Comparative economic study of the use of corifollitropin alfa and daily rFSH for controlled ovarian stimulation in older patients: Cost-minimization analysis based on the PURSUE study

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Abstract This study presents an economic assessment of controlled ovarian stimulation in assisted reproductive technology procedures in Spain, comparing the use of corifollitropin alfa and various forms of recombinant follicle-stimulating hormone (rFSH) in women of advanced maternal age. A cost-minimization analysis (CMA) was performed to assess the cost per cycle of controlled ovarian stimulation, including only direct costs associated with the stimulation phase. The CMA was based on the population characteristics, the protocol, and the results obtained from the PURSUE study, taking into account 9 days of controlled ovarian stimulation and 300 IU rFSH/day. The primary analysis included pharmacological costs alone. Different scenarios were evaluated including various doses and possible additional days (0–5) for rFSH. For the alternative analyses, the total costs (direct pharmacological costs, costs of visits and follow-up tests, and any additional pharmacological costs) were considered in both the private and public sectors. Treatment with corifollitropin alfa resulted in a lower pharmacological cost compared with rFSH (€757.25 and €950.30, respectively), creating a saving of approximately -20%. The results of the scenario analyses showed that corifollitropin alfa reduced the pharmacological cost of controlled ovarian stimulation in comparison with daily administration of doses ≥250 IU rFSH (considering same daily dose for all days), regardless of the additional days required (7–12 days) (average -€223;
Corifollitropin alfa cost-minimization analysis

range -€488 to -€44). In conclusion, in addition to the efficacy shown in the PURSUE study, the use of corifollitropin alfa results in a decrease in the direct costs associated with controlled ovarian stimulation in older women in Spain. © 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

KEYWORDS: corifollitropin alfa, cost-minimization analysis, controlled ovarian stimulation, recombinant follicle-stimulating hormone

Introduction

Approximately 6% of babies in Spain are born following treatment using assisted reproduction technology (ART) (Lorente et al., 2013). In general, the use of ART has increased in recent years (Audibert and Glass, 2015; Bosser et al., 2009; Brassesco-Julio et al., 2015; FITCAT.NET, 2013; Matorras, 2011; SEF Registry, 2014). Various factors, including an ageing population, are involved in this increase. Thus, the percentage of women aged ≥40 years who seek treatment with ART has increased.

In Spain, intracytoplasmatic sperm injection (ICSI) is the most common procedure for in-vitro fertilization (IVF) (Matorras, 2011; Sunyer and Almazán, 2012). Most treatments in Spain are performed in private centres (Prados et al., 2014). The Registry of the Spanish Fertility Society (Sociedad Española de Fertilidad, SEF) records most IVF (traditional) or ICSI (mixed) cycles performed in Spain (Prados et al., 2014). Based on the latest information available in the SEF Registry, 51,591 cycles using IVF/ICSI and the patient’s own oocytes were started in Spain in 2014 (SEF Registry, 2014). Of these, 31% (15,882 cycles) were performed in women aged <35 years, 47% (24,241 cycles) in women aged ≥35 and ≤39 years, and 19% (9,902 cycles) in women aged ≥40 years; the age of the woman was unknown for the remaining 3% (1,566 cycles) (SEF Registry, 2014). In Spain, the most commonly used drug for controlled ovarian stimulation is recombinant follicle-stimulating hormone (rFSH) (Lorente et al., 2013).

Some gonadotropins currently available for controlled ovarian stimulation (rFSH, urofollitropin (uFSH), highly purified-human menopausal gonadotropin (HP-HMG)) together with a gonadotropin-releasing hormone (GnRH) antagonist require daily administration. Elonva® (corifollitropin alfa) is a sustained follicle stimulant that can be administered in controlled ovarian stimulation (SPC Elonva, 2016). Unlike other gonadotropins, corifollitropin alfa can replace 7 days of gonadotropin treatment with a single injection. The efficacy and safety of these treatments have been assessed in three randomized, double-blind clinical trials (Boo istanfar et al., 2015; Devroey et al., 2009; Obruca et al., 2010). Corifollitropin alfa was found to have an equivalent effect to daily doses of 150 IU rFSH in the ENSURE study (Obruca et al., 2010), and to daily doses of 200 IU in the ENGAGE study (Devroey et al., 2009). The most recent direct evidence comes from the PURSUE study (Boo istanfar et al., 2015), where a single subcutaneous injection of 150 μg corifollitropin alfa was compared with the daily administration of 300 IU rFSH in a trial involving 1,390 women aged between 35 and 42 years. This age group is representative of the majority of patients seeking ART treatment in developed countries (Audibert and Glass, 2015; Prados et al., 2014; SEF Registry, 2014). Treatment with corifollitropin alfa showed non-inferiority in pregnancy rates [estimated difference -3.0% (confidence interval (CI) -7.4 to 1.4)], in the mean number of oocytes recovered [estimated difference 0.5 (CI -0.2 to 1.2)] and in the rate of live births [estimated difference -2.3% (CI -6.5 to 1.9)] (Boo istanfar et al., 2015).

In Spain, the total pharmaceutical cost associated with assisted reproduction is €98.7 million (2012 prices), with 81% of the cost (€80 million) associated with controlled ovarian stimulation (Lorente et al., 2013). The Spanish National Health System (SNHS) finances less than one-third (29%) of the total cost (Lorente et al., 2013). This lack of funding prevents many couples from accessing ART treatment (Audibert and Glass, 2015; Mator ras, 2011).

The demand for ART is expected to continue to rise. Therefore, the economic impact of the available treatments must be assessed, and ways of minimizing the cost sought (Audibert and Glass, 2015; Matorras, 2011). To our knowledge, there are no published studies in autologous oocyte cycles comparing the economic impact of using corifollitropin alfa instead of daily gonadotropins among IVF patients. Two studies have assessed the issue among egg donors (Calatayud et al., 2017; Cruz et al., 2017). In addition, the economic evaluations of rFSH available in Spain have been made in young populations (Bosch and Pellicer, 2005; Melo et al., 2010; Navarro Espigares et al., 2006). Therefore, studies in older populations are needed.

The purpose of this work was to assess and compare the cost of using corifollitropin alfa and various forms of rFSH for controlled ovarian stimulation in women of advanced maternal age in Spain, based on data from the PURSUE study (Boo istanfar et al., 2015).

Materials and methods

A cost-minimization analysis (CMA) was undertaken using Excel 2013 (Microsoft Corp, Redmond, WA, USA) to assess the efficiency associated with corifollitropin alfa and rFSH treatments based on the PURSUE study (Boo istanfar et al., 2015; López Bastida et al., 2010). CMA should be based on interventions that have been proven to be equivalent (Drummond et al., 2001; Huse raeu et al., 2013). For this reason, the current CMA was based on the PURSUE study because: it is a phase 3 randomized, double-blind, non-inferiority, multicentre trial evaluating 1,390 women aged 35–42 years; it represents the most recent direct evidence comparing these treatments; the age group evaluated corresponds to the majority of women receiving ART treatment, both in Spain and in other developed countries; and the non-inferiority design enables a CMA between corifollitropin alfa and rFSH.
CMA has been used previously to compare controlled ovarian stimulation treatments with similar clinical results (Lloyd et al., 2003; Melo et al., 2010; Revelli et al., 2006; Wex and Abou-Setta, 2013).

The main features of the PURSUE study (Table 1, Boostanfar et al., 2015) were: mean age 38 years (range ≥ 35 to ≤ 42 years); administering a single dose of 150 μg corifollitropin alfa on day 1 compared with daily doses of 300 IU rFSH for the first 7 days; total mean duration of controlled ovarian stimulation of 9 days for the corifollitropin alfa arm was controlled ovarian stimulation with corifollitropin alfa followed 7 days later by 2 additional days with 300 UI rFSH daily (total 600 IU rFSH); and total mean duration of controlled ovarian stimulation for the rFSH arm was 9 days with 300 IU rFSH daily (total 2,700 IU rFSH).

To complement the CMA, the information related to the cost per oocyte recovered was approximated. In this approach, both the non-inferiority design of the PURSUE study and the fact that the experts considered corifollitropin alfa and rFSH as equivalent options in therapeutic terms was taken into consideration. Thus, the efficacy data for corifollitropin alfa were taken into account for the number of oocytes recovered for both the corifollitropin alfa arm and the rFSH arm.

The direct cost of one cycle of controlled ovarian stimulation was assessed. Therefore, no time discounting was applied.

Three different analyses were assessed: primary analysis (private sector and drug-only costs); alternative analysis 1 (private sector and total costs); and alternative analysis 2 (SNHS and total costs).

### Primary analysis: private sector and pharmacological costs

#### Primary analysis: base case

As 75% of ART treatments in Spain are performed in private practices (Barri et al., 2002), the primary analysis considered drug-only costs in the private sector. The pharmacological costs were expressed as retail price + value added tax (SGOCP, 2017).

The cost of treatment with corifollitropin alfa included both the cost of a single subcutaneous injection of 150 μg on day 1 of controlled ovarian stimulation plus the cost of 2 additional days of 300 IU rFSH on days 8 and 9 (total 600 IU rFSH). Puregon® (follitropin beta) costs were applied for the IU administered after day 7.

Regarding the comparator in the current analysis, different available rFSH were included, namely Puregon (follitropin beta), Gonal-F® (follitropin alfa), Bemfola® (follitropin alfa biosimilar_B) and Ovaleap® (follitropin alfa biosimilar_O), and the average cost of rFSH was calculated by considering these four drugs together (Table 2). It was assumed that these four drugs had the same effectiveness, and therefore the same protocol and total dose of rFSH (2,700 IU), administered over 9 days of controlled ovarian stimulation following the PURSUE study (Boostanfar et al., 2015).

#### Primary analysis: sensitivity analysis

Following the approximation of the pharmacological cost detailed in the previous section, various scenarios with different combinations of doses/days (200–375 IU; 0–5 days) were assessed, following the protocol used in the PURSUE study. These combinations of doses/days were chosen to reflect the variation in clinical practice in Spain among the assessed population (women with a mean age of 38 years).

### Table 1  Baseline characteristics, protocol and clinical efficacy outcomes in the PURSUE study (Boostanfar et al., 2015).

| Corifollitropin alfa | rFSH |
|---------------------|------|
| Baseline characteristic |      |
| Age (years)          | 38.0 (2.2) | 38.0 (2.2) |
| Weight (kg)          | 67.8 (10.7) | 66.6 (10.8) |
| Body mass index (kg/m²) | 25.1 (3.6) | 24.7 (3.5) |
| Controlled ovarian stimulation characteristics | |
| Total duration of stimulation (days) | 9.0 | 9.0 |
| Single dose of corifollitropin alfa (μg) | 150 | — |
| Total dose of rFSH for days 1–8 (IU) | 300 | 2,400 |
| Total dose of rFSH from day 8 (IU) | 300 | 300 |
| Efficacy results for mean number of oocytes recovered | |
| Mean number of oocytes recovered per started cycle | 10.7 (7.2) c | 10.3 (6.8) |
| Women aged ≤ 38 years | 11.6 (7.1) c | 11.4 (7.2) |
| Women aged > 38 years | 9.6 (7.1) c | 8.7 (5.9) |
| Mean of metaphase 2 oocytes (ICSI only) | 8.0 c | 7.5 |

rFSH, recombinant follicle-stimulating hormone; ICSI, intracytoplasmic sperm injection; IU, international units.

Values are mean (standard deviation) or median, unless otherwise stated.

a Assumed for the four rFSH comparators included (Puregon®, Gonad-F®, Bemfola® and Ovaleap®).

b Restricted to women receiving human chorionic gonadotrophin.

c In calculating the cost per recovered oocyte, only the efficacy outcomes of corifollitropin alfa were considered for both arms.

d Estimated difference between treatments of 0.5 (95% confidence interval -0.2 to 1.2) within the margins for non-inferiority.
| Preparation | \(\mu g/ IU\) | Syringes/vials/cartridges/pens | Total \(\mu g/ IU\) | Primary analysis and alternative analysis 1 | Alternative analysis 2 |
|-------------|-------------|-------------------------------|-----------------|---------------------------------|------------------|
|             |             |                               |                 | Retail price + VAT | Retail price + VAT/ (\(\mu g/ IU\)) | Discount agreed by law | Retail price + VAT - discount | Patient contribution* | Retail price + VAT - discount - patient contribution |
| Corifollitropin alfa |             |                               |                 |                   |                   |                          |                            |                           |                                               |
| Elona® (150 \(\mu g\), one prefilled syringe 0.5 ml) | 150 | 1 | 150 | €509.51 | €3.40 | 7.50% | €471.30 | €4.26 | €467.04 |
| Follitropin beta |             |                               |                 |                   |                   |                          |                            |                           |                                               |
| Puregon® (100 IU, 10 vials 0.5 ml) | 100 | 10 | 1,000 | €381.64 | €0.38 | 15.00% | €324.39 | €4.26 | €320.13 |
| Puregon® (300 IU, one cartridge 0.36 ml) | 300 | 1 | 300 | €147.74 | €0.49 | 15.00% | €125.58 | €4.26 | €121.32 |
| Puregon® (600 IU, one cartridge 0.72 ml) | 600 | 1 | 600 | €247.74 | €0.41 | 15.00% | €210.58 | €4.26 | €206.32 |
| Puregon® (900 IU, one cartridge 1.08 ml) | 900 | 1 | 900 | €359.05 | €0.40 | 15.00% | €305.19 | €4.26 | €300.93 |
| Follitropin alfa |             |                               |                 |                   |                   |                          |                            |                           |                                               |
| Gonal-f ® (1050 IU/1.75 ml, one vial of powder + solvent and syringe 2 ml) | 1,050 | 1 | 1,050 | €346.48 | €0.33 | 0.00% | €346.48 | €4.26 | €342.22 |
| Gonal-f ® [300 IU, (22 \(\mu g\)) prefilled pen 0.5 ml] | 300 | 1 | 300 | €125.89 | €0.42 | 0.00% | €125.89 | €4.26 | €121.63 |
| Gonal-f ® [450 IU, (33 \(\mu g\)) prefilled pen 0.75 ml] | 450 | 1 | 450 | €173.54 | €0.39 | 0.00% | €173.54 | €4.26 | €169.28 |
| Gonal-f ® (75 IU, one vial of powder + one solvent and syringe 1 ml) | 75 | 1 | 75 | €31.47 | €0.42 | 0.00% | €31.47 | €3.03 | €28.44 |
| Gonal-f ® (75 IU, 10 vials of powder + 10 solvent and syringes 1 ml) | 75 | 10 | 750 | €262.61 | €0.35 | 0.00% | €262.61 | €4.26 | €258.35 |
| Gonal-f ® [900 IU, (66 \(\mu G\)) prefilled pen 1.5 ml] | 900 | 1 | 900 | €304.54 | €0.34 | 0.00% | €304.54 | €4.26 | €300.28 |
| Follitropin alfa biosimilar |             |                               |                 |                   |                   |                          |                            |                           |                                               |
| Bemfola® (150 IU, one prefilled pen 0.25 ml) | 150 | 1 | 150 | €62.94 | €0.42 | 0.00% | €62.94 | €4.26 | €58.68 |
| Bemfola® (150 IU, 10 prefilled pens 0.25 ml) | 150 | 10 | 1,500 | €472.27 | €0.31 | 0.00% | €472.27 | €4.26 | €468.01 |
| Bemfola® (225 IU, one prefilled pen 0.375 ml) | 225 | 1 | 225 | €94.41 | €0.42 | 0.00% | €94.41 | €4.26 | €90.15 |
| Bemfola® (225 IU, 10 prefilled pens 0.375 ml) | 225 | 10 | 2,250 | €687.14 | €0.31 | 0.00% | €687.14 | €4.26 | €682.88 |
| Bemfola® (300 IU, one prefilled pen 0.5 ml) | 300 | 1 | 300 | €125.89 | €0.42 | 0.00% | €125.89 | €4.26 | €121.63 |
| Bemfola® (300 IU, 10 prefilled pens 0.5 ml) | 300 | 10 | 3,000 | €896.80 | €0.30 | 0.00% | €896.80 | €4.26 | €892.54 |
| Bemfola® (450 IU, one prefilled pen 0.75 ml) | 450 | 1 | 450 | €173.54 | €0.39 | 0.00% | €173.54 | €4.26 | €169.28 |
| Bemfola® (75 IU, one prefilled pen 0.125 ml) | 75 | 1 | 75 | €31.47 | €0.42 | 0.00% | €31.47 | €3.03 | €28.44 |
| Bemfola® (75 IU, 10 prefilled pens 0.125 ml) | 75 | 10 | 750 | €262.61 | €0.35 | 0.00% | €262.61 | €4.26 | €258.35 |
| Follitropin alfa biosimilar |             |                               |                 |                   |                   |                          |                            |                           |                                               |
| Ovaleap® (300 IU, one cartridge 0.5 ml) | 300 | 1 | 300 | €125.89 | €0.42 | 0.00% | €125.89 | €4.26 | €121.63 |
| Ovaleap® (450 IU, one cartridge 0.75 ml) | 450 | 1 | 450 | €173.54 | €0.39 | 0.00% | €173.54 | €4.26 | €169.28 |
| Ovaleap® (900 IU, one cartridge 1.5 ml) | 900 | 1 | 900 | €304.54 | €0.34 | 0.00% | €304.54 | €4.26 | €300.28 |

VAT, value added tax; IU, international units.

* Calculated according to Ministerio de Sanidad, Servicios Sociales e Igualdad guidelines (MSSSI, 2017); 'Reduced contribution medication: 10% of the retail price for medication belonging to ATC groups qualifying for reduced contribution, with a maximum contribution expressed in euros. For reduced contribution medicines with a maximum of €4.26 per package'.
Additionally, two deterministic one-way sensitivity analyses were performed where the cost of gonadotropins was assessed considering the mean and the lowest cost per IU.

**Alternative analysis 1: private sector and total costs**

**Alternative analysis 1: base case**

For alternative analysis 1, we added (Table 3): the costs of follow-up visits and tests based on the cost per block/packet (i.e. total follow-up cost per controlled ovarian stimulation cycle paid by the patient regardless of total amount of healthcare resources used) in private clinics, which included the cost of required visits to the specialist, ultrasound examinations and blood tests for each cycle (data from three private centres); and other pharmacological costs corresponding to 5-day treatment with the GnRH antagonist ganirelix, which was the antagonist administered in the PURSUE study (Boostanfar et al., 2015) and is used most commonly in Spain (IMS, 2016).

All other costs were considered to be the same for all the compared options. This assumption was in line with other economic evaluations in ART (Levi Setti et al., 2015; Melo et al., 2010) and was validated by the clinical experts consulted.

**Alternative analysis 1: sensitivity analysis**

Several deterministic one-way sensitivity analyses were performed, taking into account three to five visits to a specialist, blood tests and ultrasound examinations per cycle, instead of using the cost per block/packet based on the use of resources reported by experts, and taking account of the published literature (Romeu et al., 2003).

**Alternative analysis 2: Spanish National Health System and total costs**

**Alternative analysis 2: base case**

In alternative analysis 2, the assessment was made from the public setting perspective, and included the following categories of costs: pharmacological costs (gonadotropin costs) and other pharmacological costs (GnRH antagonist) – based on the same combination of preparations as for the primary analysis and alternative analysis 1, but taking into account the discount agreed in Spanish legislation (an urgent measure enacted by the Spanish Government to reduce public spending; Boletín Oficial del Estado (BOE), 2010) and the contribution paid by the patient (MSSSI, 2017); and costs of follow-up visits and tests – based on the opinion of experts and published literature, it was considered that patients would require four visits to a specialist, blood tests and ultrasound examinations per cycle (Romeu et al., 2003). This use of resources was multiplied by the cost given in public tariffs for Spain (Table 3) (eSalud, 2017). Once again, all other costs were considered to be the same for all the compared options.

**Alternative analysis 2: sensitivity analysis**

Several sensitivity analyses were performed, taking into account three and five visits to a specialist, blood tests and ultrasound examinations.

Ethical approval was not required for this study as it is based on published data.

**Results**

**Primary analysis: private sector and pharmacological costs**

**Primary analysis: base case**

The pharmacological cost associated with treatment for 9 days of controlled ovarian stimulation with corifollitropin alfa + 600 IU rFSH was €757.25, 67% of which corresponded to the first 7 days of controlled ovarian stimulation (Table 4). The average pharmacological cost per treatment with rFSH for 9 days of controlled ovarian stimulation (total dose 2,700 IU rFSH) was €950.30, 78% of which corresponded to the first 7 days. The pharmacological cost per cycle for follitropin beta, follitropin alfa, follitropin alfa biosimilar_B and follitropin alfa biosimilar_O was €1,077.15, €913.62, €1,068.75 and €913.62, respectively.

**Ethical approval**

Ethical approval was not required for this study as it is based on published data.

**Results**

**Primary analysis: private sector and pharmacological costs**

**Primary analysis: base case**

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**Ethical approval**

Ethical approval was not required for this study as it is based on published data.

| Follow-up visits and tests | Use per cycle | €609 |
|---------------------------|---------------|------|
|                           | Mean | Min. | Max. | Private | Public |
| Specialist monitoring visit | 4 | 3 | 5 | €50 | €76 |
| Blood test | 4 | 3 | 5 | €25 | €40 |
| Ultrasound | 4 | 3 | 5 | €60 | €74 |

**Other pharmacological costs – GnRH antagonist treatment**

- **Number of days of treatment required**: 5
- **Cost per cycle private sector (retail price + VAT)**: €191.28
- **Cost per cycle public sector (retail price + VAT - discount - patient contribution)**: €172.67

| Use per cycle | €609 |
|---------------|------|
| Private | Public |

- **Alternative analysis 1 – base case**
- **Alternative analysis 1 – sensitivity analysis**
- **Alternative analysis 2 base case and sensitivity analysis**
- **Preparation considered**: Orgalutran® (0.25 μg, five prefilled syringes 0.5 ml).
Table 4  Results of primary analysis: total pharmacological cost per cycle in the private sector.

|                      | Corifollitropin alfa | Average rFSH<sup>a</sup> | Follitropin beta | Follitropin alfa | Follitropin alfa biosimilar_B | Follitropin alfa biosimilar_O |
|----------------------|-----------------------|---------------------------|------------------|------------------|-------------------------------|-------------------------------|
| **Cost for first 7 days COS (I)** |                       |                           |                  |                  |                               |                               |
| Total dose of rFSH (IU) | 2,100                 | 2,100                     | 2,100            | 2,100            | 2,100                         | 2,100                         |
| Total dose of corifollitropin alfa (μg) | 150                   | -                          | -                | -                | -                             | -                             |
| Total cost for first 7 days COS | €509.51              | €739.12                    | €837.78          | €710.59          | €697.51                       | €710.59                       |
| Absolute difference<sup>b</sup> (negative values indicate saving with corifollitropin alfa); Relative difference<sup>b</sup> (negative values indicate saving with corifollitropin alfa) | -€229.61              | -€328.27                   | -€201.08         | -€188.00          | -€201.08                      | -€201.08                      |
|                      | -31%                  | -39%                       | -28%             | -27%             | -28%                          | -28%                          |
| **Cost of additional days of COS (II)** |                       |                           |                  |                  |                               |                               |
| Total dose of rFSH (IU) | 600                   | 600                        | 600              | 600              | 600                           | 600                           |
| Total cost of additional days COS<sup>c</sup> | €247.74              | €211.18                    | €239.37          | €203.03          | €199.29                       | €203.03                       |
| Absolute difference<sup>b</sup> (negative values indicate saving with corifollitropin alfa) | €36.56               | €8.37                      | €44.71           | €48.45            | €44.71                        | €44.71                        |
| Relative difference<sup>b</sup> (negative values indicate saving with corifollitropin alfa) | 17%                  | 3%                         | 22%              | 24%               | 22%                           | 22%                           |
| **Total cost per cycle of COS (I + II)** |                       |                           |                  |                  |                               |                               |
| Total dose of rFSH (IU) | 2,700                 | 2,700                      | 2,700            | 2,700            | 2,700                         | 2,700                         |
| Total no. of days on rFSH treatment | 2                   | 9                          | 9                | 9                | 9                             | 9                             |
| Total cost of rFSH<sup>d</sup> | €247.74              | €950.30                    | €1077.15         | €913.62          | €896.80                       | €913.62                       |
| Total cost of corifollitropin alfa | €509.51              | -                          | -                | -                | -                             | -                             |
| Total cost of COS | €757.25              | €950.30                    | €1077.15         | €913.62          | €896.80                       | €913.62                       |
| Absolute difference<sup>b</sup> (negative values indicate saving with corifollitropin alfa) | -€193.05              | -€319.90                   | -€156.37         | -€139.55          | -€156.37                      | -€156.37                      |
| Relative difference<sup>b</sup> (negative values indicate saving with corifollitropin alfa) | -20%                 | -30%                       | -17%             | -16%             | -17%                          | -17%                          |

rFSH, recombinant follicle-stimulating hormone; COS, controlled ovarian stimulation; IU, international unit.

<sup>a</sup> Average pharmacological cost for follitropin beta, follitropin alfa, follitropin alfa biosimilar_B and follitropin alfa biosimilar_O.

<sup>b</sup> Difference between corifollitropin alfa and each comparator.

<sup>c</sup> For corifollitropin alfa, the cost for rFSH has been calculated based on the cost of follitropin beta.

<sup>d</sup> Presentations considered: corifollitropin alfa: one pack Elonva® 150 μg, one prefilled syringe 0.5 ml + one pack Puregon® 600 IU, one cartridge 0.72 ml; follitropin beta: three packs Puregon 900 IU, one cartridge 1.08 ml; follitropin alfa: three packs Gonal-F® 900 IU (66 μg), prefilled pen 1.5 ml; follitropin alfa biosimilar_B: one pack Bemfola® 300 IU, 10 prefilled pens 0.5 ml; follitropin alfa biosimilar_O: three packs Ovaleap® 900 IU, one cartridge 1.5 ml.
As a result, corifollitropin alfa reduced the pharmacological cost by €193 (range -€140 to -€320) compared with rFSH, creating a mean saving of -20% (range -16% to -30%).

There was no wastage of drug for corifollitropin alfa, follitropin beta, follitropin alfa and follitropin alfa biosimilar_B. The combination of preparations that considered for each treatment option are shown in Table 4.

Table 5: Sensitivity analysis of primary analysis and alternative 1 and 2 analysis.

Table:<br>Scenarios assessed | Corifollitropin alfa<sup>d</sup> (first 7 days) + additional days with rFSH | Average rFSH<sup>e</sup> | Difference | Saving<br>--- | --- | --- | --- | ---<br>Primary analysis: private sector and pharmacological costs - base case and sensitivity analysis<br>Base case<sup>a</sup> | €757 | €950 | -€193 | -20%<br>Cost of rFSH using the mean cost per IU €0.39 – 9 days of COS<sup>a</sup> | €742 | €1044 | -€303 | -29%<br>Cost of rFSH using the lowest average cost per IU €0.34 – 9 days of COS<sup>a</sup> | €712 | €911 | -€199 | -22%<br>Cost of rFSH using the mean cost per IU – 7 days COS<sup>b</sup> | €510 | €541 | €32 | -6%<br>Cost of rFSH using the mean cost per IU – 12 days COS<sup>c</sup> | €1,235 | €1,740 | €506 | -29%<br>Alternative analysis 1 (private sector total costs)<sup>a</sup> – base case and sensitivity analysis<br>Base cost (considering cost per block/packet) | €1,557 | €1,750 | -€193 | -11%<br>Unit cost and use of resources: visits, blood tests, ultrasound x4 | €1,489 | €1,682 | -€193 | -11%<br>Unit cost and use of resources: visits, blood tests, ultrasound x3 | €1,354 | €1,547 | -€193 | -12%<br>Unit cost and use of resources: visits, blood tests, ultrasound x5 | €1,624 | €1,817 | -€193 | -11%<br>Alternative analysis 2 (Spanish National Health System total costs)<sup>a</sup> – base case and sensitivity analysis<br>Base case (use of resources: visits, blood tests, ultrasound x4) | €1,606 | €1,832 | -€226 | -12%<br>Use of resources: visits, blood tests, ultrasound x3 | €1,416 | €1,642 | -€226 | -14%<br>Use of resources: visits, blood tests, ultrasound x5 | €1,796 | €2,022 | -€226 | -11%<br>COS, controlled ovarian stimulation; rFSH, recombinant follicle-stimulating hormone.<br><sup>a</sup> Taking into account 9 days of COS, total dose of rFSH 2700 IU and total dose of rFSH for corifollitropin alfa group 600 IU.<br><sup>b</sup> Taking into account 7 days of COS, total dose of rFSH 1400 IU and no additional treatment with rFSH for the corifollitropin alfa group.<br><sup>c</sup> Taking into account 12 days of COS, total dose of rFSH 4500 IU and total dose of rFSH for the corifollitropin alfa group 1875 IU.<br><sup>d</sup> Includes the days of treatment with rFSH.<br><sup>e</sup> Average pharmacological cost for follitropin beta, follitropin alfa, follitropin alfa biosimilar_B and follitropin alfa biosimilar_O.
Table 6   Primary analysis: sensitivity analysis scenarios varying the number of additional days of controlled ovarian stimulation (COS) and the daily dose of recombinant follicle-stimulating hormone (rFSH) (same daily dose for all the days of the cycle of COS).

| Additional days/daily dose | 200 | 225 | 250 | 275 | 300 | 325 | 350 | 375 |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|
| Cost of corifollitropin alfa | €510 | €510 | €510 | €510 | €510 | €510 | €510 | €510 |
| Average cost of FSH | €582 | €611 | €704 | €756 | €791 | €895 | €936 | €998 |
| Difference | -€72 | -€102 | -€195 | -€247 | -€281 | -€406 | -€453 | -€488 |
| Saving | 12% | -17% | -28% | -33% | -36% | -44% | -47% | -49% |
| Cost of corifollitropin alfa | €657 | €657 | €657 | €657 | €657 | €757 | €757 | €757 |
| Average cost of rFSH | €622 | €636 | €769 | €828 | €886 | €996 | €1,062 | €1,085 |
| Difference | - €35 | - €12 | - €17 | - €23 | - €28 | - €34 | - €38 | - €42 |
| Saving | 6% | 0% | -15% | -21% | -26% | -29% | -30% | -30% |
| Cost of corifollitropin alfa | €757 | €757 | €757 | €757 | €757 | €869 | €869 | €869 |
| Average cost of rFSH | €656 | €740 | €837 | €911 | €950 | €1,083 | €1,136 | €1,213 |
| Difference | -€101 | -€17 | €479 | -€154 | -€193 | -€214 | -€268 | -€345 |
| Saving | 15% | 2% | -9% | -17% | -20% | -20% | -24% | -28% |
| Cost of corifollitropin alfa | €757 | €869 | €869 | €869 | €869 | €910 | €905 | €905 |
| Average cost of rFSH | €717 | €784 | €915 | €994 | €1,020 | €1,180 | €1,226 | €1,310 |
| Difference | - €40 | - €84 | €47 | -€125 | -€151 | -€289 | -€231 | -€305 |
| Saving | 6% | 11% | -5% | -13% | -15% | -24% | -19% | -23% |
| Cost of corifollitropin alfa | €869 | €869 | €891 | €901 | €905 | €1,005 | €1,039 | €1,116 |
| Average cost of FSH | €739 | €882 | €912 | €925 | €935 | €989 | €1,046 | €1,116 |
| Difference | - €69 | - €14 | €334 | -€89 | €141 | €246 | €280 | €334 |
| Saving | 9% | -2% | -13% | -8% | -12% | -19% | -18% | -23% |
| Cost of corifollitropin alfa | €891 | €1,005 | €1,039 | €1,116 | €1,116 | €1,228 | €1,228 | €1,250 |
| Average cost of rFSH | €880 | €945 | €1,083 | €1,177 | €1,243 | €1,406 | €1,493 | €1,565 |
| Difference | - €11 | - €60 | - €44 | - €61 | - €127 | - €178 | - €265 | - €315 |
| Saving | 1% | 6% | -4% | -5% | -10% | -13% | -18% | -20% |

*From day 7. For corifollitropin alfa following the primary analysis, the cost of FSH was considered as the cost of follitropin beta. The results shaded green indicate a reduction in costs/greater saving with corifollitropin alfa. The results shaded orange indicate a reduction in costs/greater saving with rFSH.

Table 7   Primary analysis: sensitivity analysis scenarios varying the number of additional days of controlled ovarian stimulation (COS) and the daily dose of recombinant follicle-stimulating hormone (rFSH) (dose for first 7 days 300 IU and changes in dose for the additional days).

| Additional days/daily dose | 200 | 225 | 250 | 275 | 300 | 325 | 350 | 375 |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|
| Cost of corifollitropin alfa | €510 | €510 | €510 | €510 | €510 | €510 | €510 | €510 |
| Average cost of FSH | €791 | €791 | €791 | €791 | €791 | €791 | €791 | €791 |
| Difference | -€281 | -€281 | -€281 | -€281 | -€281 | -€281 | -€281 | -€281 |
| Saving | -36% | -36% | -36% | -36% | -36% | -36% | -36% | -36% |
| Cost of corifollitropin alfa | €637 | €637 | €637 | €637 | €637 | €757 | €757 | €757 |
| Average cost of rFSH | €512 | €512 | €512 | €512 | €512 | €657 | €657 | €689 |
| Difference | -€407 | -€407 | -€407 | -€407 | -€407 | -€407 | -€407 | -€407 |
| Saving | -24% | -23% | -26% | -26% | -26% | -18% | -18% | -18% |
| Cost of corifollitropin alfa | €737 | €757 | €757 | €757 | €757 | €869 | €869 | €869 |
| Average cost of rFSH | €915 | €921 | €950 | €950 | €950 | €1,010 | €1,012 | €1,018 |
| Difference | -€148 | -€163 | -€175 | -€175 | -€175 | -€175 | -€175 | -€175 |
| Saving | -17% | -18% | -19% | -20% | -20% | -14% | -14% | -15% |
| Cost of corifollitropin alfa | €737 | €869 | €869 | €869 | €869 | €891 | €1,005 | €1,005 |
| Average cost of FSH | €950 | €994 | €1,002 | €1,017 | €1,020 | €1,086 | €1,094 | €1,130 |
| Difference | -€439 | -€439 | -€439 | -€439 | -€439 | -€439 | -€439 | -€439 |
| Saving | -20% | -13% | -13% | -15% | -15% | -18% | -8% | -11% |
| Cost of corifollitropin alfa | €869 | €869 | €891 | €1,005 | €1,005 | €1,039 | €1,116 | €1,116 |
| Average cost of rFSH | €1,035 | €1,043 | €1,096 | €1,129 | €1,146 | €1,219 | €1,233 | €1,243 |
| Difference | -€166 | -€175 | -€205 | -€224 | -€241 | -€280 | -€317 | -€127 |
| Saving | -16% | -17% | -18% | -20% | -20% | -14% | -14% | -15% |
| Cost of corifollitropin alfa | €891 | €1,005 | €1,039 | €1,116 | €1,116 | €1,228 | €1,228 | €1,250 |
| Average cost of rFSH | €1,112 | €1,154 | €1,211 | €1,233 | €1,243 | €1,347 | €1,364 | €1,386 |
| Difference | -€221 | -€249 | -€272 | -€317 | -€347 | -€368 | -€388 | -€139 |
| Saving | -20% | -13% | -13% | -15% | -15% | -18% | -8% | -11% |

*From day 7. For corifollitropin alfa, following the primary analysis, the cost of FSH was considered as the cost of follitropin beta. The results shaded green indicate reduction in costs/greater saving with corifollitropin alfa. The results shaded orange indicate reduction in costs/greater saving with rFSH.
minimized the cost for follitropin alfa biosimilar B resulted in slight wastage (300 IU).

**Primary analysis: sensitivity analysis**

When the cost per cycle was calculated based on both the mean and the lowest cost per IU, corifollitropin alfa reduces the cost by €303 and €199, respectively (Table 5). Results of the sensitivity analysis on various scenarios showed that in those cases where a fixed daily dose was administered (between 200 and 375 IU) during the whole stimulation period, corifollitropin alfa reduced the pharmacological cost compared with the use of rFSH alone by €163 (range -€488 to +€101), with an average saving of -15% (range -49% to +15%) (Table 6). Therefore, the daily administration of rFSH was more expensive with doses of ≥225 IU compared with the use of corifollitropin alfa (average -€223, range -€488 to -€44).

When considering 300 IU/day for the first 7 days and variations during the additional days, corifollitropin alfa reduces the cost in all of the scenarios assessed compared with rFSH (average -€182, range -€281 to -€89) (Table 7).

The average cost per recovered oocyte was lower with corifollitropin alfa compared with rFSH (€71 and €89, respectively) (Fig. 2). For both treatments, the cost increased with the patient’s age. The cost per metaphase 2

**Fig. 2** Cost of treatment outcomes (oocytes recovered) based on the efficacy outcomes of the PURSUE study (Boostanfar et al., 2015). ICSI, intracytoplasmic sperm injection. Average cost, taking into account the efficacy outcomes for corifollitropin alfa in both groups. Recombinant follicle-stimulating hormone (rFSH) cost, average pharmacological cost of Puregon®, Gonal-F®, Bemfola® and Ovaleap®.
oocyte recovered (ICSI alone) was €95 for corifollitropin alfa and €119 for rFSH.

**Alternative analysis 1: private sector and total costs**

**Alternative analysis 1: base case**

The total cost per cycle of controlled ovarian stimulation with corifollitropin alfa and with rFSH was €1,557 and €1,750, respectively (range €1,697 to €1,877) (Fig. 3). The proportionate reduction for corifollitropin alfa of -€193 (range -€320 to -€140) represented a total cost saving of -11% (range -17% to -8%).

**Alternative analysis 1: sensitivity analysis**

Changes in the use of resources relating to follow-up visits and tests performed during the sensitivity analysis did not alter the results of the base case (Table 5).

**Alternative analysis 2: Spanish National Health System and total costs**

**Alternative analysis 2: base case**

Considered from the perspective of the SNHS, the total cost per cycle of controlled ovarian stimulation with corifollitropin alfa was €1,606 compared with €1,832 for rFSH. This reduction in costs of -€226 represented a total cost saving of -12% (Fig. 4).

**Alternative analysis 2: sensitivity analysis**

Variations in the number of medical follow-up visits and tests performed during the sensitivity analysis did not alter the results of the base case, and corifollitropin alfa provided a saving of between -11% and -14% (Table 5).

**Discussion**

Regardless of different scenarios, corifollitropin alfa represented a cheaper option compared with the daily administration of ≥200 IU rFSH when the 7 days of controlled ovarian stimulation were considered. In addition, corifollitropin alfa was less costly when the stimulation treatment was prolonged, provided that the daily dose of gonadotropins was ≥250 IU. This is also the usual dose for women aged 35–42 years based on the opinion of the clinical experts. Finally, when taking into account the initial fixed dose of 300 IU gonadotropins, and variable doses after day 8 of controlled ovarian stimulation, all the scenarios assessed showed an average saving of -19% with the use of corifollitropin alfa.

Alternative analysis 1 (private sector and total cost) provided greater detail of the main categories of costs and their contribution to the total cost of controlled ovarian stimulation, where together, the pharmacological cost represented 61% (€949) and 65% (€1,142) for corifollitropin alfa and rFSH, respectively. This is in line with evidence which shows that the cost of medication is the main deciding factor, and increases as the patient's age increases because of the greater need for doses of rFSH (Bouwmans et al., 2008).

Alternative analysis 2 (SNHS and total costs) confirmed the results of the primary analysis and alternative analysis 1. On the whole, corifollitropin alfa created savings compared with rFSH of between -11% and -20% depending on the perspective assessed and the type of costs included.

Economic studies for rFSH have been published in Spain (Balasch and Barri, 2001; Barri et al., 2002; Bosch and Pellicer, 2005; Hernandez Torres et al., 2015; Lorente et al., 2013; Romeu et al., 2003; Ruiz-Balda et al., 2005; Slof, 2010; Wex-Wechowski, 2011). On the whole, these studies looked at younger populations than the present study, and therefore the mean dose of rFSH required (IU) was lower. Thus, we considered a higher total dose per cycle of controlled ovarian stimulation of 2,700 IU rFSH (the range observed in these other Spanish studies was 1,900–2,500 UI). However, Ruiz-Balda et al. (2005) indicated that the average dose per cycle needed by patients aged ≥36 years was 2,715 IU rFSH (36.2 vials of 75 IU per cycle), in line with the present study.

In many of these studies, the cost used per IU of rFSH was higher than that used in this study (€0.39), varying between

![Fig. 4](image-url) Results of alternative analysis 2: Spanish National Health System and total costs. Recombinant follicle-stimulating hormone (rFSH), average pharmacological cost of Puregon®, Gonal-F®, Bemfola® and Ovaleap®.
recovered (14.30 with corifollitropin alfa and 13.05 with no significant difference in the total number of oocytes HP-HMG (et al. (2017) found no significant difference between the results from the study by Calatayud et al. (2017) showed the cost of corifollitropin alfa in donor cycles in Spain. The 2008; Prados et al., 2014; Ruiz-Balda et al., 2005). The current study shares most similarities with the study by Slof (2010), which compared rFSH alfa and rFSH beta. Consequently, some assessments are applicable, such as the fact that the packaging with the least cost per IU does not always represent a lower treatment cost, given that the cost associated with the excess dose could counteract the saving in terms of cost per IU (Slof, 2010).

In this study, the cost per treatment outcome based on the number of oocytes recovered was lower with corifollitropin alfa than with rFSH for both the overall population as well as age subgroups. This reduction could be greater if the results from a recent meta-analysis, highlighting the greater capacity of corifollitropin alfa to generate oocytes, are taken into consideration (Fensore et al., 2015; Griesinger et al., 2016; Pouwer et al., 2016). Cruz et al. (2017) carried out a cost-effectiveness analysis on egg donors who received treatment with corifollitropin alfa, rFSH or HP-HMG, expressing the results based on the cost per recovered oocyte and per metaphase 2 oocyte, without encountering statistically significant differences between the treatments.

Features of controlled ovarian stimulation other than cost – such as effectiveness, number of injections/comfort level and convenience of administration – may have an impact on patient preference (Palumbo et al., 2011; van den Wijngaard et al., 2015). These aspects could favor the choice of corifollitropin alfa compared with rFSH. For example, in the study by Requena et al. (2013), egg donors who received a previous cycle with rFSH were more satisfied after switching to corifollitropin alfa and, hence, it is expected that this protocol will also improve compliance (Requena et al., 2013). Recently, use of corifollitropin alfa was shown to result in a greater level of convenience or comfort than rFSH for the donor in the number of days of injections required (3.20 and 8.55 days, respectively; \textit{P}<0.005) (Calatayud et al., 2017).

Calatayud et al. (2017) and Cruz et al. (2017) evaluated the cost of corifollitropin alfa in donor cycles in Spain. The results from the study by Calatayud et al. (2017) showed no significant difference in the total number of oocytes recovered (14.30 with corifollitropin alfa and 13.05 with rFSH) or in the mean cost of treatment (€736.18 for corifollitropin alfa and €747.81 for rFSH). Likewise, Cruz et al. (2017) found no significant difference between the cost of treatment with corifollitropin alfa, rFSH or HP-HMG (€1,394.3, €1,194.0 and €1,205.1, respectively).

One of the strengths of the present study is that it takes into account the PURSUE study, where age is the determining factor for both the specific dose of gonadotropin and the results of efficacy outcomes (Booestanfar et al., 2015). Age is a variable of particular interest in controlled ovarian stimulation within ART, as it influences the clinical outcomes and the economic consequences (Bouwmans et al., 2008; Prados et al., 2014; Ruiz-Balda et al., 2005). Therefore, it is important to assess the economic impact in older patients to allow more personalized care.

Another strength of the present study is that it takes a conservative view of the calculated cost for rFSH; it considered the combination of packages that resulted in the lowest cost incurred, assuming the total dose required was known in advance. In actual practice, it is not possible to know the total dose of rFSH that the patient will need at the outset; therefore, the amount of remaining medication required could be greater.

The CMA assessed both the daily dose of 300 IU rFSH (base case) and other doses (range 200–375 IU in the sensitivity analysis) to try to reflect the existing variability in current clinical practice where the dose of rFSH is adapted depending on the response of the ovaries (Balasch and Barri, 2001; Lorente et al., 2013; Melo et al., 2010; Slof, 2010; Wex-Wechowski, 2011). According to clinical experts and the published literature (Slof, 2010), these doses are most commonly used in women of advanced maternal age (mean age 38 years). Other studies undertaken in Spain, in other European countries and in the United States of America also report using a daily dose of 300 IU rFSH for all days of controlled ovarian stimulation (Berkkanoglu and Ozgur, 2010; Delgado-Garcia et al., 2015; Drakopoulos et al., 2017; Gleicher et al., 2015; Naether et al., 2015; Reveli et al., 2015; Rubio et al., 2017; Ubaldi et al., 2016), or during the additional days of controlled ovarian stimulation after administering 150 µg corifollitropin alfa on the first day (Nielsen et al., 2016; Polyzos et al., 2013a, 2013b).

Current guidelines recommend the use of an individualized starting dose based on factors such as age, body mass index, presence of polycystic ovaries and ovarian reserve (NICE, 2013). Most protocols contemplate a starting daily dose of 150–300 IU gonadotropin (Junghenn et al., 2015). Although higher doses of gonadotropins may be required to recruit oocytes in older women (Booestanfar et al., 2015), it should be noted that the dose required may be lower in younger populations (Naether et al., 2015). In fact, a daily dose of 300 IU rFSH should not be considered as the current practice of care for controlled ovarian stimulation in expected normal responders, as the optimal daily rFSH dose for these patients is 150–225 UI (Jayaprakasan et al., 2010; Sterrenburg et al., 2011). In the present study, in the scenario analysis where a daily dose of 200 IU rFSH was considered for all days of the cycle, corifollitropin alfa would present savings across 7 days of controlled ovarian stimulation, while rFSH would be the most efficient option when considering 8–12 days of controlled ovarian stimulation.

In addition, the dose used in our base case was based on a clinical trial, whereas it would be useful to have data from clinical practice. Unfortunately, the published data from the European and Spanish registries does not provide this information (Ferraretti et al., 2013; Prados et al., 2014).

One of the limitations of this study could lie in assuming a similar effectiveness for all comparators. However, assuming similar effectiveness between corifollitropin alfa and rFSH is supported by other studies (Devoe et al., 2009; Obruca et al., 2010) and recent meta-analyses (Fensore et al., 2015; Griesinger et al., 2016; Pouwer et al., 2016). As regards comparing similar effectiveness between different rFSH, Gizzo et al. (2016) considered follitropin alfa biosimilar_B to be less effective than follitropin alfa, which is in contrast to the findings of this study.
Corifollitropin alfa cost-minimization analysis

uFSH and HP-HMG were not included in the current analysis given the lack of evidence. Studies published in Spain on rFSH and uFSH found greater cost efficiency for pregnancies with rFSH because, despite costing more to purchase, fewer cycles were needed to achieve pregnancy and, consequently, the dose required and associated cost were lower (Balasch and Barri, 2001; Barri et al., 2002; Romeu et al., 2003). In turn, the majority of economic evaluations between rFSH and HP-HMG published in Spain indicated that HP-HMG was the most efficient (Bosch and Pellicer, 2005; Melo et al., 2010; Ruiz-Balda et al., 2005; Wex-Wechowski, 2011). In women with a mean age of 38 years, another commonly used protocol is 225 FSH + 75 HP-HMG. Looking at it conservatively, the cost for 9 days of controlled ovarian stimulation could be approximated using the lower cost per IU for commercially available preparations (€0.27 for HP-HMG and €0.30 for rFSH), giving €786.60 per cycle. Using the results of this study, corifollitropin alfa would reduce this cost by -4%.

This study included direct costs alone. It did not account for other costs relevant to the patient’s environment and/or lifestyle, such as absences from work or travel. This restriction was also observed in other economic assessment studies on controlled ovarian stimulation (Barri et al., 2002; Romeu et al., 2003).

The costs associated with ART have generated debates on subjects such as how treatment should be financed, benefits to couples, and benefits to society as a whole. In this regard, Matorras et al. (2016) analysed whether investment in ART could generate tax benefits for the NHS in the long term given the contributions that the child conceived would make, and improving access, equity and quality of life for infertility couples. Consequently, further studies assessing the efficiency of corifollitropin alfa are needed to support clinical management and healthcare planning.

In conclusion, the current CMA based on the PURSUE study, and therefore focused on women with a mean age of 38 years (range 35–42 years), suggests that treatment with corifollitropin alfa for controlled ovarian stimulation would be more efficient than rFSH within the Spanish context, as it reduces pharmacological costs.

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