Society of Reproductive Medicine Stage III or IV endometriosis; or (4) residual ovarian cyst with a mean diameter > 25 mm or estradiol > 100 pg/mL at baseline examination.

### Interventions

Prior to treatment, patients were given instructions on how to use the prefilled pen device and how to record entries in a daily treatment diary. Treatment was started on cycle day 2–3, and the first day of treatment was designated as stimulation day 1. Because ovarian response to gonadotropins decreases with age, patients were stratified according to age and assigned to receive either 75 IU (patients aged 18–34 years) or 150 IU (patients aged 35–40 years) follitropin alfa by subcutaneous injection using the ready-to-use prefilled pen device. Patients received a fixed dose for 5 days, and then returned to the clinic on stimulation day 6 for ultrasound and estradiol monitoring, with dose adjustment if necessary. Stimulation monitoring was then repeated every 2–3 days, until a lead follicle reached a mean diameter  $\geq 14$  mm, thereafter visits were scheduled every 1–2 days.

Recombinant choriogonadotropin alfa injection, 250 mcg (r-hCG [Ovidrel Prefilled Syringe, Serono, Inc., Rockland, MA, USA]) was administered when

at least one follicle, but no more than three, reached a mean diameter  $\geq 17$  mm and estradiol levels were within an acceptable range (approximately 150 pg/mL per mature follicle). Intrauterine insemination or natural intercourse occurred within 48 hours of r-hCG administration. The cycle was cancelled for patients who failed to meet r-hCG administration criteria or who showed an excessive ovarian response.

### Patient experience assessments

Prior to the first gonadotropin injection on stimulation day 1, each patient was asked to complete a pre-treatment questionnaire to evaluate her previous experience with gonadotropin administration, recalling treatment(s) used within the last 6 months. Each question used a qualitative scale, such as 'very', 'somewhat', 'not at all', 'not applicable', according to the specific question asked (Appendix A). The 14-question assessment was similar to those used to assess diabetic patient experience with insulin pen devices<sup>9-12,17</sup> and another gonadotropin pen device<sup>13,14</sup>. On stimulation day 6, patients were asked to complete an in-treatment questionnaire evaluating their experiences to date with the follitropin alfa prefilled pen (Appendix B). This questionnaire consisted of 18 questions, 78% of which were identical to those asked in the pre-treatment questionnaire. Additionally, at the study termination visit, patients were asked to compare the stress they experienced with the pen device compared to previous injection methods. In regards to the stress, the responses available were "substantially less", "slightly less", "same amount", "slightly more", and "substantially more". A healthcare provider administered all questionnaires.

### Clinical assessments

Prior to the first follitropin alfa injection on stimulation day 1, a pregnancy test was given to exclude pre-existing pregnancy, a transvaginal ultrasound confirmed the absence of ovarian cysts or follicles, and a blood sample was collected to assess estradiol levels. At each visit from day 6 onwards, and also within 24 hours after r-hCG administration, a transvaginal ultrasound examination was performed and serum estradiol levels were measured. Two blood samples were collected 24-48 hours apart, 6-9 days after r-hCG administration, to assess progesterone levels.

Patients with a positive pregnancy test ( $\beta$ -hCG  $> 10$  IU/L) 15-18 days after r-hCG administration had the test repeated within 2-4 days and returned to the clinic 35-42 days after r-hCG administration for a confirmatory ultrasound examination. Adverse events were assessed at all scheduled visits.

### Study endpoints

The primary endpoint for this trial was the proportion of patients who indicated that they preferred the prefilled pen device when responding to the question: 'Given your previous treatment experience, which method do you prefer for injecting your medication - pen device or syringe method?'. Secondary endpoints included patient questionnaire responses, ovulation rate, follicle size and number of follicles by size on the day of r-hCG administration, cumulative dose of follitropin alfa administered, duration of therapy, and pregnancy rates.

### Statistical methods

The intent-to-treat (ITT) population included all patients who received at least one injection of follitropin alfa and who indicated on the in-treatment questionnaire which of the methods, pen device or syringe, was preferable for injecting medication, given their previous experience. This population was used to assess patient satisfaction with the prefilled pen and efficacy.

Baseline characteristics of the ITT population were summarized using descriptive statistics. The percentage of patients who preferred the prefilled pen device compared with a previously used injectable method for gonadotropin treatment was calculated and the 95% CI for this percentage was determined using the binomial distribution. Responses to other questions on the in-treatment questionnaire that asked patients to compare some aspect of their experience with the prefilled pen device to that of their previously used injectable method, were assessed in this same manner. McNemar's test for  $2 \times 2$  tables was used to analyze the matched dichotomous response data from the pre-treatment and in-treatment questionnaires. All significance tests for efficacy endpoints were performed at the  $\alpha = 0.05$  level.

The safety population included all patients who received at least one injection of follitropin alfa. The safety data (i.e., adverse events, incidence and severity of OHSS, vital signs and exposure to study drug) were summarized using descriptive statistics.

A sample size of 184 patients was estimated to provide 77% power to detect that the percent of subjects who preferred the pen device to a previously used injectable method for treatment of infertility exceeded 60% using an exact test of a single proportion.

## Results

### Patients

Recruitment started on 12 July 2004 and the study was completed on 1 November 2005. Because study recruit-

ment proceeded more slowly than anticipated, the study was stopped after 73 patients enrolled. Of these, 60 patients completed the pre-treatment questionnaire. Sixty-two patients started treatment with follitropin alfa (safety population), and 61 completed the in-treatment questionnaire. One patient was excluded from the intent-to-treat (ITT) population because she did not complete the question for the primary endpoint indicating which method she preferred for injecting her medication. However, she was included in the efficacy and safety populations.

Permission was granted for some patients to enroll in the study that violated at least one inclusion criterion ( $n = 9$ ) or exclusion criterion ( $n = 6$ ), where these violations were considered to be non-critical to the study results. One woman included in the ITT population was over the age of 40 years (aged 41 years). Three patients in the ITT population had undergone their previous cycle of treatment with injectable gonadotropins more than 6 months prior to enrolment. Two women who had a BMI  $> 35.0$  kg/m<sup>2</sup> received treatment in the study, but one was excluded from the ITT population because she was unable to decide whether she preferred the follitropin alfa prefilled pen

to previous injection methods, the primary endpoint of the study.

Fifty-eight patients received r-hCG. Of the four patients who withdrew, two had failed to respond to ovarian stimulation, one patient withdrew due to an excessive risk of OHSS, and one patient withdrew because she was concerned about multiple births.

Demographic and clinical characteristics of the ITT patients are shown in Table 1. The mean age of patients in the ITT population was 32.0 years, with a median BMI of 24.4 kg/m<sup>2</sup>. On average, couples had been infertile for more than 3 years. Female and male fertility were present in 24.5% of the couples and 73.8% had only female factor. Ovulatory dysfunction was responsible for most cases of female infertility (oligoamenorrhea, 53%; menstrual irregularity, 42%).

### Pre-treatment, in-treatment, and termination visit questions

In the following sections, the results are grouped topically for ease of comparison, although the questionnaires were administered at different times during the treatment cycle.

**Table 1.** Baseline demographic and clinical characteristics of study participants

Characteristic	Intent-to-treat population* ( $n = 61$ )
Age, years	32.0 (4.2) 32.0 [23–41]
Body mass index, kg/m <sup>2</sup>	25.2 (4.8) 24.4 [18.6–37.8]
Duration of infertility, months	40.9 (35.6) 26.0 [11–158]
Type of infertility, $n$ (%)	
Female factor only	45 (74)
Female and male infertility	15 (25)
Unexplained	1 (1.6)
Number of follicles $< 11$ mm in right ovary	8.2 (7.3) 7.0 [0–25]
Number of follicles $< 11$ mm in left ovary	8.0 (7.4) 5.5 [0–25]

\*All values are shown as mean (SD), median, [range] unless specified otherwise

**Table 2.** Incidence of pain or burning at injection site for each gonadotropin treatment administered by vial/ampoule and syringe during the 6-month period prior to treatment with follitropin alfa prefilled pen. Data were available for 60 subjects

Gonadotropin treatment*	Number (%) of subjects	None $n$ (%)	Mild $n$ (%)	Moderate $n$ (%)	Severe $n$ (%)
Follitropin alfa ampoules	16 (26.7)	7 (43.8)	5 (31.3)	4 (25.0)	0
Follitropin alfa multi-dose	3 (5.0)	3 (100.0)	0	0	0
Follitropin beta vials	8 (13.3)	0	5 (62.2)	3 (37.5)	0
Urofollitropin	21 (35.0)	7 (33.3)	9 (42.9)	3 (14.3)	2 (9.5)
Menotropins (Repronex)	24 (40.0)	7 (29.2)	9 (37.5)	7 (29.2)	1 (4.2)
Menotropins (Pergonal)	2 (3.3)	0	1 (50.0)	1 (50.0)	0

\*The questionnaire asked subjects to check all treatments that applied

## Gonadotropin treatment history

Table 2 summarizes the gonadotropin treatment history of the study patients. Over the 6-month period prior to the study, the most frequently used types of gonadotropins were a menotropins preparation (Repronex [Ferring, Suffern, NY, USA]), urofollitropin (Bravelle [Ferring, Suffern, NY, USA]) and follitropin alfa ampoules. A small number of patients had experience with follitropin beta (Follistim [Organon, Roseland, NJ, USA]), follitropin alfa multi-dose, and/or another menotropins preparation (Pergonal [Serono, Inc., Rockland, MA, USA and Serono, Geneva, Switzerland]). The relatively small proportion of patients who had previously used follitropin alfa multi-dose may be related to the fact that these patients were originally excluded from study enrolment prior to a protocol amendment on 6 December 2004.

When patients were asked to recall and rate the level of injection-site pain and burning they had experienced following administration of these gonadotropins, all gonadotropin treatments, except for follitropin alfa multi-dose, were associated with some pain or burning by at least two patients (Table 2). Most patients who reported injection-site pain or burning rated it as mild or moderate.

### Comparison of follitropin alfa prefilled pen with previous gonadotropin treatment

**Primary endpoint.** All 61 patients who answered the primary endpoint question preferred the follitropin alfa prefilled pen to previously used (during the prior 6 months) gonadotropin injection methods with syringes (95% CI 94.1–100.0%). As the 95% CI of the preference rate was [94.1–100.0%], the lower patient enrolment did not impact the significance of the outcome. Therefore, by randomly selecting 61 subjects from the target population each time for 100 times, 95% of the time the true preference rate will be at least as high as 94.1%.

**Secondary endpoints.** Forty-four of 59 patients (75%) had self-administered gonadotropin injections during a previous treatment cycle, and 32/44 (73%) had self-administered on every occasion. This was similar for the prefilled pen; 47 of 61 patients (77%) self-administered their injection, and of these 47 patients, 37 (79%) self-administered on every occasion.

While away from home, 19 of 61 (31%) of patients self-administered with the follitropin alfa prefilled pen, compared with 24 of 59 patients (41%) that reported self-administration while away from home with previously used gonadotropin treatments. Of the 24 patients who self-administered some of their previous gonadotropin therapies away from home, 14 (58%), felt that it was not at all discreet, and 12 of these patients felt that it

was not at all convenient. In contrast, 16 of 19 (84%) patients who self-administered some of their prefilled pen injections away from home considered it to be very convenient. Of the patients who administered injections with the prefilled pen away from home, 17 of 19 (89%) felt this procedure took the same amount of time as at home. Of the 14 patients who had self-administered both the prefilled pen and previous therapies away from home, all 14 considered the prefilled pen to be substantially more discreet than syringes. Almost all patients, 58 of 61 (95%), considered storage of the prefilled pen very convenient, and the three remaining patients found storage somewhat convenient.

The proportion of patients who reported that injections interfered slightly or not at all with their normal daily activities was significantly different with the prefilled pen (61/61, 100%) compared with previous gonadotropin treatments (50/59, 85%; two patients had missing data;  $p = 0.003$  McNemar's test). Approximately twice as many patients, 45 of 61 (74%), felt that injections did not interfere with their normal daily activities when using the prefilled pen compared with previous gonadotropin therapies (22/59, 37%; two patients had missing data). Nine patients (15%) felt that injections with previous gonadotropins had interfered moderately with their normal daily activities.

Most of the patients found the instructions on how to use the prefilled pen very easy to understand (54/61, 89%), and the rest found them somewhat easy to understand (7/61, 11%). In comparison, fewer patients found instructions for administering their previously used gonadotropin therapies very easy to understand (17/59, 29%); the majority found them somewhat easy to understand (34/59, 58%). Some patients found the instructions for their previous therapies not at all easy to understand (8/59, 14%), which is significantly different from the 0% of patients with this opinion about the prefilled pen ( $p = 0.005$ ; McNemar's test).

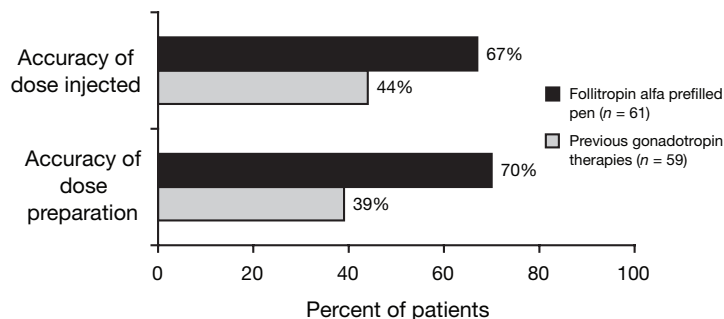
A significantly smaller proportion of patients reported contacting their healthcare provider to ask questions two or more times regarding dose preparation during the prefilled pen treatment cycle (2/61, 3%) than during the first cycle of treatment with their previous gonadotropin therapy (11/59, 19%;  $p = 0.007$ , McNemar's test). In addition, a smaller proportion of patients reported contacting their healthcare provider to ask questions two or more times regarding dose injection during the prefilled pen treatment cycle (2/61, 3%) than during the first cycle of treatment with their previous gonadotropin therapy (7/59, 12%), although this difference was not significant.

More patients felt very confident about the accuracy of both dose preparation and dose injected with the prefilled pen compared with previous gonadotropin

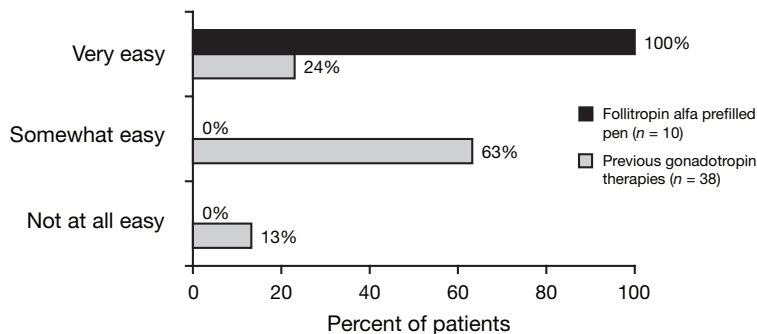
therapies (Figure 1). Although only 10 patients found they had to modify their daily dose with the prefilled pen, all of them found this procedure very easy (Figure 2). Of the 26 patients who made a direct comparison between the prefilled pen and their previous injection method with regard to the process of changing the dose, 23 (88%) reported that the prefilled pen was substantially

easier to use than the previous method, and the remaining three (12%) subjects reported that the prefilled pen was slightly easier than their previous injection method.

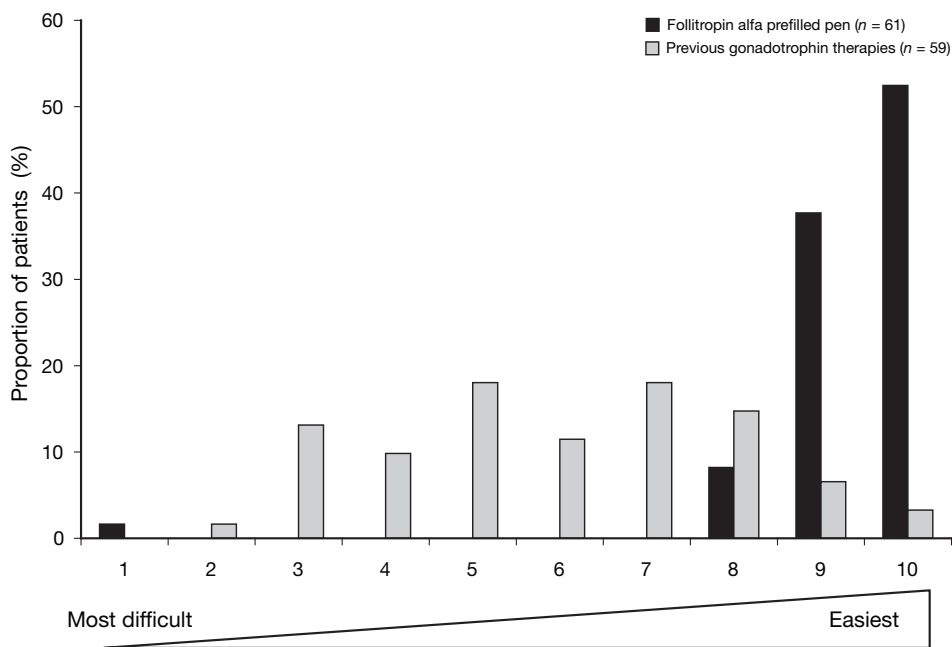
Overall ease-of-use ratings given by the patients were generally more favorable for the prefilled pen than for previous gonadotropin therapies (Figure 3). When asked specifically to compare the prefilled pen



**Figure 1.** Percentage of patients responding as 'very confident' regarding accuracy of dose preparation and injection for the follitropin alfa prefilled pen (n = 61) and previous gonadotropin therapies (n = 59)



**Figure 2.** Ratings for ease of dose modification given by those patients needing to modify their daily dose for the follitropin alfa prefilled pen (n = 10) and previous gonadotropin therapies (n = 38)



**Figure 3.** Overall ease-of-use ratings given by patients for the follitropin alfa prefilled pen (n = 61) and previous gonadotropin therapies (n = 59)

with their previous treatment in terms of the amount of stress they experienced during use, all 61 patients (100%) reported that the prefilled pen was less stressful. The majority of patients reported that using the prefilled pen was associated with substantially less stress than using the previous injection method (52/61, 85%), and the remainder reported that the prefilled pen was associated with slightly less stress (9/61, 15%). All 61 patients reported that they would recommend the prefilled pen to another woman considering gonadotropin treatment (100%; 95% CI 94.1–100.0%).

### Efficacy

Efficacy outcomes for the ITT patients are summarized in Table 3. The average cumulative dose of follitropin alfa used per patient was 1173.2 IU, and the patient's ovarian stimulation lasted 10 days, on average. The majority of women ovulated (79%) and pregnancy was achieved in 12 women (20%). Of these 12 pregnancies, eight were clinical (fetal sac), three were biochemical, and one was ectopic.

### Safety

A total of 10/62 patients (16%) reported 18 treatment-emergent adverse events (AEs) (Table 4). No patient withdrew from the study due to AEs. Headache, which occurred in seven patients (11%; seven events), was the most commonly reported treatment-emergent AE. Gastrointestinal disorders were reported by three

patients (5%; three events). The treatment-emergent AEs were generally mild (nine patients, 16 events), except for one patient who experienced an episode of moderate dysmenorrhea, and one patient who experienced severe injection site hemorrhage.

Two patients developed mild OHSS as post-treatment emergent AEs. Neither episode required hospitalization and both cases resolved. Only one serious AE – an ectopic pregnancy – occurred in a patient who received at least one injection of the study drug. This was also a post-treatment AE since it occurred after the last dose of follitropin alfa prefilled pen, and was judged by the investigator to be moderate, and probably related to the study drug. The patient made a full recovery.

All patients' injection site reactions were assessed at each visit and daily in their diary. The injection site reactions that occurred were generally mild-to-moderate at worst (Figure 4), with only one report of a severe reaction for each of the following: injection site bruising, burning, and other reactions.

No clinically significant changes in vital signs or hematology, blood biochemistry, or urinalysis values were noted during the study.

## Discussion

This is a report of the experiences of 62 oligoanovulatory patients using the follitropin alfa ready-to-use prefilled pen for OI, and their perceptions of the pen relative to their perceptions of their previously used (within the past 6 months) injectable gonadotropins. The

**Table 3.** Ovulation induction efficacy outcomes

Outcome	Intent-to-treat population* (n = 61)
r-hCG administered, n (%)	57 (93)
Follicles on day of r-hCG administration†	
Number ≥ 11 mm	7.2 (5.3) 6.0 [1–25]
Number ≥ 17 mm	1.6 (0.8) 1.0 [0–3]
Estradiol on day of r-hCG administration, pg/mL‡	963.5 (781.0) 670.2 [160.0–3090.8]
Duration of follitropin alfa therapy, days	10.2 (3.0) 10.0 [5–17]
Cumulative dose of follitropin alfa, IU	1173.2 (493.7) 1125.0 [375.0–3000.0]
Ovulation rate, n (%)	48 (79)
Progesterone level of patients who ovulated, ng/mL	45.6 (40.8) 30.4 [8.2–189.0]
Pregnancy rate, n (%)	12 (20%)

\*All values are shown as mean (SD), median, [range], unless specified otherwise

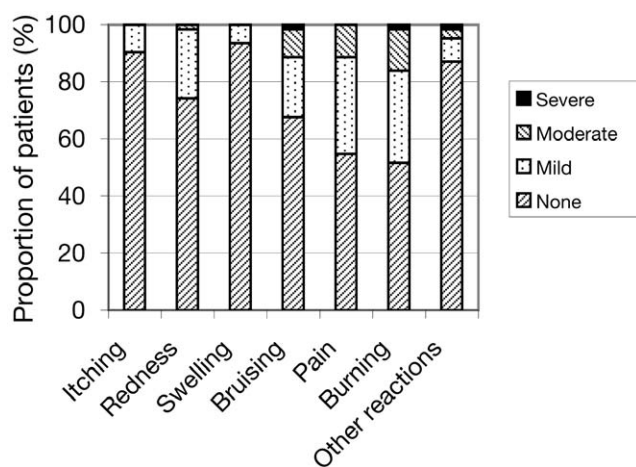
†Data were available for 57 patients

‡Data were available for 49 patients

r-hCG = recombinant human chorionic gonadotropin

**Table 4.** Treatment-emergent adverse events for the follitropin alfa prefilled pen (all treated subjects, n = 62)

	Subjects n (%)	Events n (%)
Total subjects with events and total	10 (16.1)	18
Nervous system disorders	7 (11.3)	7 (38.9)
Headache	7 (11.3)	7 (38.9)
Gastrointestinal disorders	3 (4.8)	3 (16.7)
Abdominal distension	1 (1.6)	1 (5.6)
Gastrointestinal pain	1 (1.6)	1 (5.6)
Vomiting	1 (1.6)	1 (5.6)
Infections and infestations	2 (3.2)	2 (11.1)
Sinusitis	1 (1.6)	1 (5.6)
Vaginal candidiasis	1 (1.6)	1 (5.6)
Musculoskeletal and connective tissue disorders	2 (3.2)	3 (16.7)
Arthralgia	1 (1.6)	
Neck pain	1 (1.6)	
Shoulder pain	1 (1.6)	
Reproductive system and breast disorders	2 (3.2)	2 (11.1)
Dysmenorrhea	2 (3.2)	2 (11.1)
General disorders and administration site conditions	1 (1.6)	1 (5.6)
Injection site hemorrhage	1 (1.6)	1 (5.6)



**Figure 4.** Worst case severity of injection site reactions given by patients for the follitropin alfa prefilled pen (n = 62)

results indicate that patients perceived the follitropin alfa prefilled pen as convenient, discreet, and easy to use. After using the prefilled pen, all patients reported that they preferred the pen used during the study to a conventional syringe with vials or ampoules used within the prior 6 months of this study, and would recommend the prefilled pen to another woman considering gonadotropin treatment.

Comparisons between the follitropin alfa prefilled pen and previous gonadotropin therapies indicated a number of advantages associated with use of the pen, in the effect it had on the patients' daily lives. Patients found the instructions accompanying the pen easier to understand than those supplied with conventional syringes, and they required less support from their

healthcare provider during the treatment cycle when using the pen. Patients felt more confident about the accuracy of dose preparation, the accuracy of dose injected, and the ease of dose modification with the prefilled pen, compared with a conventional syringe, and overall found the pen easier to use. Similarly, patients requiring insulin for the treatment of diabetes found injector pens easier to read<sup>9</sup> and easier to use<sup>10,11</sup> than conventional syringes used for insulin injections.

Patients felt that injections using the pen were less stressful and interfered less with their normal daily activities than using the conventional syringe. Of the patients who administered their treatment away from home, the majority found that the prefilled pen was more suitable for self-administration of injections away from home, compared with the conventional syringe. The procedure was no more time-consuming than self-administering injections at home, and patients considered self-administration away from home more convenient and discreet using the prefilled pen than using the conventional syringe. These findings are in line with experiences of patients with diabetes, who consider insulin injector pens to have minimal interference with daily activities<sup>11</sup>, to be more convenient<sup>10</sup>, as well as more socially acceptable<sup>11</sup> and discreet for use in public<sup>9</sup> than a conventional syringe.

The study follows several previous open-label, multicenter investigations which examined patient experience with a pen device for gonadotropin administration<sup>13,14</sup>. Although non-comparative, the studies by Pang *et al.*<sup>13</sup> and Kettel *et al.*<sup>14</sup> noted that 90% and 100% of subjects, respectively, found the pen

device easy to use for the administration of follitropin beta. In contrast to these studies, we asked patients to assess their prior experience (within the past 6 months) with traditional gonadotropin injection methods (vials/ampoules and syringe) prior to initiating treatment with the follitropin alfa prefilled pen. None of these patients had prior experience with a pen device for gonadotropin administration, which would thereby preclude an inherent bias in favor of a pen device. The studies by Pang *et al.*<sup>13</sup> and Kettel *et al.*<sup>14</sup> did not appear to specifically exclude patients who had prior experience with the pen device. Although our study was not designed to examine treatment bias, it is interesting to consider that the patients' multiple experiences with the vial/ampoule and syringe in one or more prior cycles may have generated a skewed response in favor of the traditional injection method. Nonetheless, patients undergoing OI preferred administering gonadotropins using the follitropin alfa prefilled pen compared to their prior use of vials/ampoules and a syringe.

Ovarian stimulation outcomes achieved using the follitropin alfa prefilled pen were similar to those reported in previous studies investigating the use of recombinant gonadotropins for OI in anovulatory women (low-dose step-up protocol)<sup>1,5</sup>. On average, gonadotropin treatment lasted 10 days and a total dose of 1173 IU follitropin alfa was consumed per patient. The cycle cancellation rate (5%) was marginally lower than rates reported in previous studies using follitropin alfa (6.5%)<sup>1</sup> or follitropin beta (13.5%)<sup>5</sup>. A total of 79% of women ovulated, and this value is comparable to previous ovulation rates achieved for OI using follitropin alfa (63–71%)<sup>1</sup>. A pregnancy rate of 20% was achieved, similar to the rates reported previously for OI using follitropin alfa (20–33%)<sup>1</sup> or follitropin beta (14.4%)<sup>5</sup>.

The follitropin alfa prefilled pen was generally well tolerated and showed a favorable safety profile in the women participating in the study. Each patient completed a daily injection diary, rating injection site reactions associated with the follitropin alfa prefilled pen. As the median duration of treatment was 10 days, more than 6000 injections were administered and evaluated. Previously, two studies evaluated pen device injection site tolerability from questionnaire responses given on two occasions per patient, firstly at 24 hours after the initial injection, and secondly on treatment day 7 prior to the seventh dose<sup>13,14</sup>. As the current study assessed site tolerability of each injection given, rather than basing evaluations on two pre-determined time points, direct comparisons between these studies are inconclusive. However, injection site itching, bruising, and swelling for the follitropin alfa prefilled pen were found to be similar to rates reported in the previous studies, with pain and redness modestly elevated. Rates of OHSS were low (3%) and similar to those reported in previous studies using

recombinant gonadotropins (2–6%)<sup>1,5</sup>. Only one ectopic pregnancy was reported among those who received study drug and the patient recovered fully.

## Conclusion

The results indicated a high level of patient satisfaction with the follitropin alfa prefilled pen, which became commercially available shortly after the study started. We found that oligoanovulatory patients requiring gonadotropins for OI prefer using the follitropin alfa ready-to-use prefilled pen to previously used injectable gonadotropins administered using vials/ampoules and a syringe. Furthermore, patients using the pen found it less stressful, easier to use and more convenient than a conventional syringe and would recommend the prefilled pen to another woman considering gonadotropin treatment.

## Acknowledgments

**Declaration of interest:** This study was sponsored by Serono Inc.

The authors would like to acknowledge Imogen Horsey for her help in the preparation of this manuscript.

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## Appendix A

### Pre-treatment Questionnaire

Please answer these questions based on your infertility treatment(s) during the last 6 months.

1. Please check the boxes below to indicate which stimulation drug(s) you used in your previous treatment cycles (during the past 6 months) and whether you experienced any pain or burning from injecting these medications.

Stimulation drug used. Check all that apply	Did you experience injection pain or burning at the injection site?
Gonal-f ampoules	<input type="checkbox"/> No <input type="checkbox"/> Yes – if yes, was the pain or burning: <input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe
Gonal-f Multi-Dose	<input type="checkbox"/> No <input type="checkbox"/> Yes – if yes, was the pain or burning: <input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe
Follistim	<input type="checkbox"/> No <input type="checkbox"/> Yes – if yes, was the pain or burning: <input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe
Bravelle	<input type="checkbox"/> No <input type="checkbox"/> Yes – if yes, was the pain or burning: <input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe
Repronex	<input type="checkbox"/> No <input type="checkbox"/> Yes – if yes, was the pain or burning: <input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe
Pergonal	<input type="checkbox"/> No <input type="checkbox"/> Yes – if yes, was the pain or burning: <input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe

2. During your previous treatment cycle(s), did you administer any of the injections yourself?

- Yes
- No

If yes, how often did you administer the injections yourself?

- 100% of the time
- About 75% of the time
- About 50% of the time
- About 25% of the time
- Less than 25% of the time

3. Did you give yourself any injections away from home during your previous treatment cycle(s)?

- Yes
- No

If yes, how convenient was it to carry your medication with you?

- Very convenient
- Somewhat convenient
- Not at all convenient

4. When you were injecting your medication away from home, how discreet was the syringe injection method?

- Very discreet
- Somewhat discreet
- Not at all discreet
- Not applicable

5. In your previous treatment cycle(s), did the use of the syringes interfere with your normal daily activities?

- Substantially interfered with my normal daily activities
- Moderately interfered with my normal daily activities
- Slightly interfered with my normal daily activities
- Did not interfere at all with my normal daily activities

6. Overall during your past treatment cycle(s), how confident did you feel that you accurately prepared your daily dose of medication?

- Very confident
- Somewhat confident
- Not at all confident

7. Overall during your past treatment cycle(s), how confident did you feel that you accurately injected the correct daily dose of medication?

- Very confident
- Somewhat confident
- Not at all confident

8. During any of your previous treatment cycle(s), did you have to modify your daily dose of medication during the cycle?

- Yes
- No

If yes, how easy was it to change your daily dose with the syringe injection method?

- Very easy
- Somewhat easy
- Not at all easy

9. How easy were the instructions for administering your medication using the syringe injection method to understand during your previous treatment cycle(s)?
- Very easy
  - Somewhat easy
  - Not at all easy

10. Please check the boxes below to indicate which tools you used to learn how to prepare and inject your medication during your previous treatment cycle(s). Then indicate how helpful you thought those tools were:

Tools used. Check all that apply	How helpful in learning how to <u>prepare</u> the daily dose?	How helpful in learning how to <u>inject</u> the daily dose?
<input type="checkbox"/> Hands-on demonstration	<input type="checkbox"/> Very helpful <input type="checkbox"/> Somewhat helpful <input type="checkbox"/> Not at all helpful	<input type="checkbox"/> Very helpful <input type="checkbox"/> Somewhat helpful <input type="checkbox"/> Not at all helpful
<input type="checkbox"/> Instruction card	<input type="checkbox"/> Very helpful <input type="checkbox"/> Somewhat helpful <input type="checkbox"/> Not at all helpful	<input type="checkbox"/> Very helpful <input type="checkbox"/> Somewhat helpful <input type="checkbox"/> Not at all helpful
<input type="checkbox"/> Video	<input type="checkbox"/> Very helpful <input type="checkbox"/> Somewhat helpful <input type="checkbox"/> Not at all helpful	<input type="checkbox"/> Very helpful <input type="checkbox"/> Somewhat helpful <input type="checkbox"/> Not at all helpful
<input type="checkbox"/> CD-ROM	<input type="checkbox"/> Very helpful <input type="checkbox"/> Somewhat helpful <input type="checkbox"/> Not at all helpful	<input type="checkbox"/> Very helpful <input type="checkbox"/> Somewhat helpful <input type="checkbox"/> Not at all helpful

11. Which single tool do you feel would have been most helpful in learning how to prepare and inject your medication using the syringe injection method? Choose only one:

- Hands-on demonstration
- Instruction card
- Video
- CD-ROM

12. During your first treatment cycle using the syringe injection method, how often did you contact your health care provider with questions about how to prepare your daily dose?

- More than 5 times
- 4 times
- 3 times
- Twice
- Once
- Never

13. During your first treatment cycle using the syringe injection method, how often did you contact your health care provider with questions about how to inject your daily dose?

- More than 5 times
- 4 times
- 3 times
- Twice
- Once
- Never

14. On a scale from 1 to 10, with 1 being most difficult and 10 being the easiest, how would you rate the overall ease-of-use of the syringe injection method?

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10

## Appendix B

### In-treatment Questionnaire

Answer the following questions based on your experience using the pen device (to be completed by the subject on stimulation day 6)

1. Did you administer any of the injections with the pen device yourself?

- Yes
- No

If yes, how often did you administer the injections yourself?

- 100% of the time
- About 75% of the time
- About 50% of the time
- About 25% of the time
- Less than 25% of the time

2. How convenient was it to store the pen device during your treatment?

- Very convenient
- Somewhat convenient
- Not at all convenient

3. Did you give yourself any injections away from home during this treatment cycle?

- Yes
- No

If yes, how convenient was it to carry the pen device with you?

- Very convenient
- Somewhat convenient
- Not at all convenient

4. When you were injecting your medication away from home, did you feel that the pen device was more discreet than using the syringes?

- Yes
- No
- Not applicable

If yes, was the pen device:

- Substantially more discreet than using the syringes
- Slightly more discreet than using the syringes

5. How much did the use of the pen device interfere with your normal daily activities?

- Substantially interfered with my normal daily activities
- Moderately interfered with my normal daily activities

- Slightly interfered with my normal daily activities  
 Did not interfere at all with my normal daily activities
6. When using the pen device, was the amount of time required to prepare and inject your medication away from home:
- More than at home  
 About the same as at home  
 Less than at home  
 Not applicable
7. Overall during your treatment cycle, how confident were you that you accurately prepared your daily dose of medication using the pen device?
- Very confident  
 Somewhat confident  
 Not at all confident
8. Overall during your treatment cycle, how confident were you that you injected the correct daily dose of medication using the pen device?
- Very confident  
 Somewhat confident  
 Not at all confident
9. Did you have to modify your daily dose of medication during this treatment cycle?
- Yes  
 No
- If yes, how easy was it to change your daily dose of medication with the pen device?
- Very easy  
 Somewhat easy  
 Not at all easy
10. Compared to your previous treatment cycle(s), would you say the process of changing your daily dose of medication with the pen device was:
- Substantially easier than with the syringe method  
 Slightly easier than with the syringe method  
 About the same as the syringe method  
 Not applicable
11. How easy were the instructions on how to use the pen device to understand?
- Very easy  
 Somewhat easy  
 Not at all easy
12. Please check the boxes below to indicate which tools you used to learn how to prepare and inject your medication using the pen device. Then indicate how helpful you thought those tools were:

Tools used. Check all that apply	How helpful in learning how to <u>prepare</u> the daily dose?	How helpful in learning how to <u>inject</u> the daily dose?
<input type="checkbox"/> Hands-on demonstration	<input type="checkbox"/> Very helpful <input type="checkbox"/> Somewhat helpful <input type="checkbox"/> Not at all helpful	<input type="checkbox"/> Very helpful <input type="checkbox"/> Somewhat helpful <input type="checkbox"/> Not at all helpful
<input type="checkbox"/> Instruction card	<input type="checkbox"/> Very helpful <input type="checkbox"/> Somewhat helpful <input type="checkbox"/> Not at all helpful	<input type="checkbox"/> Very helpful <input type="checkbox"/> Somewhat helpful <input type="checkbox"/> Not at all helpful

13. How did the amount of time needed to prepare and inject your medication using the pen device compare to the syringe injection method you used in your previous treatment cycle(s)?
- Pen device required significantly less time than the syringe method
  - Pen device required slightly less time than the syringe method
  - Pen device required the same amount of time than the syringe method
  - Pen device required slightly more time than the syringe method
  - Pen device required significantly more time than the syringe method
14. During this treatment cycle, how often did you contact your health care provider with questions about how to prepare your daily dose with the pen device?
- More than 5 times
  - 4 times
  - 3 times
  - Twice
  - Once
  - Never
15. During this treatment cycle, how often did you contact your health care provider with questions about how to inject your daily dose with the pen device?
- More than 5 times
  - 4 times
  - 3 times
  - Twice
  - Once
  - Never
16. On a scale from 1 to 10, with 1 being most difficult and 10 being the easiest, how would you rate the overall ease-of-use of the pen device?
- 1
  - 2
  - 3
  - 4
  - 5
  - 6
  - 7
  - 8
  - 9
  - 10
17. Would you recommend the pen device to another woman considering gonadotropin treatment?
- Yes
  - No
18. Given your previous treatment experience, which method do you prefer for injecting your medication:
- Pen device
  - Syringe method

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<http://www.cmrojournal.com>  
Paper CMRO-3494\_4, Accepted for publication: 08 August 2006  
Published Online: 20 September 2006  
doi:10.1185/030079906X132604